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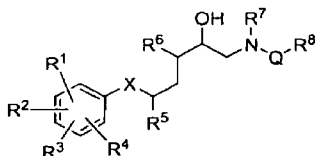
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(54) Title: 1-HETEROCYCLYLAMINO-2-HYDROXY-3-AMINO- ω -ARYLALKANES



(I)

(57) Abstract: 1-Heterocyclylamino-2-hydroxy-3-amino- ω -arylalkanes of formula (I) and the salts thereof have renin-inhibiting properties and can be used as antihypertensive, medicinally active ingredients.

1-HETEROCYCLYLAMINO-2-HYDROXY-3-AMINO- ω -ARYLALKANES

RELATED APPLICATIONS

5 This application claims the benefit of U.S. Provisional No. 60/787,936, filed March 31, 2006, the entire teachings of which are incorporated herein by reference.

BACKGROUND

10 In the renin-angiotensin-aldosterone system (RAAS) the biologically active peptide angiotensin II (Ang II) is generated by a two-step mechanism. The highly specific aspartic protease 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 AT₁ and AT₂. Whereas AT₁ seems to transmit most of the known functions of Ang II, the role of AT₂ is still unknown.

15 Modulation of the RAAS represents a major advance in the treatment of cardiovascular diseases (Zaman, M. A. et al *Nature Reviews Drug Discovery* **2002**, *1*, 621-636). ACE inhibitors and AT₁ blockers have been accepted as treatments of hypertension (Waeber B. et al., "The renin-angiotensin system: role in experimental and human hypertension", in Berkenhager W. H., Reid J. L. (eds): *Hypertension*, Amsterdam, Elsevier Science Publishing Co, **1996**, 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

25 infarction (Pfeffer M. A. et al., *N Engl. J. Med.*, **1992**, *327*, 669).

Interest in the development of renin inhibitors stems from 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 bypassed by chymase, a serine protease (Husain A., *J. Hypertens.*, **1993**, *11*, 1155). In patients, inhibition of ACE

30 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 AT₁ receptor (e.g., by

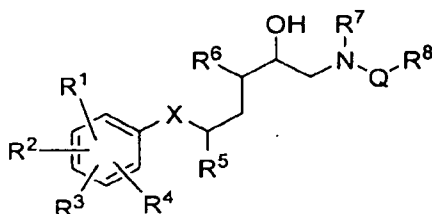
losartan) on the other hand overexposes other AT-receptor subtypes to Ang II, whose concentration is dramatically increased by the blockade of AT₁ receptors. In summary, renin inhibitors are not only expected to be superior to ACE inhibitors and AT₁ blockers with regard to safety, but more importantly also with regard to their efficacy in blocking the RAAS.

Only limited clinical experience (Azizi M. *et al.*, *J. Hypertens.*, **1994**, *12*, 419; Neutel J. M. *et al.*, *Am. Heart*, **1991**, *122*, 1094) has been generated with renin inhibitors because their peptidomimetic character imparts insufficient oral activity (Kleinert H. D., *Cardiovasc. Drugs*, **1995**, *9*, 645). The clinical development of several compounds has been stopped because of this problem together with the high cost of goods. It appears that only one compound has entered clinical trials (Rahuel J. *et al.*, *Chem. Biol.*, **2000**, *7*, 493; Mealy N. E., *Drugs of the Future*, **2001**, *26*, 1139). Thus, metabolically stable, orally bioavailable and sufficiently soluble renin inhibitors that can be prepared on a large scale are not available. Recently, the first non-peptide renin inhibitors were described which show high *in vitro* activity (Oefner C. *et al.*, *Chem. Biol.*, **1999**, *6*, 127; Patent Application WO 97/09311; Maerki H. P. *et al.*, *Il Farmaco*, **2001**, *56*, 21). The present invention relates to the unexpected identification of renin inhibitors of a non-peptidic nature and of low molecular weight. 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, are described.

All documents cited herein are incorporated by reference.

SUMMARY OF THE INVENTION

It has now been found that 1-heterocyclamino-2-hydroxy-3-amino- ω -arylalkanes of formula I



and the salts thereof have renin-inhibiting properties and can be used as antihypertensive, medicinally active ingredients.

C₆)alkoxycarbonylamino(C₁-C₆)alkylamino, (C₁-C₆)alkylaminocarbonyl-amino(C₁-C₆)alkyl, (C₁-C₆)alkylaminocarbonylamino(C₁-C₆)alkoxy, (C₁-C₆)alkylaminocarbonyl-amino(C₁-C₆)alkylthio, (C₁-C₆)alkylaminocarbonylamino(C₁-C₆)alkylamino, aminocarbonyl(C₁-C₆)alkyl, aminocarbonyl(C₁-C₆)alkoxy, aminocarbonyl(C₁-C₆)alkylthio, aminocarbonyl(C₁-C₆)alkylamino, (C₁-C₆)alkylaminocarbonyl(C₁-C₆)alkyl, (C₁-C₆)alkylaminocarbonyl(C₁-C₆)alkoxy, (C₁-C₆)alkyl-aminocarbonyl(C₁-C₆)alkylthio, (C₁-C₆)alkylaminocarbonyl(C₁-C₆)alkylamino, aminocarboxy(C₁-C₆)alkyl, aminocarboxy(C₁-C₆)alkoxy, aminocarboxy(C₁-C₆)alkylthio, aminocarboxy(C₁-C₆)-alkylamino, (C₁-C₆)alkylaminocarboxy(C₁-C₆)alkyl, (C₁-C₆)alkylaminocarboxy(C₁-C₆)alkoxy, (C₁-C₆)alkylaminocarboxy(C₁-C₆)alkylthio, (C₁-C₆)alkylaminocarboxy(C₁-C₆)alkylamino, (C₁-C₁₂)alkoxycarbonylamino, (C₁-C₁₂)-alkylaminocarbonylamino, or (C₁-C₁₂)alkanoylamino,

wherein (1) hydrogen atoms in these groups are optionally substituted by (a) 1 to 5 halogen atoms and (b) by 1 group selected from cyano, hydroxyl, (C₁-C₃)alkyl, (C₁-C₃)alkoxy, (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkoxy, halo(C₁-C₃)alkyl, halo(C₁-C₃)alkoxy, halo(C₃-C₆)cycloalkyl, and halo(C₃-C₆)cycloalkoxy; and
 (2) divalent sulfur atoms are optionally oxidized to sulfoxide or sulfone, and
 (3) a carbonyl group is optionally replaced by a thiocarbonyl group,

R³ is hydrogen, halogen, cyano, carbamoyl, lower alkyl, lower haloalkyl, lower alkoxy-lower alkyl, cycloalkoxy-lower alkyl, hydroxy-lower alkyl, lower alkylthio-lower alkyl, lower alkanesulfonyl-lower alkyl, optionally partially hydrogenated or N-oxidized pyridyl-lower alkyl, thiazolyl-thio-lower alkyl or thiazolylthio-lower alkyl, imidazolylthio-lower alkyl, optionally N-oxidized pyridylthio-lower alkyl, pyrimidinylthio-lower alkyl, amino-lower alkyl, lower alkylamino-lower alkyl, di-lower alkylamino-lower alkyl, lower alkanoyl-amino-lower alkyl, lower alkanesulfonylamino-lower alkyl, polyhalo-lower alkane-sulfonylamino-lower alkyl, pyrrolidino-lower alkyl, piperidino-lower alkyl, piperazino-lower alkyl, N'-lower alkylpiperazino-lower alkyl or N'-lower alkanoylpiperazino-lower alkyl, morpholino-lower alkyl, thiomorpholino-lower alkyl, S-oxothiomorpholino-lower alkyl or S,S-dioxothiomorpholino-lower alkyl, cyano-lower alkyl, carboxy-lower alkyl, lower alkoxy-carbonyl-lower alkyl, carbamoyl-lower alkyl, N-mono- or N,N-di-lower alkyl-carbamoyl-lower alkyl, cycloalkyl; phenyl or naphthyl that is unsubstituted or substituted with one to three groups independently selected from lower alkyl, lower alkoxy, hydroxy, lower alkylamino, di-lower alkylamino, halogen, trifluoromethyl, trifluoromethoxy, and cyano; hydroxy, lower alkoxy, cycloalkoxy, lower alkoxy-lower alkoxy, cycloalkoxy-lower alkoxy, hydroxy-lower alkoxy, aryl, lower haloalkoxy, lower alkylthio-lower alkoxy, lower haloalkylthio-lower alkoxy, lower alkanesulfonyl-lower alkoxy, lower haloalkanesulfonyl-lower alkoxy, optionally hydrogenated heteroaryl-lower alkoxy, heterocyclyl-lower alkoxy, optionally partially or fully

hydrogenated heteroarylthio-lower alkoxy, such as thiazolylthio-lower alkoxy or thiazolynylthio-lower alkoxy, imidazolylthio-lower alkoxy, optionally N-oxidized pyridylthio-lower alkoxy, pyrimidinylthio-lower alkoxy, amino-lower alkoxy, lower alkylamino-lower alkoxy, di-lower alkylamino-lower alkoxy, lower alkanoylamino-lower alkoxy, lower alkanesulfonylamino-lower alkoxy, polyhalo-lower alkanesulfonylamino-lower alkoxy, pyrrolidino-lower alkoxy, piperidino-lower alkoxy, piperazino-lower alkoxy, N'-lower alkylpiperazino-lower alkoxy or N'-lower alkanoylpiperazino-lower alkoxy, morpholino-lower alkoxy, thiomorpholino-lower alkoxy, S-oxothiomorpholino-lower alkoxy or S,S-dioxothiomorpholino-lower alkoxy, cyano-lower alkoxy, carboxy-lower alkoxy, lower alkoxycarbonyl-lower alkoxy, carbamoyl-lower alkoxy, N-mono- or N,N-di-lower alkylcarbamoyl-lower alkoxy, carboxy-lower alkyl, lower alkoxycarbonyl-lower alkyl, carbamoyl-lower alkyl, or N-mono- or N,N-di-lower alkylcarbamoyl-lower alkyl; or

R^2 and R^3 taken together with the atoms through which they are attached form a fused dioxolane, dioxane, benzene, or cyclohexene ring, wherein said ring is substituted with up to 2 substituents independently selected from lower alkyl and lower alkoxy-lower alkyl;

R^4 is hydrogen, lower alkyl, hydroxy, lower alkoxy, cycloalkoxy, lower alkoxy-lower alkoxy, or cycloalkyl-lower alkoxy; or

R^3 and R^4 taken together with the atoms through which they are attached form a fused dioxolane, dioxane, benzene, or cyclohexene ring, wherein said ring is substituted with up to 2 substituents independently selected from lower alkyl and lower alkoxy-lower alkyl; provided that R^3 does not form a ring with R^2 ;

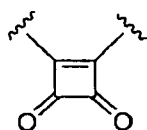
X is methylene or hydroxymethylene;

R^5 is lower alkyl, lower haloalkyl, cycloalkyl, halocycloalkyl, lower alkyl-cycloalkyl, lower haloalkyl-cycloalkyl, cycloalkyl-lower alkyl, aryl, aryl-lower alkyl, heterocyclyl, or heterocyclyl-lower alkyl;

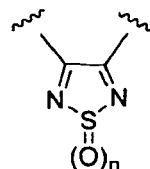
R^6 is amino, lower alkylamino, di-lower alkylamino, or lower alkanoylamino;

R^7 is hydrogen, lower alkyl, lower haloalkyl, cycloalkyl, lower alkoxy-lower alkyl, or lower haloalkoxy-lower alkyl;

Q is a group of formula Q1 or Q2, wherein $n = 0, 1$ or 2 ;



Q1



Q2

R^8 is lower alkyl, lower haloalkyl, (C_8-C_{15}) alkyl, (C_8-C_{15}) haloalkyl, cycloalkyl, halocycloalkyl, lower alkyl-cycloalkyl, cycloalkyl-lower alkyl, halocycloalkyl-lower alkyl,
 5 lower alkoxy-loweralkyl, lower haloalkoxy-lower alkyl, cycloalkoxy-lower alkyl, cycloalkoxy-cycloalkyl, lower alkylthio-lower alkyl, lower haloalkylthio-lower alkyl, lower alkanesulfonyl-lower alkyl, lower haloalkanesulfonyl-lower alkyl, lower alkylthio-cycloalkyl, lower haloalkylthio-cycloalkyl, lower alkanesulfonyl-cycloalkyl, lower haloalkanesulfonyl-cycloalkyl, aryl, aryl-lower alkyl, aryl-lower hydroxyalkyl, arylcycloalkyl, aryloxy-lower alkyl,
 10 aryloxy cycloalkyl, arylthio-lower alkyl, arylsulfonyl-lower alkyl, arylthio-cycloalkyl, arylsulfonyl-cycloalkyl, or NR^9R^{10} ;

R^9 and R^{10} are independently selected from 1) hydrogen, lower alkyl, lower haloalkyl, (C_8-C_{15}) alkyl, (C_8-C_{15}) haloalkyl, cycloalkyl, halocycloalkyl, lower alkyl-cycloalkyl, lower
 15 haloalkyl-cycloalkyl, cycloalkyl-lower alkyl, halocycloalkyl-lower alkyl, lower alkoxy-loweralkyl, lower haloalkoxy-lower alkyl, cycloalkoxy-lower alkyl, cycloalkoxy-cycloalkyl, lower alkylthio-lower alkyl, lower haloalkylthio-lower alkyl, lower alkanesulfonyl-lower alkyl, lower haloalkanesulfonyl-lower alkyl, lower alkylthio-cycloalkyl, lower haloalkylthio-cycloalkyl, lower alkanesulfonyl-cycloalkyl, lower haloalkanesulfonyl-cycloalkyl,
 20 aminocarbonyl-lower alkyl, lower alkylaminocarbonyl-lower alkyl, di-lower alkylaminocarbonyl-lower alkyl, or lower acylamino-lower alkyl, or 2) aryl, aryl-lower alkyl, aryl-lower hydroxyalkyl, arylcycloalkyl, arene fused-cycloalkyl, aryloxy-lower alkyl, aryloxy cycloalkyl, arylthio-lower alkyl, arylsulfonyl-lower alkyl, arylthio-cycloalkyl, or arylsulfonyl-cycloalkyl

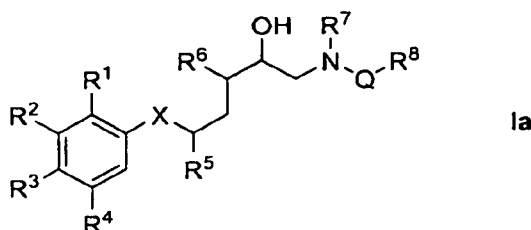
25 wherein the aryl groups are optionally substituted with up to four groups independently selected from halo, cyano, optionally halogenated lower alkyl, optionally halogenated lower alkoxy, optionally halogenated lower alkylthio, optionally halogenated lower alkanesulfonyl, morpholino, and lower alkoxycarbonyl;

30 or R^9 and R^{10} taken together with the nitrogen to which they are attached form a 4-, 5-, 6- or 7-membered heterocyclic ring composed of carbon atoms and 0 or 1 hetero atoms in addition to the nitrogen atom to which R^9 and R^{10} are attached, said hetero atoms being

selected from 0 or 1 nitrogen atoms, 0 or 1 oxygen atoms, and 0 or 1 sulfur atoms, said ring atoms being substituted with the appropriate number of hydrogen atoms, said ring being optionally substituted with up to four groups independently selected from halogen, (C₁-C₈)alkyl, halo(C₁-C₆)alkyl, aryl, aryl-lower alkyl and oxo, such that substitution of one oxo group on a carbon atom forms a carbonyl group and substitution of one or two oxo groups on sulfur forms a sulfoxide or a sulfone group respectively; wherein the aryl and arylalkyl groups are substituted with up to four groups independently selected from halo, cyano, optionally halogenated lower alkyl, optionally halogenated lower alkoxy, optionally halogenated lower alkylthio, optionally halogenated lower alkanesulfonyl, and lower alkoxy-carbonyl;

or an enantiomer, diastereomer, pharmaceutically acceptable salt thereof.

A preferred embodiment of the invention is a compound of the formula Ia



in which the substituents R¹-R¹⁰, X, and Q are as defined for Formula I above or an enantiomer, distereomer, or pharmaceutically acceptable salt thereof.

Another embodiment of the invention is a compound of formula Ia, wherein

R¹ is hydrogen or aryl;

R² is hydrogen, (C₁-C₈)alkyl, (C₄-C₈)cycloalkylalkyl, fluoro(C₁-C₈)alkyl, fluoro(C₄-C₈)cycloalkylalkyl, (C₁-C₈)alkoxy, (C₄-C₈)cycloalkylalkoxy, fluoro(C₁-C₈)alkoxy, hydroxy(C₁-C₈)alkyl, (C₁-C₅)alkoxy(C₁-C₅)alkyl, halo(C₁-C₅)alkylamino(C₁-C₅)alkyl, (C₁-C₅)alkoxy(C₁-C₅)hydroxyalkyl, (C₃-C₄)cycloalkoxy(C₁-C₅)alkyl, fluoro(C₁-C₅)alkoxy(C₁-C₅)alkyl, fluoro(C₃-C₄)cycloalkoxy(C₁-C₅)alkyl, (C₁-C₅)alkylthio(C₁-C₅)alkyl, (C₁-C₅)alkoxy(C₁-C₅)alkoxy, hydroxy(C₁-C₈)alkoxy, (C₃-C₄)cycloalkoxy(C₁-C₅)alkoxy, fluoro(C₁-C₅)alkoxy(C₁-C₅)alkoxy, fluoro(C₃-C₄)cycloalkoxy(C₁-C₅)alkoxy, (C₁-C₃)alkoxy(C₁-C₃)alkoxy(C₁-C₃)alkyl, fluoro(C₁-C₃)alkoxy(C₁-C₃)alkoxy(C₁-C₃)alkyl, aminocarbonylamino(C₁-C₈)alkyl, aminocarbonylamino(C₁-C₈)alkoxy, (C₁-C₅)alkanoylamino(C₁-C₅)alkyl, (C₁-C₅)alkanoylamino(C₁-C₅)alkoxy, fluoro(C₁-C₅)alkanoyl-amino(C₁-C₅)alkyl, fluoro(C₁-C₅)alkanoylamino(C₁-C₅)alkoxy, (C₁-C₃)alkoxy(C₁-C₅)alkanoyl-amino(C₁-C₅)alkyl, (C₁-C₃)alkoxy(C₁-C₅)alkanoylamino(C₁-C₅)alkoxy, (C₃-C₄)cycloalkane-carbonyllamino(C₁-C₅)alkyl, (C₃-C₄)cycloalkanecarbonyllamino(C₁-C₅)alkoxy, aminosulfonylamino(C₁-C₈)alkyl,

aminosulfonylamino(C₁-C₈)alkoxy, (C₁-C₅)alkanesulfonyl-amino(C₁-C₅)alkyl, (C₁-C₅)alkanesulfonylamino(C₁-C₅)alkoxy, formylamino(C₁-C₅)alkyl, formylamino(C₁-C₅)alkoxy, (C₁-C₅)alkoxycarbonylamino(C₁-C₅)alkyl, (C₁-C₅)alkoxycarbonyl-amino(C₁-C₅)alkoxy, (C₁-C₅)alkylaminocarbonylamino(C₁-C₅)alkyl, (C₁-C₅)alkylaminocarbonyl-amino(C₁-C₅)alkyl, di(C₁-C₅)alkylaminocarbonylamino(C₁-C₅)alkoxy, aminocarbonyl(C₁-C₅)alkyl, aminocarbonyl(C₁-C₅)alkoxy, (C₁-C₅)alkylaminocarbonyl(C₁-C₅)alkyl, (C₁-C₅)alkylaminocarbonyl-(C₁-C₅)alkoxy, aminocarboxy(C₁-C₅)alkyl, aminocarboxy(C₁-C₅)alkoxy, (C₁-C₅)alkylamino-carboxy(C₁-C₅)alkyl, (C₁-C₅)alkylaminocarboxy(C₁-C₅)alkoxy, (C₁-C₈)alkoxycarbonylamino, (C₁-C₈)alkylaminocarbonylamino, (C₁-C₈)alkanoylamino, fluoro(C₁-C₈)alkoxycarbonylamino, fluoro(C₁-C₈)alkylaminocarbonylamino, or fluoro(C₁-C₈)alkanoylamino;

R³ is hydrogen, halogen, cyano, lower alkyl, lower haloalkyl, aryl, hydroxy, lower alkoxy, or polyhalo-lower alkoxy; or

R² and R³ taken together with the atoms through which they are attached form a fused dioxolane ring, wherein said ring is substituted with up to 2 substituents independently selected from lower alkyl and lower alkoxy-lower alkyl;

R⁴ is hydrogen, lower alkoxy-lower alkoxy, lower alkoxy-lower alkyl, or cycloalkyl-lower alkoxy; or

R³ and R⁴ taken together with the atoms through which they are attached form a fused dioxolane ring, wherein said ring is substituted with up to 2 substituents independently selected from lower alkyl and lower alkoxy-lower alkyl; provided that R³ does not form a ring with R²;

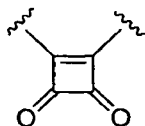
X is methylene or hydroxymethylene;

R⁵ is lower alkyl or cycloalkyl;

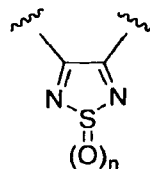
R⁶ is amino, lower alkylamino, di-lower alkylamino, or lower alkanoylamino;

R⁷ is hydrogen or methyl;

Q is a group of formula Q1, or formula Q2 wherein n = 2;



Q1



Q2

R⁸ is lower alkyl, lower haloalkyl, (C₈-C₁₅)alkyl, (C₈-C₁₅)haloalkyl, cycloalkyl, halocycloalkyl, lower alkyl-cycloalkyl, cycloalkyl-lower alkyl, halocycloalkyl-lower alkyl, lower alkoxy-lower alkyl, lower haloalkoxy-lower alkyl, cycloalkoxy-lower alkyl, cycloalkoxy-cycloalkyl, aryl, aryl-lower alkyl, aryloxy-lower alkyl, or is NR⁹R¹⁰;

R⁹ is selected from 1) hydrogen, lower alkyl, lower haloalkyl, (C₈-C₁₅)alkyl, (C₈-C₁₅)haloalkyl, cycloalkyl, halocycloalkyl, lower alkyl-cycloalkyl, lower haloalkyl-cycloalkyl, cycloalkyl-lower alkyl, halocycloalkyl-lower alkyl, lower alkoxy-loweralkyl, lower haloalkoxy-lower alkyl, cycloalkoxy-lower alkyl, cycloalkoxy-cycloalkyl, lower alkylthio-lower alkyl, lower haloalkylthio-lower alkyl, lower alkanesulfonyl-lower alkyl, lower haloalkanesulfonyl-lower alkyl, lower alkylthio-cycloalkyl, lower haloalkylthio-cycloalkyl, lower alkanesulfonyl-cycloalkyl, lower haloalkanesulfonyl-cycloalkyl, aminocarbonyl-lower alkyl, lower alkylaminocarbonyl-lower alkyl, di-lower alkylaminocarbonyl-lower alkyl, or lower acylamino-lower alkyl, or 2) aryl, aryl-lower alkyl, arene fused-cycloalkyl, heteroaryl-lower alkyl, arylcycloalkyl, aryloxy-lower alkyl, aryloxy cycloalkyl, arylthio-lower alkyl, arylsulfonyl-lower alkyl, arylthio-cycloalkyl, or arylsulfonyl-cycloalkyl

wherein the aryl groups are optionally substituted with up to four groups

independently selected from halo, cyano, nitro, optionally halogenated lower alkyl, optionally halogenated lower alkoxy, optionally halogenated lower alkylthio, optionally halogenated lower alkanesulfonyl, morpholino, and lower alkoxycarbonyl;

R¹⁰ is selected from 1) hydrogen, lower alkyl, lower haloalkyl, C₈-C₁₅alkyl, C₈-C₁₅haloalkyl, cycloalkyl, halocycloalkyl, lower alkyl-cycloalkyl, cycloalkyl-lower alkyl, halocycloalkyl-lower alkyl, lower alkoxy-loweralkyl, or lower haloalkoxy-lower alkyl, or 2) aryl, aryl-lower alkyl, or aryloxy-lower alkyl, wherein the aryl and aryloxy groups are optionally substituted with up to four groups independently selected from halo, cyano, optionally halogenated lower alkyl, optionally halogenated lower alkoxy, optionally halogenated lower alkylthio, optionally halogenated lower alkanesulfonyl, and lower alkoxycarbonyl;

or R⁹ and R¹⁰ taken together with the nitrogen to which they are attached form a 4-, 5-, 6- or 7-membered heterocyclic ring composed of carbon atoms and 0 or 1 hetero atom in addition

to the nitrogen atom to which R⁹ and R¹⁰ are attached, said hetero atom being selected from 0 or 1 nitrogen atoms, 0 or 1 oxygen atoms, and 0 or 1 sulfur atoms, said ring atoms being substituted with the appropriate number of hydrogen atoms, said ring being optionally substituted with up to four groups independently selected from halogen, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl, aryl, aryl-lower alkyl or oxo, such that substitution of one oxo group on a carbon atom forms a carbonyl group and substitution of one or two oxo groups on sulfur forms a sulfoxide or a sulfone group respectively; wherein the aryl and arylalkyl groups are substituted with up to four groups independently selected from halo, cyano, optionally halogenated lower alkyl, optionally halogenated lower alkoxy, optionally halogenated lower alkylthio, optionally halogenated lower alkanesulfonyl, and lower alkoxycarbonyl;

or an enantiomer, diastereomer, or pharmaceutically acceptable salt thereof.

Another embodiment of the invention is a compound of formula **Ia** wherein

R¹ is hydrogen;

R² is (C₃-C₄)cycloalkyl(C₁-C₄)alkyl, fluoro(C₃-C₄)cycloalkyl(C₁-C₄)alkyl, (C₁-C₈)alkoxy, (C₃-C₄)cycloalkyl(C₁-C₄)alkoxy, hydroxy(C₁-C₈)alkyl, (C₁-C₄)alkoxy(C₁-C₄)alkoxy, (C₁-C₄)alkoxy-(C₁-C₄)alkyl, (C₁-C₄)alkoxy(C₁-C₄)hydroxyalkyl, (C₃-C₄)cycloalkoxy(C₁-C₄)alkyl, hydroxy(C₁-C₈)alkoxy, (C₃-C₄)cycloalkoxy(C₁-C₄)alkoxy, (C₁-C₃)alkoxy(C₁-C₃)alkoxy(C₁-C₃)alkyl, aminocarbonylamino(C₁-C₄)alkyl, aminocarbonylamino(C₁-C₄)alkoxy, (C₁-C₄)alkanoylamino(C₁-C₄)alkyl, (C₁-C₄)alkanoylamino(C₁-C₄)alkoxy, (C₃-C₄)cycloalkanecarbonyllamino(C₁-C₄)alkyl, (C₃-C₄)cycloalkanecarbonyllamino(C₁-C₄)alkoxy, aminosulfonylamino(C₁-C₄)alkyl, aminosulfonylamino(C₁-C₄)alkoxy, (C₁-C₄)alkanesulfonylamino(C₁-C₄)alkyl, (C₁-C₄)alkanesulfonylamino(C₁-C₄)alkoxy, formylamino(C₁-C₄)alkyl, formylamino(C₁-C₄)alkoxy, (C₁-C₄)alkoxycarbonylamino(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonylamino(C₁-C₄)alkoxy, (C₁-C₄)alkylaminocarbonylamino(C₁-C₄)alkyl, aminocarbonyl(C₁-C₄)alkyl, aminocarbonyl(C₁-C₄)alkoxy, (C₁-C₄)alkylaminocarbonyl(C₁-C₄)alkyl, (C₁-C₄)alkylaminocarbonyl-(C₁-C₄)alkoxy, aminocarboxy(C₁-C₄)alkyl, aminocarboxy(C₁-C₄)alkoxy, (C₁-C₄)alkylamino-carboxy(C₁-C₄)alkyl, or (C₁-C₄)alkylaminocarboxy(C₁-C₄)alkoxy;

R³ is fluoro, chloro, bromo, cyano, (C₁-C₄)alkyl, (C₁-C₄) haloalkyl, aryl, (C₁-C₄)alkoxy, or (C₁-C₄)haloalkoxy;

R⁴ is hydrogen;

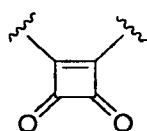
X is methylene;

R^5 is (C₃-C₅)alkyl;

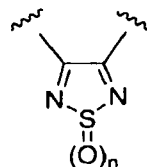
R^6 is amino;

5 R^7 is hydrogen or methyl;

Q is a group of formula Q1, or formula Q2 wherein n = 2;



Q1



Q2

10 R^8 is (C₁-C₁₂)alkyl, (C₁-C₁₂)haloalkyl, or NR⁹R¹⁰;

R^9 is 1) hydrogen, (C₁-C₁₂)alkyl, halo(C₁-C₁₂)alkyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl(C₅-C₉)alkyl, halo(C₃-C₇)cycloalkyl(C₅-C₉)alkyl, (C₅-C₉)alkyl(C₃-C₇)cycloalkyl, halo(C₅-C₉)alkyl(C₃-C₇)cycloalkyl, (C₁-C₆)alkoxy(C₁-C₆)alkyl, or halo(C₁-C₆)alkoxy(C₁-C₆)alkyl or 2) aryl(C₁-C₆)alkyl, aryl(C₃-C₇)cycloalkyl, arene fused-cycloalkyl, aminocarbonyl(C₁-C₆)alkyl, (C₁-C₆)acylamino(C₁-C₆)alkyl, or heteroaryl(C₁-C₆)alkyl each optionally substituted with up to four substituents independently selected from fluorine, chlorine, cyano, nitro, (C₁-C₃)alkyl, halo(C₁-C₃)alkyl, (C₁-C₃)alkoxy, halo(C₁-C₃)alkoxy, (C₁-C₃)alkanesulfonyl, and morpholino;

20 R^{10} is hydrogen, (C₁-C₆)alkyl, or halo(C₁-C₆)alkyl; or

R^9 and R^{10} taken together with the nitrogen to which they are attached form a 5- or 6-membered heterocyclic ring composed of carbon atoms and 0 or 1 hetero atom in addition to the nitrogen atom to which R^9 and R^{10} are attached, said hetero atom being selected from 0 or 1 nitrogen atoms, 0 or 1 oxygen atoms, said ring atoms being substituted with the appropriate number of hydrogen atoms, said ring being optionally substituted with up to four groups independently selected from halogen, (C₁-C₃)alkyl, halo(C₁-C₃)alkyl, aryl, aryl-lower alkyl, and oxo, such that substitution of one oxo group on a carbon atom forms a carbonyl group; wherein the aryl and arylalkyl groups are substituted with up to two groups independently selected from halo, cyano, optionally halogenated lower alkyl, optionally halogenated lower alkoxy, optionally halogenated lower alkylthio, optionally halogenated lower alkanesulfonyl, and lower alkoxy carbonyl;

or an enantiomer, diastereomer, or pharmaceutically acceptable salt thereof.

Another embodiment of the invention is compounds of formula **1a** wherein:

R^1 is hydrogen;

R^2 is 3-(cyclopropyl)propyl, 4-(cyclopropyl)butyl, 3-hydroxypropyl, 4-hydroxybutyl, 4-hydroxypentyl, 4-hydroxyhexyl, 3-ethoxypropyl, 4-methoxybutyl, 4-ethoxybutyl, 3-methoxypropoxy, 3-ethoxypropoxy, 3-propoxypropoxy, 2-cyclopropylethoxy, 3-cyclopropylpropoxy, 3-(acetylamino)propyl, 3-(propionylamino)propyl, 3-(butanoylamino)propyl, 2-(acetylamino)ethoxy, 2-(propionylamino)ethoxy, 2-(butanoylamino)ethoxyl, 3-(methoxycarbonylamino)propyl, 3-(ethoxycarbonylamino)propyl, 2-(methoxycarbonyl-amino)ethoxy, 2-(ethoxycarbonylamino)ethoxy, 2-(methylaminocarbonyl)ethyl, 2-(ethylaminocarbonyl)ethyl, (methylaminocarbonyl)methoxy, or (ethylaminocarbonyl)methoxy;

R^3 is fluoro, chloro, bromo, cyano, methyl, ethyl, isopropyl, tert-butyl, trifluoromethyl, pentafluoroethyl, phenyl, methoxy, difluoromethoxy, or trifluoromethoxy;

R^4 is hydrogen;

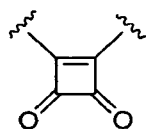
X is methylene;

R^5 is branched (C_3 - C_5)alkyl;

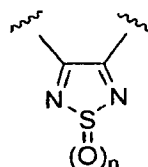
R^6 is amino;

R^7 is hydrogen;

Q is a group of formula Q1 or Q2 wherein $n = 2$



Q1



Q2

R^8 is hexyl or NR^9R^{10}

R^9 is H, methyl, ethyl, propyl, butyl, 2-methyl-1-propyl, 1-pentyl, 2,2,-dimethyl-1-propyl, 2-methyl-2-butyl, 3-methyl-2-butyl, 2-methylbutyl, 3-methylbutyl, 2-pentyl, 2-methyl-2-pentyl, 2,4,4-trimethylthyl-2-pentyl, 1-hexyl, 2-hexyl, 2-heptyl, 2-methyl-2-hexyl, 2-octyl, cyclopropylmethyl, cyclopropylethyl, cyclohexylmethyl, cyclohexylethyl, 2,2,2-trifluoroethyl, 2,2,3,3,4,4,4-heptafluorobutyl, 2-methoxyethyl, benzyl, 2-phenylethyl, 2-(2-

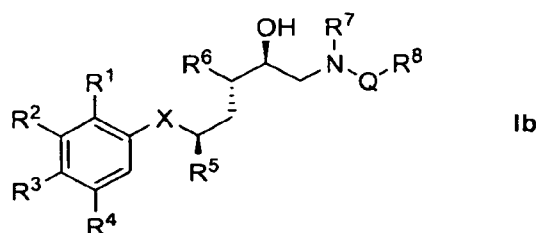
chlorophenyl)ethyl, 2-(3-chlorophenyl)ethyl, 2-(4-chlorophenyl)ethyl, 2-(2-methylphenyl)ethyl, 2-(2,4-dimethylphenyl)ethyl, 2-(2,3-dimethoxyphenyl)ethyl, 2-(2,5-dimethoxyphenyl)ethyl, 2-(4-nitrophenyl)ethyl, 3-phenylpropyl, 4-phenylbutyl, 2-phenylcyclopropyl, 2-indanyl, 2-(aminocarbonyl)-2-methylthyl-1-propyl, 3-(acetylamino)-2,2-dimethylthylpropyl, or 2-(4-morpholino)-2-(3-pyridyl)-ethyl;

R¹⁰ is H, methyl, ethyl, or propyl; or

R⁹ and R¹⁰ taken together are -(CH₂)₅-, -(CH₂)₂O(CH₂)₂-, -(CH₂)₂NMe(CH₂)₂-, -(CH₂)₄CHEt-, -(CH₂)CHPhCH₂CH₂-, -(CH₂)₂CHPh(CH₂)₂-, or -CH₂CHBn(CH₂)₃-;

or an enantiomer, diastereomer, or pharmaceutically acceptable salt thereof.

Especially effective are those compounds of formula **1a** wherein at least one, two, or preferably all three of the asymmetric carbon atoms of the main chain have the stereochemical configuration shown in formula **1b**



or a pharmaceutically acceptable salt thereof.

Preferred compounds of formulae **I**, **1a**, and **1b** are those wherein X is methylene and R⁵ is isopropyl.

Especially preferred are pharmaceutically acceptable salts of compounds of formulae **I**, **1a**, and **1b**.

Another embodiment of the invention is each of the following compounds or an enantiomer, diastereomer or a pharmaceutically acceptable salt thereof:

Cpd. No.	Name
I-1	3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-aminocyclobut-3-ene-1,2-dione
I-2	3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(methylamino)cyclobut-3-ene-1,2-dione
I-3	3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(ethylamino)cyclobut-3-ene-1,2-dione
I-4	3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(propylamino)cyclobut-3-ene-1,2-dione
I-5	3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-

- methylheptylamino)-4-(cyclopropylmethylamino)cyclobut-3-ene-1,2-dione
- I-6 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(butylamino)cyclobut-3-ene-1,2-dione
- I-7 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(isobutylamino)cyclobut-3-ene-1,2-dione
- I-8 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(2-methoxyethylamino)cyclobut-3-ene-1,2-dione
- I-9 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(piperidin-1-yl)cyclobut-3-ene-1,2-dione
- I-10 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(2-cyclopropylethylamino)cyclobut-3-ene-1,2-dione
- I-11 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-hexylcyclobut-3-ene-1,2-dione
- I-12 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-morpholinocyclobut-3-ene-1,2-dione
- I-13 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(neopentylamino)cyclobut-3-ene-1,2-dione
- I-14 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(pentan-2-ylamino)cyclobut-3-ene-1,2-dione
- I-15 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(tert-pentylamino)cyclobut-3-ene-1,2-dione
- I-16 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(3-methylbutan-2-ylamino)cyclobut-3-ene-1,2-dione
- I-17 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-((S)-2-methylbutylamino)cyclobut-3-ene-1,2-dione
- I-18 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(isopentylamino)cyclobut-3-ene-1,2-dione
- I-19 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(pentylamino)cyclobut-3-ene-1,2-dione
- I-20 3-(N-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptyl)-N-methylamino)-4-(butylamino)cyclobut-3-ene-1,2-dione
- I-21 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(N-butyl-N-methylamino)cyclobut-3-ene-1,2-dione
- I-22 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(2,2,2-trifluoroethylamino)cyclobut-3-ene-1,2-dione
- I-23 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(4-methylpiperazin-1-yl)cyclobut-3-ene-1,2-dione
- I-24 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(dipropylamino)cyclobut-3-ene-1,2-dione
- I-25 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(2-methylpentan-2-ylamino)cyclobut-3-ene-1,2-dione
- I-26 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(hexan-2-ylamino)cyclobut-3-ene-1,2-dione
- I-27 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(hexylamino)cyclobut-3-ene-1,2-dione
- I-28 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(N-methyl-N-pentylamino)cyclobut-3-ene-1,2-dione
- I-29 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(N-methyl-N-pentylamino)cyclobut-3-ene-1,2-dione
- I-30 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(2-methylpentan-2-ylamino)cyclobut-3-ene-1,2-dione
- I-31 3-((2R,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(2-methylpentan-2-ylamino)cyclobut-3-ene-1,2-dione
- I-32 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(benzylamino)cyclobut-3-ene-1,2-dione
- I-33 (2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-1-(4-(butylamino)-1,1-dioxo-1,2,5-thiadiazol-3-ylamino)-3-amino-6-methylheptan-2-ol
- I-34 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(cyclohexylmethylamino)cyclobut-3-ene-1,2-dione
- I-35 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(2-ethylpiperidin-1-yl)cyclobut-3-ene-1,2-dione
- I-36 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(heptylamino)cyclobut-3-ene-1,2-dione
- I-37 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(heptan-2-ylamino)cyclobut-3-ene-1,2-dione
- I-38 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(2-methylhexan-2-ylamino)cyclobut-3-ene-1,2-dione

I-39	3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(N-methyl-N-(2-methylpentan-2-yl)amino)cyclobut-3-ene-1,2-dione
I-40	3-(2-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-3,4-dioxocyclobut-1-enylamino)-2,2-dimethylpropanamide
I-41	3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(phenethylamino)cyclobut-3-ene-1,2-dione
I-42	(2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-1-(4-(pentylamino)-1,1-dioxo-1,2,5-thiadiazol-3-ylamino)-3-amino-6-methylheptan-2-ol
I-43	3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(2-cyclohexylethylamino)cyclobut-3-ene-1,2-dione
I-44	3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(octan-2-ylamino)cyclobut-3-ene-1,2-dione
I-45	3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(2,4,4-trimethylpentan-2-ylamino)cyclobut-3-ene-1,2-dione
I-46	3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(N-methyl-N-(2-methylhexan-2-yl)amino)cyclobut-3-ene-1,2-dione
I-47	3-((1S,2R)-2-phenylcyclopropylamino)-4-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)cyclobut-3-ene-1,2-dione
I-48	3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(2,3-dihydro-1H-inden-2-ylamino)cyclobut-3-ene-1,2-dione
I-49	3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(3-phenylpropylamino)cyclobut-3-ene-1,2-dione
I-50	3-(N-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptyl)-N-methylamino)-4-(phenethylamino)cyclobut-3-ene-1,2-dione
I-51	3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(N-methyl-N-phenethylamino)cyclobut-3-ene-1,2-dione
I-52	3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-((2-methyl)phenethylamino)cyclobut-3-ene-1,2-dione
I-53	N-(3-(2-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-3,4-dioxocyclobut-1-enylamino)-2,2-dimethylpropyl)acetamide
I-54	3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(3-phenylpyrrolidin-1-yl)cyclobut-3-ene-1,2-dione
I-55	3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(4-phenylbutylamino)cyclobut-3-ene-1,2-dione
I-56	3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(2,4-dimethylphenethylamino)cyclobut-3-ene-1,2-dione
I-57	3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(2-chlorophenethylamino)cyclobut-3-ene-1,2-dione
I-58	3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(3-chlorophenethylamino)cyclobut-3-ene-1,2-dione
I-59	3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(4-chlorophenethylamino)cyclobut-3-ene-1,2-dione
I-60	(2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-1-(4-(phenethylamino)-1,1-dioxo-1,2,5-thiadiazol-3-ylamino)-3-amino-6-methylheptan-2-ol
I-61	3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(4-phenylpiperidin-1-yl)cyclobut-3-ene-1,2-dione
I-62	3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(4-nitrophenethylamino)cyclobut-3-ene-1,2-dione
I-63	3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(3-benzylpiperidin-1-yl)cyclobut-3-ene-1,2-dione
I-64	3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(2,5-dimethoxyphenethylamino)cyclobut-3-ene-1,2-dione
I-65	3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(2,3-dimethoxyphenethylamino)cyclobut-3-ene-1,2-dione
I-66	3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(2,2,3,3,4,4,4-heptafluorobutylamino)cyclobut-3-ene-1,2-dione
I-67	3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(2-morpholino-2-(pyridin-3-yl)ethylamino)cyclobut-3-ene-1,2-dione

The following are preferred compounds of the invention:

Cpd. No.	Name
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- I-6 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(butylamino)cyclobut-3-ene-1,2-dione
- I-7 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(isobutylamino)cyclobut-3-ene-1,2-dione
- I-9 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(piperidin-1-yl)cyclobut-3-ene-1,2-dione
- I-10 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(2-cyclopropylethylamino)cyclobut-3-ene-1,2-dione
- I-14 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(pentan-2-ylamino)cyclobut-3-ene-1,2-dione
- I-17 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-((S)-2-methylbutylamino)cyclobut-3-ene-1,2-dione
- I-18 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(isopentylamino)cyclobut-3-ene-1,2-dione
- I-19 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(pentylamino)cyclobut-3-ene-1,2-dione
- I-21 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(N-butyl-N-methylamino)cyclobut-3-ene-1,2-dione
- I-25 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(2-methylpentan-2-ylamino)cyclobut-3-ene-1,2-dione
- I-26 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(hexan-2-ylamino)cyclobut-3-ene-1,2-dione
- I-27 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(hexylamino)cyclobut-3-ene-1,2-dione
- I-28 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(N-methyl-N-pentylamino)cyclobut-3-ene-1,2-dione
- I-29 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(N-methyl-N-pentylamino)cyclobut-3-ene-1,2-dione
- I-30 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(2-methylpentan-2-ylamino)cyclobut-3-ene-1,2-dione
- I-34 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(cyclohexylmethylamino)cyclobut-3-ene-1,2-dione
- I-37 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(heptan-2-ylamino)cyclobut-3-ene-1,2-dione
- I-38 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(2-methylhexan-2-ylamino)cyclobut-3-ene-1,2-dione
- I-39 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(N-methyl-N-(2-methylpentan-2-yl)amino)cyclobut-3-ene-1,2-dione
- I-41 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(phenethylamino)cyclobut-3-ene-1,2-dione
- I-43 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(2-cyclohexylethylamino)cyclobut-3-ene-1,2-dione
- I-45 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(2,4,4-trimethylpentan-2-ylamino)cyclobut-3-ene-1,2-dione
- I-46 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(N-methyl-N-(2-methylhexan-2-yl)amino)cyclobut-3-ene-1,2-dione
- I-51 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(N-methyl-N-phenethylamino)cyclobut-3-ene-1,2-dione
- I-52 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-((2-methyl)phenethylamino)cyclobut-3-ene-1,2-dione
- I-56 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(2,4-dimethylphenethylamino)cyclobut-3-ene-1,2-dione
- I-57 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(2-chlorophenethylamino)cyclobut-3-ene-1,2-dione
- I-58 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(3-chlorophenethylamino)cyclobut-3-ene-1,2-dione
- I-59 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(4-chlorophenethylamino)cyclobut-3-ene-1,2-dione
- I-62 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(4-nitrophenethylamino)cyclobut-3-ene-1,2-dione

The following terms are used herein.

Aryl and aryl in aryloxy, arylthio, arylsulfonyl, aryl-lower alkoxy, aryl-lower alkyl and the like are, for example, phenyl or naphthyl that is unsubstituted or mono-, di- or tri-substituted by optionally halogenated lower alkyl, optionally halogenated lower alkoxy, hydroxy, amino, lower alkylamino, di-lower alkylamino, halogen, cyano, carbamoyl, lower alkoxy, carbonyl, trifluoromethoxy, and/or by trifluoromethyl;

Cycloalkoxy and cycloalkyl in cycloalkoxy-lower alkoxy is, for example, 3- to 8-membered, preferably 3-, 5- or 6-membered, cycloalkoxy, such as cyclopropyloxy, cyclopentyloxy, cyclohexyloxy, also cyclobutyloxy, cycloheptyloxy, or cyclooctyloxy.

Cycloalkyl is, for example, 3- to 8-membered, preferably 3-, 5- or 6-membered, cycloalkyl, such as cyclopropyl, cyclopentyl, cyclohexyl, also cyclobutyl, cycloheptyl, or cyclooctyl.

Heterocyclyl is, for example, a 3- to 8-membered, preferably a 5- or 6-membered, saturated heterocycle, for example tetrahydrofuryl, tetrahydrothienyl, pyrrolidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, and piperidinyl.

Free or esterified or amidated carboxy-lower alkoxy is, for example, carboxy-lower alkoxy, lower alkoxy, carbonyl-lower alkoxy, carbamoyl-lower alkoxy, or N-mono- or N,N-di-lower alkylcarbamoyl-lower alkoxy.

Optionally lower alkanoylated, halogenated or sulfonylated hydroxy-lower alkoxy is, for example, lower alkanoyloxy-lower alkyl, hydroxy-lower alkoxy, halo-(hydroxy)-lower alkoxy, or lower alkanesulfonyl-(hydroxy)-lower alkoxy.

Optionally hydrogenated heteroaryl-lower alkoxy is, for example, optionally partially hydrogenated or N-oxidized pyridyl-lower alkoxy, thiazolyl-lower alkoxy, thiazolyl-lower alkoxy or especially morpholino-lower alkoxy.

Optionally hydrogenated heteroarylthio-lower alkoxy is, for example, optionally partially or fully hydrogenated heteroarylthio-lower alkoxy, such as thiazolylthio-lower alkoxy, thiazolylthio-lower alkoxy, imidazolylthio-lower alkoxy, imidazolylthio-lower alkoxy optionally N-oxidized pyridylthio-lower alkoxy, or pyrimidinylthio-lower alkoxy.

Free or esterified or amidated carboxy-lower alkyl is, for example, carboxy-lower alkyl, lower alkoxy, carbonyl-lower alkyl, carbamoyl-lower alkyl, or N-mono- or N,N-di-lower alkylcarbamoyl-lower alkyl.

Optionally halogenated lower alkyl is, for example, lower alkyl, monohalo-lower alkyl or polyhalo-lower alkyl.

Optionally halogenated lower alkoxy is, for example, lower alkoxy, monohalo-lower alkoxy or polyhalo-lower alkoxy.

Optionally S-oxidized lower alkylthio-lower alkyl is, for example, lower alkylthio-lower alkyl, lower alkanesulfinyl-lower alkyl, or lower alkanesulfonyl-lower alkyl.

Optionally S-oxidized lower alkylthio-lower alkoxy is, for example, lower alkylthio-lower alkoxy, lower alkanesulfinyl-lower alkoxy, or lower alkanesulfonyl-lower alkoxy.

Optionally hydrogenated heteroaryl-lower alkyl or optionally N-oxidized heteroaryl-lower alkyl is, for example, optionally partially hydrogenated, or N-oxidized pyridyl-lower alkyl.

Optionally hydrogenated heteroarylthio-lower alkyl or optionally N-oxidized heteroarylthio-lower alkyl is, for example, thiazolylthio-lower alkyl or thiazolylthio-lower alkyl, imidazolylthio-lower alkyl, optionally N-oxidized pyridylthio-lower alkyl, or pyrimidinylthio-lower alkyl.

Amino-lower alkyl that is unsubstituted or N-mono- or N,N-di-lower alkylated, N-lower alkanoylated or N-lower alkanesulfonylated or N,N-disubstituted by lower alkylene, by unsubstituted or N'-lower alkylated or N'-lower alkanoylated aza-lower alkylene, by oxa-lower alkylene or by optionally S-oxidized thia-lower alkylene is, for example, amino-lower alkyl, lower alkylamino-lower alkyl, di-lower alkylamino-lower alkyl, lower alkanoylamino-lower alkyl, lower alkanesulfonylamino-lower alkyl, polyhalo-lower alkanesulfonylamino-lower alkyl, pyrrolidino-lower alkyl, piperidino-lower alkyl, piperazino-, N'-lower alkylpiperazino- or N'-lower alkanoylpiperazino-lower alkyl, morpholino-lower alkyl, thiomorpholino-, S-oxothiomorpholino-, or S,S-dioxothiomorpholino-lower alkyl.

Amino-lower alkoxy that is unsubstituted or N-mono- or N,N-di-lower alkylated, N-lower alkanoylated or N-lower alkanesulfonylated or N,N-disubstituted by lower alkylene, by unsubstituted or N'-lower alkylated amino-lower alkylene or lower alkanoylated-amino-lower alkylene, by oxa-lower alkylene or by optionally S-oxidized thia-lower alkylene is, for example, amino-lower alkoxy, lower alkylamino-lower alkoxy, di-lower alkylamino-lower alkoxy, lower alkanoylamino-lower alkoxy, lower alkanesulfonylamino-lower alkoxy, polyhalo-lower alkanesulfonylamino-lower alkoxy, pyrrolidino-lower alkoxy, piperidino-lower alkoxy, piperazino-, N'-lower alkylpiperazino- or N'-lower alkanoylpiperazino-lower alkoxy, morpholino-lower alkoxy, thiomorpholino-, S-oxothiomorpholino-, or S,S-dioxothiomorpholino-lower alkoxy.

Unsubstituted or N-mono- or N,N-di-lower alkylated or N-lower alkanoylated amino is, for example, amino, lower alkylamino, di-lower alkylamino, or lower alkanoylamino.

Free or aliphatically esterified or etherified hydroxy-lower alkyl is, for example, hydroxy-lower alkyl, lower alkanoyloxy-lower alkyl, lower alkoxy-lower alkyl, or lower alkenyloxy-lower alkyl.

Amino-lower alkyl that is unsubstituted or N-lower alkanoylated, N-mono- or N,N-di-lower alkylated or N,N-disubstituted by lower alkylene, by hydroxy-, lower alkoxy- or lower alkanoyloxy-lower alkylene, by unsubstituted or lower alkanoylated-amino-lower alkylene, by oxa-lower alkylene or by optionally S-oxidized thia-lower alkylene is, for example, amino-

lower alkyl, lower alkanoylamino-lower alkyl, N-mono- or N,N-di-lower alkylamino-lower alkyl, optionally hydroxylated or lower alkoxyated piperidino-lower alkyl, such as piperidino-lower alkyl, hydroxypiperidino-lower alkyl or lower alkoxy-piperidino-lower alkyl, piperazino-, ω -lower alkylpiperazino- or N'-lower alkanoyl-piperazino-lower alkyl, unsubstituted or lower alkylated morpholino-lower alkyl, such as morpholino-lower alkyl or dimethylmorpholino-lower alkyl, or optionally S-oxidized thio-morpholino-lower alkyl, such as thiomorpholino-lower alkyl or S,S-dioxothiomorpholino-lower alkyl.

Free or esterified or amidated carboxy-(hydroxy)-lower alkyl is, for example, carboxy-(hydroxy)-lower alkyl, lower alkoxy-carbonyl-(hydroxy)-lower alkyl or carbamoyl-(hydroxy)-lower alkyl.

Free or esterified or amidated carboxycycloalkyl-lower alkyl is, for example, 5- or 6-membered carboxycycloalkyl-lower alkyl, lower alkoxy-carbonylcycloalkyl-lower alkyl, carbamoylcycloalkyl-lower alkyl, or N-mono- or N,N-di-lower alkylcarbamoylcyclo-alkyl-lower alkyl.

Unsubstituted or N-mono- or N,N-di-lower alkylated sulfamoyl-lower alkyl is, for example, sulfamoyl-lower alkyl, lower alkylsulfamoyl-lower alkyl, or di-lower alkyl-sulfamoyl-lower alkyl.

Lower radicals and compounds are, for example, those having up to and including 7, preferably up to and including 4, carbon atoms.

5- or 6-Membered carboxycycloalkyl-lower alkyl, lower alkoxy-carbonylcycloalkyl-lower alkyl, carbamoylcycloalkyl-lower alkyl, N-mono- or N,N-di-lower alkylcarbamoylcyclo-alkyl-lower alkyl is, for example, ω -(1-carboxycycloalkyl)-C₁-C₄ alkyl, ω -(1-lower alkoxy-carbonylcycloalkyl)-C₁-C₄ alkyl, ω -(1-carbamoylcycloalkyl)-C₁-C₄ alkyl, ω -(1-lower alkylcarbamoylcycloalkyl)-C₁-C₄ alkyl, or ω -(1-di-lower alkylcarbamoylcycloalkyl)-C₁-C₄ alkyl, wherein cycloalkyl is, for example, cyclopentyl or cyclohexyl; lower alkoxy-carbonyl is, for example, C₁-C₄ alkoxy-carbonyl, such as methoxy- or ethoxy-carbonyl; lower alkylcarbamoyl is, for example, C₁-C₄ alkylcarbamoyl, such as methylcarbamoyl; di-lower alkylcarbamoyl is, for example, di-C₁-C₄ alkylcarbamoyl, such as dimethylcarbamoyl; and lower alkyl is, for example, C₁-C₄ alkyl, such as methyl, ethyl, propyl, or butyl, especially (1-carboxycyclopentyl)methyl.

5- or 6-Membered cycloalkoxy-lower alkoxy is, for example, cyclopentyloxy-(C₁-C₄)alkoxy or cyclohexyloxy-(C₁-C₄)alkoxy, such as cyclopentyloxy-methoxy, cyclohexyloxy-methoxy, 2-cyclopentyloxy-ethoxy, 2-cyclohexyloxy-ethoxy, 2- or 3-cyclopentyloxy-propyloxy, 2- or 3-cyclohexyloxy-propyloxy, 4-cyclopentyloxy-butyloxy or 4-cyclohexyloxy-butyloxy, especially cyclopentyloxy-methoxy or cyclohexyloxy-methoxy.

5- or 6-Membered cycloalkoxy-lower alkyl is, for example, cyclopentyloxy-(C₁-C₄)alkyl or cyclohexyloxy-(C₁-C₄)alkyl, such as cyclopentyloxy-methyl, cyclohexyloxy-methyl, 2-cyclopentyloxy-ethyl, 2-cyclohexyloxy-ethyl, 2- or 3-cyclopentyloxy-propyl, 2- or 3-cyclohexyloxy-propyl, 2-cyclopentyloxy-2-methyl-propyl, 2-cyclohexyloxy-2-methyl-propyl, 2-cyclopentyloxy-2-ethyl-butyl, 2-cyclohexyloxy-2-ethyl-butyl, 4-cyclopentyloxy-butyl or 4-cyclohexyloxy-butyl, especially cyclopentyloxy-methyl or cyclohexyloxy-methyl.

Amino-lower alkoxy is, for example, amino-C₁-C₄ alkoxy, such as 2-aminoethoxy or 5-aminopentyloxy, also 3-aminopropoxy or 4-aminobutyloxy.

Amino-lower alkyl is, for example, amino-C₁-C₄alkyl, such as 2-aminoethyl, 3-aminopropyl or 4-aminobutyl.

Carbamoyl-(hydroxy)-lower alkyl is, for example, carbamoyl-C₁-C₇ (hydroxy)alkyl, such as 1-carbamoyl-2-hydroxyethyl.

Carbamoyl-lower alkoxy is, for example, carbamoyl-C₁-C₄ alkoxy, such as carbamoylmethoxy, 2-carbamoylethoxy, 3-carbamoylpropoxy, or 4-carbamoylbutyloxy, especially carbamoylmethoxy.

Carbamoyl-lower alkyl is, for example, carbamoyl-C₁-C₇ alkyl, such as carbamoylmethyl, 2-carbamoylethyl, 3-carbamoylpropyl, 2-(3-carbamoyl)propyl, 2-carbamoylpropyl, 3-(1-carbamoyl)propyl, 2-(2-carbamoyl)propyl, 2-(carbamoyl-2-methyl)propyl, 4-carbamoylbutyl, 1-carbamoylbutyl, 1-(1-carbamoyl-2-methyl)butyl, or 3-(4-carbamoyl-2-methyl)butyl.

Carboxy-(hydroxy)-lower alkyl is, for example, carboxy-C₁-C₇ (hydroxy)alkyl, such as 1-carboxy-2-hydroxy-ethyl.

Carboxy-lower alkoxy is, for example, carboxy-C₁-C₄ alkoxy, such as carboxymethoxy, 2-carboxyethoxy, 2- or 3-carboxypropoxy, or 4-carboxybutyloxy, especially carboxy-methoxy.

Carboxy-lower alkyl is, for example, carboxy-C₁-C₄ alkyl, such as carboxymethyl, 2-carboxyethyl, 2- or 3-carboxypropyl, 2-carboxy-2-methyl-propyl, 2-carboxy-2-ethyl-butyl, or 4-carboxybutyl, especially carboxymethyl.

Cyano-lower alkoxy is, for example, cyano-C₁-C₄ alkoxy, such as cyanomethoxy, 2-cyano-ethoxy, 2- or 3-cyanopropoxy, or 4-cyanobutyloxy, especially cyanomethoxy.

Cyano-lower alkyl is, for example, cyano-C₁-C₄ alkyl, such as cyanomethyl, 2-cyanoethyl, 2- or 3-cyanopropyl, 2-cyano-2-methyl-propyl, 2-cyano-2-ethyl-butyl, or 4-cyanobutyl, especially cyanomethyl.

Di-(N-mono- or N,N-di-lower alkylcarbamoyl)-lower alkyl is, for example, di-(N-mono- or N,N-di-C₁-C₄ alkylcarbamoyl)-C₁-C₄ alkyl, such as 1,2-di-(N-mono- or N,N-di-C₁-C₄ alkylcarbamoyl)ethyl, or 1,3-di-(N-mono- or N,N-di-C₁-C₄ alkylcarbamoyl)propyl.

Dicarbamoyl-lower alkyl is, for example, dicarbamoyl-C₁-C₄ alkyl, such as 1,2-dicarbamoylethyl or 1,3-dicarbamoylethyl.

Dimethylmorpholino-lower alkoxy can be N-oxidized and is, for example, 2,6-dimethylmorpholino- or 3,5-dimethylmorpholino-C₁-C₄ alkoxy, such as 2,6-dimethylmorpholino- or 3,5-dimethylmorpholino-methoxy, 2-(2,6-dimethylmorpholino- or 3,5-dimethylmorpholino)-ethoxy, 3-(2,6-dimethylmorpholino- or 3,5-dimethylmorpholino)-propyloxy, 2-(2,6-dimethylmorpholino- or 3,5-dimethylmorpholino-3-methyl)propyloxy, or 1- or 2-[4-(2,6-dimethylmorpholino- or 3,5-dimethylmorpholino)]-butyloxy.

Dimethylmorpholino-lower alkyl can be N-oxidized and is, for example, 2,6-dimethylmorpholino- or 3,5-dimethylmorpholino-C₁-C₄ alkyl, such as 2,6-dimethylmorpholino- or 3,5-dimethylmorpholino-methoxy, 2-(2,6-dimethylmorpholino- or 3,5-dimethylmorpholino)-ethoxy, 3-(2,6-dimethylmorpholino- or 3,5-dimethylmorpholino)-propyl, 2-(2,6-dimethylmorpholino- or 3,5-dimethylmorpholino-3-methyl)-propyl, or 1- or 2-[4-(2,6-dimethylmorpholino- or 3,5-dimethylmorpholino)]-butyl.

Di-lower alkylamino is, for example, di-C₁-C₄ alkylamino, such as dimethylamino, N-methyl-N-ethylamino, diethylamino, N-methyl-N-propylamino, or N-butyl-N-methylamino.

Di-lower alkylamino-lower alkoxy is, for example, N,N-di-C₁-C₄ alkylamino-C₁-C₄ alkoxy, such as 2-dimethylaminoethoxy, 3-dimethylaminopropyloxy, 4-dimethylaminobutyloxy, 2-diethylaminoethoxy, 2-(N-methyl-N-ethyl-amino)ethoxy, or 2-(N-butyl-N-methyl-amino)ethoxy.

Di-lower alkylamino-lower alkyl is, for example, N,N-di-C₁-C₄ alkylamino-C₁-C₄ alkyl, such as 2-dimethylaminoethyl, 3-dimethylaminopropyl, 4-dimethylaminobutyl, 2-diethylaminoethyl, 2-(N-methyl-N-ethyl-amino)ethyl, or 2-(N-butyl-N-methyl-amino)ethyl.

Di-lower alkylcarbamoyl-lower alkoxy is, for example, N,N-di-C₁-C₄ alkylcarbamoyl-C₁-C₄ alkoxy, such as methyl- or dimethyl-carbamoyl-C₁-C₄ alkoxy, such as N-methyl-, N-butyl- or N,N-dimethyl-carbamoylmethoxy, 2-(N-methylcarbamoyl)ethoxy, 2-(N-butylcarbamoyl)ethoxy, 2-(N,N-dimethylcarbamoyl)ethoxy, 3-(N-methylcarbamoyl)propyloxy, 3-(N-butylcarbamoyl)propyloxy, 3-(N,N-dimethylcarbamoyl)propyloxy or 4-(N-methylcarbamoyl)butyloxy, 4-(N-butylcarbamoyl)-butyloxy, or 4-(N,N-dimethylcarbamoyl)butyloxy, especially N-methyl-, N-butyl- or N,N-dimethyl-carbamoylmethoxy.

Di-lower alkylcarbamoyl-lower alkyl is, for example, N,N-di-C₁-C₄ alkylcarbamoyl-C₁-C₄ alkyl, such as 2-dimethylcarbamoylethyl, 3-dimethylcarbamoylethyl, 2-dimethylcarbamoylethyl, 2-(dimethylcarbamoyl-2-methyl)propyl, or 2-(1-dimethylcarbamoyl-3-methyl)butyl.

Di-lower alkylsulfamoyl-lower alkyl is, for example, N,N-di-C₁-C₄ alkylsulfamoyl-C₁-C₄ alkyl, N,N-dimethylsulfamoyl-C₁-C₄ alkyl, such as N,N-dimethylsulfamoylmethyl, 2-(N,N-

dimethylcarbamoyl)ethyl, 3-(N,N-dimethylcarbamoyl)propyl, or 4-(N,N-dimethylcarbamoyl)butyl, especially N,N-dimethylcarbamoylmethyl.

Unsubstituted or N-lower alkanoylated piperidyl-lower alkyl is, for example, 1-C₁-C₇-lower alkanoylpiperidin-4-yl-C₁-C₄ alkyl, such as 1-acetylpiperidinylmethyl or 2-(1-acetyl-
5 piperidinyl)ethyl.

Optionally partially hydrogenated pyridyl-lower alkoxy or N-oxidized pyridyl-lower alkoxy is, for example, optionally partially hydrogenated pyridyl-C₁-C₄ alkoxy or N-oxopyridyl-C₁-C₄ alkoxy, such as pyridyl-methoxy, dihydropyridyl-methoxy or N-oxopyridyl-methoxy, 2-(pyridyl)ethoxy, 2-(pyridyl)propyloxy, 3-(pyridyl)propyloxy, or 4-(pyridyl)butyloxy, especially
10 (3-pyridyl)methoxy or (4-pyridyl)methoxy.

Optionally partially hydrogenated pyridyl-lower alkyl or N-oxidized pyridyl-lower alkyl is, for example, optionally partially hydrogenated pyridyl-C₁-C₄ alkyl or N-oxopyridyl-C₁-C₄ alkyl, such as pyridyl-methyl, dihydropyridyl-methyl, N-oxopyridyl-methyl, 2-(pyridyl)ethyl, 2-(pyridyl)propyl, 3-(pyridyl)propyl, or 4-(pyridyl)butyl, especially (3-pyridyl)methyl or (4-
15 pyridyl)methyl.

Halo-(hydroxy)-lower alkoxy is, for example, halo-C₁-C₇ (hydroxy)alkoxy, especially halo-C₂-C₄ (hydroxy)alkoxy, such as 3-halo-, such as 3-chloro-2-hydroxy-propyloxy.

Hydroxy-lower alkoxy is, for example, hydroxy-C₂-C₇ alkoxy, especially hydroxy-C₂-C₄ alkoxy, such as 2-hydroxybutyloxy, 3-hydroxypropyloxy or 4-hydroxybutyloxy.

Hydroxy-lower alkyl is, for example, hydroxy-C₂-C₇ alkyl, especially hydroxy-C₂-C₄ alkyl, such as 2-hydroxyethyl, 3-hydroxypropyl or 4-hydroxybutyl.

Hydroxypiperidino-lower alkyl is, for example, 3- or 4-hydroxypiperidino-C₁-C₄ alkyl, such as 3-hydroxypiperidinomethyl, 4-hydroxypiperidinomethyl, 2-(3-hydroxypiperidino)ethyl, 2-(4-hydroxypiperidino)ethyl, 3-(3-hydroxypiperidino)propyl, 3-(4-hydroxypiperidino)propyl, 4-(3-hydroxypiperidino)butyl or 4-(4-hydroxypiperidino)butyl.

Imidazolyl-lower alkyl is, for example, imidazolyl-C₁-C₄ alkyl, such as imidazol-4-yl-methyl, 2-(imidazol-4-yl)ethyl, 3-(imidazol-4-yl)propyl, or 4-(imidazol-4-yl)butyl.

Imidazolyl-lower alkoxy is, for example, imidazolyl-C₁-C₄ alkoxy, such as imidazol-4-yl-methoxy, 2-(imidazol-4-yl)ethoxy, 3-(imidazol-4-yl)propyloxy, or 4-(imidazol-4-yl)butyloxy.

Morpholinocarbonyl-lower alkyl is, for example, morpholinocarbonyl-C₁-C₄ alkyl, such as 1-morpholinocarbonylethyl, 3-morpholinocarbonylpropyl, or 1-(morpholinocarbonyl-2-methyl)propyl.

Morpholino-lower alkyl can be N-oxidized and is, for example, N-oxomorpholino-C₁-C₄ alkyl, such as N-oxomorpholinomethyl, 2-(N-oxomorpholino)ethyl, 3-(N-oxomorpholino)propyl, or 4-(N-oxomorpholino)butyl.

Morpholino-lower alkoxy is, for example, morpholino-C₁-C₄ alkoxy, such as 1-morpholinoethoxy, 3-morpholinopropyloxy, or 1-(morpholino-2-methyl)propyloxy.

Morpholino-lower alkoxy can be N-oxidized and is, for example, N-oxomorpholino-C₁-C₄ alkoxy, such as N-oxomorpholinomethoxy, 2-(N-oxomorpholino)ethoxy, 3-(N-oxomorpholino)propyloxy, or 4-(N-oxomorpholino)butyloxy.

5 Lower alkanoyl is, for example, C₁-C₇ alkanoyl, especially C₂-C₆ alkanoyl, such as acetyl, propionyl, butyryl, isobutyryl or pivaloyl.

Lower alkanoylamino is, for example, N-C₁-C₇ alkanoylamino, such as acetylamino or pivaloylamino.

Lower alkanoylamino-lower alkyl is, for example, N-C₁-C₄ alkanoylamino-C₁-C₄ alkyl, such as 2-acetylaminoethyl.

10 Lower alkanoyl-lower alkoxy (oxo-lower alkoxy) carries the lower alkanoyl group in a position higher than the α -position and is, for example, C₁-C₇ alkanoyl-C₁-C₄ alkoxy, such as 4-acetoxy-butoxy.

15 Lower alkanoyloxy-lower alkyl carries the lower alkanoyloxy group in a position higher than the α -position and is, for example, C₁-C₇ alkanoyloxy-C₁-C₄ alkyl, such as 4-acetoxy-butyl.

Lower alkanesulfonyl-(hydroxy)-lower alkoxy is, for example, C₁-C₇ alkanesulfonyl-C₁-C₄ (hydroxy)alkoxy, such as 3-methanesulfonyl-2-hydroxy-propyloxy.

Lower alkanesulfonyl-lower alkoxy is, for example, C₁-C₇ alkanesulfonyl-C₁-C₄ alkoxy, such as methanesulfonylmethoxy or 3-methanesulfonyl-propyloxy.

20 Lower alkanesulfonylamino-lower alkoxy is, for example, C₁-C₇ alkanesulfonylamino-C₁-C₄ alkoxy, such as ethanesulfonylaminomethoxy, 2-ethanesulfonylaminoethoxy, 3-ethane-sulfonylaminopropyloxy, or 3-(1,1-dimethylethanesulfonylamino)propyloxy.

25 Lower alkanesulfonylamino-lower alkyl is, for example, C₁-C₇ alkanesulfonylamino-C₁-C₄ alkyl, such as ethanesulfonylaminomethyl, 2-ethanesulfonylaminoethyl, 3-ethanesulfonyl-aminopropyl, or 3-(1,1-dimethylethanesulfonylamino)propyl.

Lower alkanesulfonyl-lower alkyl is, for example, C₁-C₇ alkanesulfonyl-C₁-C₄ alkyl, such as ethanesulfonylmethyl, 2-ethanesulfonylethyl, 3-ethanesulfonylpropyl, or 3-(1,1-dimethyl-ethanesulfonyl)propyl.

Lower alkenyl is, for example, C₂-C₇ alkenyl, such as vinyl or allyl.

30 Lower alkenyloxy is, for example, C₂-C₇ alkenyloxy, such as allyloxy.

Lower alkenyloxy-lower alkoxy is, for example, C₃-C₇ alkenyloxy-C₁-C₄ alkoxy, such as allyloxymethoxy.

Lower alkenyloxy-lower alkyl is, for example, C₃-C₇ alkenyloxy-C₁-C₄ alkyl, such as allyloxymethyl.

35 Lower alkoxy is, for example, C₁-C₇ alkoxy, preferably C₁-C₅ alkoxy, such as methoxy, ethoxy, propyloxy, isopropyloxy, butyloxy, isobutyloxy, secondary butyloxy, tertiary butyloxy, pentyloxy, or a hexyloxy or heptyloxy group.

Lower alkoxy carbonyl is, for example, C₁-C₇ alkoxy carbonyl, preferably C₁-C₅ alkoxy carbonyl, such as methoxy carbonyl, ethoxy carbonyl, propyloxy carbonyl, isopropoxy carbonyl, butyloxy carbonyl, isobutyloxy carbonyl, secondary butyloxy carbonyl, tertiary butyloxy, pentyloxy carbonyl, or a hexyloxy carbonyl or heptyloxy carbonyl group.

Lower alkoxy carbonyl-(hydroxy)-lower alkyl is, for example, C₁-C₄ alkoxy carbonyl-C₁-C₇ (hydroxy)alkyl, such as 1-methoxy carbonyl- or 1-ethoxy carbonyl-2-hydroxy-ethyl.

Lower alkoxy carbonylamino-lower alkoxy is, for example, C₁-C₇ alkoxy carbonylamino-C₂-C₇ alkoxy, preferably C₂-C₅ alkoxy carbonylamino-C₂-C₇ alkoxy, such as methoxy carbonylamino-C₂-C₇ alkoxy, ethoxy carbonylamino-C₂-C₇ alkoxy, propyloxy carbonylamino-C₂-C₇ alkoxy, isobutyloxy carbonylamino-C₂-C₇ alkoxy, butyloxy carbonylamino-C₂-C₇ alkoxy, isobutyloxy carbonylamino-C₂-C₇ alkoxy, secondary butyloxy carbonylamino-C₂-C₇ alkoxy or tertiary butyloxy amino-C₂-C₇ alkoxy, wherein C₂-C₇ alkoxy is, for example, methoxy, ethoxy, propyloxy, butyloxy, pentyloxy, or hexyloxy.

Lower alkoxy carbonylamino-lower alkyl is, for example, C₁-C₇ alkoxy carbonylamino-C₂-C₇ alkyl, preferably C₂-C₅ alkoxy carbonylamino-C₂-C₇ alkyl, such as methoxy carbonyl-C₂-C₇ alkyl, ethoxy carbonylamino-C₂-C₇ -alkyl, propyloxy carbonylamino-C₂-C₇ alkyl, isopropoxy-carbonylamino-C₂-C₇ alkyl, butyloxy carbonylamino-C₂-C₇ alkyl, isobutyloxy carbonylamino-C₂-C₇ alkyl, secondary butyloxy carbonylamino-C₂-C₇ alkyl, or tertiary butyloxy amino-C₂-C₇ alkyl, wherein C₂-C₇ alkyl is, for example, ethyl, propyl, butyl, pentyl, or hexyl.

Lower alkoxy carbonyl-lower alkoxy is, for example, C₁-C₄ alkoxy carbonyl-C₁-C₄ alkoxy, such as methoxy carbonyl- or ethoxy carbonyl-methoxy, 2-methoxy carbonyl- or 2-ethoxy carbonyl-ethoxy, 2- or 3-methoxy carbonyl- or 2- or 3-ethoxy carbonyl-propyloxy or 4-methoxy carbonyl- or 4-ethoxy carbonyl-butyloxy, especially methoxy carbonyl- or ethoxy carbonyl-methoxy or 3-methoxy carbonyl- or 3-ethoxy carbonyl-propyloxy.

Lower alkoxy carbonyl-lower alkyl is, for example, C₁-C₄ alkoxy carbonyl-C₁-C₄ alkyl, such as methoxy carbonyl-methyl, ethoxy carbonyl-methyl, 2-methoxy carbonyl-ethyl, 2-ethoxy carbonyl-ethyl, 3-methoxy carbonyl-propyl, 3-ethoxy carbonyl-propyl or 4-ethoxy carbonyl-butyl.

Lower alkoxy-lower alkenyl is, for example, C₁-C₄ alkoxy-C₂-C₄ alkenyl, such as 4-methoxybut-2-enyl.

Lower alkoxy-lower alkoxy is, for example, C₁-C₄ alkoxy-C₂-C₄ alkoxy, such as 2-methoxy-, 2-ethoxy- or 2-propyloxy-ethoxy, 3-methoxy- or 3-ethoxy-propyloxy, or 4-methoxybutyloxy, especially 3-methoxypropyloxy or 4-methoxybutyloxy.

Lower alkoxy-lower alkoxy-lower alkyl is, for example, C₁-C₄ alkoxy-C₁-C₄ alkoxy-C₁-C₄ alkyl, such as 2-methoxy-, 2-ethoxy- or 2-propyloxy-ethoxymethyl, 2-(2-methoxy-, 2-ethoxy- or 2-propyloxy-ethoxy)ethyl, 3-(3-methoxy- or 3-ethoxy-propyloxy)propyl, or 4-(2-

methoxybutyloxy)-butyl, especially 2-(3-methoxypropyloxy)ethyl or 2-(4-methoxybutyloxy)ethyl.

Lower alkoxy-lower alkyl is, for example, C₁-C₄ alkoxy-C₁-C₄ alkyl, such as ethoxymethyl, propyloxymethyl, butyloxymethyl, 2-methoxy-, 2-ethoxy- or 2-propyloxy-ethyl,
5 3-methoxy- or 3-ethoxy-propyl or 4-methoxybutyl, especially 3-methoxypropyl, or 4-methoxybutyl.

Piperidino-lower alkyl is, for example, piperidino- C₁-C₄ alkyl or hydroxypiperidino-C₁-C₄ alkyl, such as piperidinomethyl or 4-hydroxypiperidinomethyl.

Lower alkoxy-piperidino-lower alkyl is, for example, C₁-C₄ alkoxy-piperidino-C₁-C₄ alkyl, such as 4-(C₁-C₄ alkoxy)-piperidinomethyl, especially 4-methoxypiperidinomethyl.
10

Lower alkyl may be straight-chained or branched and/or bridged and is, for example, corresponding C₁-C₇ alkyl, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, secondary butyl or tertiary butyl, or a pentyl, hexyl or heptyl group. Lower alkyl R² or R³ is especially C₂-C₇ alkyl; lower alkyl R⁵ or R⁷ is especially branched C₃-C₇ alkyl; and lower alkyl R⁸ or R³ is,
15 for example, straight-chained, branched or bridged C₃-C₇ alkyl.

Lower alkylamino is, for example, C₁-C₄ alkylamino, such as methylamino, ethylamino, propylamino, butylamino, isobutylamino, secondary butylamino, or tertiary butylamino.

Lower alkylamino-lower alkoxy is, for example, C₁-C₄ alkylamino-C₁-C₄ alkoxy, such as propylaminomethoxy, 2-methylamino-, 2-ethylamino-, 2-propylamino- or 2-butylamino-ethoxy, 3-ethylamino- or 3-propylamino-propyloxy or 4-methylaminobutoxy.
20

Lower alkylamino-lower alkyl is, for example, C₁-C₄ alkylamino-C₁-C₄ alkyl, such as propylaminomethyl, 2-methylamino-, 2-ethylamino-, 2-propylamino- or 2-butylamino-ethyl, 3-ethylamino- or 3-propylamino-propyl or 4-methylaminobutyl.

Lower alkylcarbamoyl-lower alkoxy is, for example, N- C₁-C₇ alkylcarbamoyl-C₁-C₄ alkoxy, such as methyl- or dimethyl-carbamoyl-C₁-C₄ alkoxy, e.g., methylcarbamoylmethoxy, 2-methylcarbamoylethoxy, or 3-methylcarbamoylpropyloxy.
25

Lower alkylenedioxy is, for example, methylenedioxy or ethylenedioxy, but can also be 1,3- or 1,2-propylenedioxy.

Lower alkylsulfamoyl-lower alkyl is, for example, N-C₁-C₇ alkylsulfamoyl-C₁-C₄ alkyl, such as N-methyl-, N-ethyl-, N-propyl- or N-butyl-sulfamoyl-C₁-C₄ alkyl, such as N-methyl-, N-ethyl-, N-propyl- or N-butyl-sulfamoylmethyl, 2-(N-methylsulfamoyl)ethyl, 2-(N-butylsulfamoyl)ethyl, 3-(N-methylsulfamoyl)propyl, 3-(N-butylsulfamoyl)propyl, or 4-(N-methylsulfamoyl)butyl, 4-(N-butylsulfamoyl)butyl or 4-(N,N-dimethylsulfamoyl)butyl,
35 especially N-methyl-, N-butyl-, or N,N-dimethyl-sulfamoylmethyl.

Lower alkylthio-(hydroxy)-lower alkoxy is, for example, C₁-C₄ alkylthio-C₁-C₄ (hydroxy)alkoxy, such as 2-hydroxy-3-methylthiopropyloxy.

Lower alkylthio-lower alkyl is, for example, C₁-C₄ alkylthio-C₁-C₄ alkyl, such as methylthio-C₁-C₄ alkyl, e.g. methylthiomethyl, 2-methylthioethyl, or 3-methylthiopropyl.

N'-Lower alkanoylpiperazino-lower alkyl is, for example, N'-C₂-C₇-lower alkanoyl-piperazino-C₁-C₄ alkyl, such as 4-acetylpiperazinomethyl.

Oxo-lower alkoxy is, for example, oxo-C₁-C₄ alkoxy, such as 3,3-dimethyl-2-oxo-butyloxy.

Piperidino-lower alkoxy is, for example, piperidino-C₁-C₄ alkoxy, such as piperidinomethoxy, 2-piperidinoethoxy, or 3-piperidinopropoxy.

Polyhalo-lower alkanesulfonylamino-lower alkoxy is, for example, trifluoro-C₁-C₇ alkanesulfonyl-C₁-C₄ alkoxy, such as trifluoromethanesulfonylaminobutyloxy.

Pyrimidinylthio-lower alkoxy is, for example, pyrimidinylthio-C₁-C₄ alkoxy, such as pyrimidinylthiomethoxy, 2-(pyrimidinylthio)ethoxy, or 3-(pyrimidinylthio)propyloxy.

Pyrrolidino-lower alkyl is, for example, pyrrolidino-C₁-C₄ alkyl, such as pyrrolidinomethyl, 2-pyrrolidinoethyl, or 3-pyrrolidinopropyl.

S-Oxothiomorpholino-lower alkyl is, for example, S-oxothiomorpholino-C₁-C₄ alkyl, such as S-oxothiomorpholinomethyl or 2-(S-oxo)thiomorpholinoethyl.

Thiazolinyllower alkoxy is, for example, thiazolinyll-C₁-C₄ alkoxy, such as thiazolinyllmethoxy, 2-(thiazolinyll)ethoxy or 3-(thiazolinyll)propyloxy.

Thiazolinyllower alkyl is, for example, thiazolinyllower alkyl, such as thiazolinylmethyl, 2-(thiazolinyl)ethyl, or 3-(thiazolinyl)propyl.

Thiazolyllower alkoxy is, for example, thiazolyllower alkoxy, such as thiazolylmethoxy, 2-(thiazolyl)ethoxy, or 3-(thiazolyl)propyloxy.

5 Thiazolyllower alkyl is, for example, thiazolyllower alkyl, such as thiazolylmethyl, 2-(thiazolyl)ethyl, or 3-(thiazolyl)propyl.

Thiomorpholino-lower alkyl or S,S-dioxothiomorpholino-lower alkyl is, for example, thiomorpholino-C₁-C₄ alkyl, such as -methyl or -ethyl, or S,S-dioxothiomorpholino-C₁-C₄ alkyl, such as -methyl or -ethyl.

10

Certain of the disclosed compounds may exist in various tautomeric forms. The invention encompasses all such forms, including those forms not depicted structurally.

Certain of the disclosed compound may exist in various stereoisomeric forms. Stereoisomers are compounds which differ only in their spatial arrangement. Enantiomers are pairs of stereoisomers whose mirror images are not superimposable, most commonly because they contain an asymmetrically substituted carbon atom that acts as a chiral center. "Enantiomer" means one of a pair of molecules that are mirror images of each other and are not superimposable. Diastereomers are stereoisomers that are not related as mirror images, most commonly because they contain two or more asymmetrically substituted carbon atoms. "R" and "S" represent the configuration of substituents around one or more chiral carbon atoms. Thus, "R" and "S" denote the relative configurations of substituents around one or more chiral carbon atoms. When a chiral center is not defined as R or S and the configuration at the chiral center is not defined by other means, either configuration can be present or a mixture of both configurations is present.

15

20 "Racemate" or "racemic mixture" means a compound of equimolar quantities of two enantiomers, wherein such mixtures exhibit no optical activity; i.e., they do not rotate the plane of polarized light.

25

When the stereochemistry of a disclosed compound is named or depicted by structure, the named or depicted stereoisomer is at least 60%, 70%, 80%, 90%, 99% or 99.9% by weight pure relative to the other stereoisomers. When a single enantiomer is named or depicted by structure, the depicted or named enantiomer is at least 60%, 70%, 80%, 90%, 99% or 99.9% by weight optically pure. Percent optical purity by weight is the ratio of the weight of the enantiomer over the weight of the enantiomer plus the weight of its optical isomer.

30

When a disclosed compound is named or depicted by structure without indicating the stereochemistry, and the inhibitor has at least one chiral center, it is to be understood that the name or structure encompasses one enantiomer of inhibitor free from the corresponding optical isomer, a racemic mixture of the inhibitor and mixtures enriched in one enantiomer relative to its corresponding optical isomer.

When a disclosed compound is named or depicted by structure without indicating the stereochemistry and has at least two chiral centers, it is to be understood that the name or structure encompasses a diastereomer free of other diastereomers, a pair of diastereomers free from other diastereomeric pairs, mixtures of diastereomers, mixtures of diastereomeric pairs, mixtures of diastereomers in which one diastereomer is enriched relative to the other diastereomer(s) and mixtures of diastereomeric pairs in which one diastereomeric pair is enriched relative to the other diastereomeric pair(s). Salts of compounds having salt-forming groups are especially acid addition salts, salts with bases or, where several salt-forming groups are present, can also be mixed salts or internal salts.

Salts are especially the pharmaceutically acceptable or non-toxic salts of compounds of formula I.

Such salts are formed, for example, by compounds of formula I having an acid group, for example a carboxy group or a sulfo group, and are, for example, salts thereof with suitable bases, such as non-toxic metal salts derived from metals of groups Ia, Ib, IIa and IIb of the Periodic Table of the Elements, for example alkali metal salts, especially lithium, sodium or potassium salts, or alkaline earth metal salts, for example magnesium or calcium salts, also zinc salts or ammonium salts, as well as salts formed with organic amines, such as unsubstituted or hydroxy-substituted mono-, di- or tri-alkylamines, especially mono-, di- or tri-lower alkylamines, or with quaternary ammonium bases, for example with methyl-, ethyl-, diethyl- or triethyl-amine, mono-, his- or tris-(2-hydroxy-lower alkyl)-amines, such as ethanol-, diethanol- or triethanol-amine, tris-(hydroxymethyl)-methylamine or 2-hydroxy-tert-butylamines, N,N-di-lower alkyl-N-(hydroxy-lower alkyl)-amines, such as N,N-dimethyl-N-(2-hydroxyethyl)-amine, or N-methyl-D-glucamine, or quaternary ammonium hydroxides, such as tetrabutylammonium hydroxide. The compounds of formula I having a basic group, for example an amino group, can form acid addition salts, for example with suitable inorganic acids, for example hydrohalic acids, such as hydrochloric acid or hydrobromic acid, or sulfuric acid with replacement of one or both protons, phosphoric acid with replacement of one or more protons, e.g., orthophosphoric acid or metaphosphoric acid, or pyrophosphoric acid with replacement of one or more protons, or with organic carboxylic, sulfonic, sulfo or phosphonic acids or N-substituted sulfamic acids, for example, acetic acid, propionic acid, glycolic acid, succinic acid, maleic acid, hydroxymaleic acid, methylmaleic acid, fumaric acid,

malic acid, tartaric acid, gluconic acid, glucaric acid, glucuronic acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, salicylic acid, 4-aminosalicylic acid, 2-phenoxybenzoic acid, 2-acetoxybenzoic acid, embonic acid, nicotinic acid or isonicotinic acid, as well as with amino acids, such as the α -amino acids mentioned hereinbefore, and with methanesulfonic acid, ethanesulfonic acid, 2-hydroxyethanesulfonic acid, ethane-1,2-disulfonic acid, benzenesulfonic acid, 4-toluenesulfonic acid, naphthalene-2-sulfonic acid, 2- or 3-phosphoglycerate, glucose-6-phosphate, or N-cyclohexylsulfamic acid (forming cyclamates) or with other acidic organic compounds, such as ascorbic acid. Compounds of formula I having acid and basic groups can also form internal salts.

For isolation and purification purposes it is also possible to use pharmaceutically unacceptable salts.

Another embodiment of the invention is a pharmaceutical composition comprising an effective amount of compounds of formula I, Ia, or Ib and a pharmaceutically acceptable carrier therefor.

The compounds of the invention may be used, for example, in the preparation of pharmaceutical compositions that comprise an effective amount of the active ingredient together or in admixture with a significant amount of inorganic or organic, solid or liquid, pharmaceutically acceptable carriers.

The pharmaceutical compositions of the invention are compositions for enteral, such as nasal, rectal or oral, or parenteral, such as intramuscular or intravenous, administration to warm-blooded animals (mammals, especially human beings) that comprise an effective dose of the pharmacologically active ingredient alone or together with a pharmaceutically acceptable carrier. The dose of the active ingredient depends on the species of warm-blooded animal, body weight, age and individual condition, individual pharmacokinetic data, the disease to be treated, and the mode of administration.

The pharmaceutical compositions comprise from approximately 1% to approximately 95%, preferably from approximately 20% to approximately 90%, active ingredient.

Pharmaceutical compositions according to the invention may be, for example, in unit dose form, such as in the form of ampoules, vials, suppositories, dragees, tablets, or capsules.

The pharmaceutical compositions of the invention are prepared in a manner known *per se*, for example by means of conventional dissolving, lyophilising, mixing, granulating, or confectioning processes.

Solutions of the active ingredient, and also suspensions, and especially isotonic aqueous solutions or suspensions, are preferably used, it being possible, for example in the case of lyophilised compositions that comprise the active ingredient alone or together with a carrier, for such solutions or suspensions to be made up prior to use. The pharmaceutical

compositions may be sterilised and/or may comprise excipients, for example preservatives, stabilisers, wetting agents and/or emulsifiers, solubilisers, salts for regulating the osmotic pressure and/or buffers, and are prepared in a manner known *per se*, for example by means of conventional dissolving or lyophilising processes. The said solutions or suspensions may
5 comprise conventional viscosity-increasing substances, such as sodium carboxymethylcellulose, carboxymethylcellulose, dextran, polyvinylpyrrolidone, and gelatin.

Suspensions in oil comprise as the oil component the vegetable, synthetic or semi-synthetic oils customary for injection purposes, for example, liquid fatty acid esters that contain as the acid component a long-chained fatty acid having from 8 to 22, especially from
10 12 to 22, carbon atoms. Examples include lauric acid, tridecylic acid, myristic acid, pentadecylic acid, palmitic acid, margaric acid, stearic acid, arachidic acid, behenic acid or corresponding unsaturated acids, for example oleic acid, elaidic acid, erucic acid, brassidic acid or linoleic acid, if desired with the addition of antioxidants, for example vitamin E, β -carotene, or 3,5-di-tert-butyl-4-hydroxytoluene. The alcohol component of those fatty acid
15 esters has a maximum of 6 carbon atoms and is a mono- or poly-hydric, for example a mono-, di- or tri-hydric, alcohol, for example methanol, ethanol, propanol, butanol or pentanol, or the isomers thereof, but especially glycol and glycerol. Examples of fatty acid esters include ethyl oleate, isopropyl myristate, isopropyl palmitate, polyoxyethylene glycerol trioleate, triglyceride of saturated fatty acids with a chain length of C₈-C₁₂, but especially
20 vegetable oils, such as cottonseed oil, almond oil, olive oil, castor oil, sesame oil, soybean oil, and groundnut oil.

The injectable compositions are prepared in the customary manner under sterile conditions. The same applies to introducing the compositions into ampoules or vials and sealing the containers.

25 Pharmaceutical compositions for oral administration can be obtained by combining the active ingredient with solid carriers, if desired granulating a resulting mixture, and processing the mixture, if desired or necessary, after the addition of appropriate excipients, into tablets, dragee cores or capsules. They can also be incorporated into plastics carriers that allow the active ingredients to diffuse or be released in measured amounts.

30 Suitable carriers are especially fillers, such as sugars, for example lactose, saccharose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tri-calcium phosphate or calcium hydrogen phosphate, and also binders, such as starch pastes using, for example, corn, wheat, rice or potato starch, gelatin, tragacanth, methylcellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose and/or
35 polyvinylpyrrolidone, and/or, if desired, disintegrators, such as the above-mentioned starches, also carboxy-methyl starch, crosslinked polyvinylpyrrolidone, agar, alginic acid or a salt thereof, such as sodium alginate. Excipients are especially flow conditioners and

lubricants, for example silicic acid, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol. Dragee cores are provided with suitable, optionally enteric, coatings, there being used, *inter alia*, concentrated sugar solutions which may comprise gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, or coating solutions in suitable organic solvents, or, for the preparation of enteric coatings, solutions of suitable cellulose preparations, such as ethylcellulose phthalate or hydroxypropylmethylcellulose phthalate. Capsules are dry-filled capsules made of gelatin and also soft, sealed capsules made of gelatin and a plasticiser, such as glycerol or sorbitol. The dry-filled capsules may comprise the active ingredient in the form of granules, for example with fillers, such as lactose, binders, such as starches, and/or glidants, such as talc or magnesium stearate, and if desired with stabilisers. In soft capsules the active ingredient is preferably dissolved or suspended in suitable oily excipients, such as fatty oils, paraffin oil or liquid polyethylene glycols, it likewise being possible for stabilisers and/or antibacterial agents to be added. Dyes or pigments may be added to the tablets or dragee coatings or to the capsule casings, for example for identification purposes or to indicate different doses of active ingredient.

The compositions of the invention are renin inhibitors. Said compositions contain compounds having a mean inhibition constant (IC_{50}) against renin of between about 50,000 nM to about 0.001 nM; preferably between about 50 nM to about 0.001 nM; and more preferably between about 5 nM to about 0.001 nM.

The compositions of the invention reduce blood pressure. Said compositions include compounds having an IC_{50} for renin of between about 50,000 nM to about 0.001 nM; preferably between about 50 nM to about 0.001 nM; and more preferably between about 10 nM to about 0.001 nM.

The invention includes a therapeutic method for treating or ameliorating a renin mediated disorder in a subject in need thereof comprising administering to a subject in need thereof an effective amount of a compound of formula I, or the enantiomers, diastereomers, or salts thereof or composition thereof. Renin mediated disorders include hypertension, heart failure such as (acute and chronic) congestive heart failure; left ventricular dysfunction; cardiac hypertrophy; cardiac fibrosis; cardiomyopathy (e.g., diabetic cardiac myopathy and post-infarction cardiac myopathy); supraventricular and ventricular arrhythmias; arial fibrillation; atrial flutter; detrimental vascular remodeling; myocardial infarction and its sequelae; atherosclerosis; angina (whether unstable or stable); renal failure conditions, such as diabetic nephropathy; glomerulonephritis; renal fibrosis; scleroderma; glomerular sclerosis; microvascular complications, for example, diabetic retinopathy; renal vascular hypertension; vasculopathy; neuropathy; complications resulting from diabetes, such as

nephropathy, vasculopathy and neuropathy; diseases of the coronary vessels; proteinuria; albumenuria; post-surgical hypertension; metabolic syndrome; obesity, restenosis following angioplasty, ocular vascular complications, for example, raised intra-ocular pressure, glaucoma, and retinopathy; abnormal vascular growth, angiogenesis-related disorders, such as neovascular age related macular degeneration; hyperaldosteronism; anxiety states; and cognitive disorders (Fisher N.D.; Hollenberg N. K. *Expert Opin. Investig. Drugs*. **2001**, *10*, 417-26).

Administration methods include administering an effective amount (i.e., a therapeutically effective amount) of a compound or composition of the invention at different times during the course of therapy or concurrently in a combination form. The methods of the invention include all known therapeutic treatment regimens.

"Prodrug" means a pharmaceutically acceptable form of an effective derivative of a compound (or a salt thereof) of the invention, wherein the prodrug may be: 1) a relatively active precursor which converts *in vivo* to a compound of the invention; 2) a relatively inactive precursor which converts *in vivo* to a compound of the invention; or 3) a relatively less active component of the compound that contributes to therapeutic activity after becoming available *in vivo* (i.e., as a metabolite). See "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

"Metabolite" means a pharmaceutically acceptable form of a metabolic derivative of a compound (or a salt thereof) of the invention, wherein the derivative is an active compound that contributes to therapeutic activity after becoming available *in vivo*.

"Effective amount" means that amount of active compound agent that elicits the desired biological response in a subject. Such response includes alleviation of the symptoms of the disease or disorder being treated. The effective amount of a compound of the invention in such a therapeutic method to be administered to warm-blooded animals, for example human beings, of, for example, approximately 70 kg body weight, especially the doses effective in the inhibition of the enzyme renin, in lowering blood pressure and/or in improving the symptoms of glaucoma, are from approximately 3 mg to approximately 3 g, preferably from approximately 10 mg to approximately 1 g, for example approximately from 20 mg to 200 mg, per person per day, divided preferably into 1 to 4 single doses which may, for example, be of the same size. Usually, children receive about half of the adult dose. The dose necessary for each individual can be monitored, for example by measuring the serum concentration of the active ingredient, and adjusted to an optimum level.

The invention includes the use of a compound of the invention for the preparation of a composition for treating or ameliorating a renin mediated chronic disorder or disease or

infection in a subject in need thereof, wherein the composition comprises a mixture one or more compounds of the invention and an optional pharmaceutically acceptable carrier.

"Pharmaceutically acceptable carrier" means compounds and compositions that are of sufficient purity and quality for use in the formulation of a composition of the invention and that, when appropriately administered to an animal or human, do not produce an adverse reaction.

"Renin mediated disorder or disease" includes disorders or diseases associated with the elevated expression or overexpression of renin and conditions that accompany such diseases.

An embodiment of the invention includes administering a renin inhibiting compound of formula I or composition thereof in a combination therapy (see USP 5,821,232, USP 6,716,875, USP 5,663,188, Fossa, A. A.; DePasquale, M. J.; Ringer, L. J.; Winslow, R. L. "Synergistic effect on reduction in blood pressure with coadministration of a renin inhibitor or an angiotensin-converting enzyme inhibitor with an angiotensin II receptor antagonist" *Drug Development Research* **1994**, 33(4), 422-8) with one or more additional agents for the treatment of hypertension including α -blockers, β -blockers, calcium channel blockers, diuretics, natriuretics, saluretics, centrally acting antihypertensives, angiotensin converting enzyme (ACE) inhibitors, dual ACE and neutral endopeptidase (NEP) inhibitors, angiotensin-receptor blockers (ARBs), aldosterone synthase inhibitor, aldosterone-receptor antagonists, or endothelin receptor antagonist.

α -Blockers include doxazosin, prazosin, tamsulosin, and terazosin.

β -Blockers for combination therapy are selected from atenolol, bisoprol, metoprolol, acetutolol, esmolol, celiprolol, taliprolol, acebutolol, oxprenolol, pindolol, propranolol, bupranolol, penbutolol, mepindolol, carteolol, nadolol, carvedilol, and their pharmaceutically acceptable salts.

Calcium channel blockers include dihydropyridines (DHPs) and non-DHPs. The preferred DHPs are selected from the group consisting of amlodipine, felodipine, ryosidine, isradipine, lacidipine, nicardipine, nifedipine, nigulpidine, niludipine, nimodipine, nisoldipine, nitrendipine, and nivaldipine and their pharmaceutically acceptable salts. Non-DHPs are selected from flunarizine, prenylamine, diltiazem, fendiline, gallopamil, mibefradil, anipamil, tiapamil, and verapamil and their pharmaceutically acceptable salts.

A diuretic is, for example, a thiazide derivative selected from amiloride, chlorothiazide, hydrochlorothiazide, methylchlorothiazide, and chlorothalidon.

Centrally acting antihypertensives include clonidine, guanabenz, guanfacine and methyl dopa.

ACE inhibitors include alacepril, benazepril, benazaprilat, captopril, ceronapril, cilazapril, delapril, enalapril, enalaprilat, fosinopril, lisinopril, moexipril, moveltopril, perindopril, quinapril, quinaprilat, ramipril, ramiprilat, spirapril, temocapril, trandolapril, and zofenopril. Preferred ACE inhibitors are benazepril, enalapril, lisinopril, and ramipril.

5 Dual ACE/NEP inhibitors are, for example, omapatrilat, fasidotril, and fasidotrilat.

Preferred ARBs include candesartan, eprosartan, irbesartan, losartan, olmesartan, tasosartan, telmisartan, and valsartan.

Preferred aldosterone synthase inhibitors are anastrozole, fadrozole, and exemestane.

10 Preferred aldosterone-receptor antagonists are spironolactone and eplerenone.

A preferred endothelin antagonist is, for example, bosentan, enrasentan, atrasentan, darusentan, sitaxentan, and tezosentan and their pharmaceutically acceptable salts.

15 An embodiment of the invention includes administering an aspartic protease inhibitor disclosed herein or composition thereof in a combination therapy with one or more additional agents for the treatment of AIDS including reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, other HIV protease inhibitors, HIV integrase inhibitors, entry inhibitors (including attachment, co-receptor and fusion inhibitors), antisense drugs, and immune stimulators.

20 Specific reverse transcriptase inhibitors are zidovudine, didanosine, zalcitabine, stavudine, lamivudine, abacavir, tenofovir, and emtricitabine.

Specific non-nucleoside reverse transcriptase inhibitors are nevirapine, delaviridine, and efavirenz.

Specific HIV protease inhibitors are saquinavir, ritonavir, indinavir, nelfinavir, amprenavir, lopinavir, atazanavir, and fosamprenavir.

25 Specific HIV integrase inhibitors are L-870,810 and S-1360.

Entry inhibitors include compounds that bind to the CD4 receptor, the CCR5 receptor or the CXCR4 receptor. Specific examples of entry inhibitors include enfuvirtide (a peptidomimetic of the HR2 domain in gp41) and sifurvitide.

A specific attachment and fusion inhibitor is enfuvirtide.

30 An embodiment of the invention includes administering a compound disclosed herein or composition thereof in a combination therapy with one or more additional agents for the treatment of Alzheimer's disease including tacrine, donepezil, rivastigmine, galantamine, and memantine.

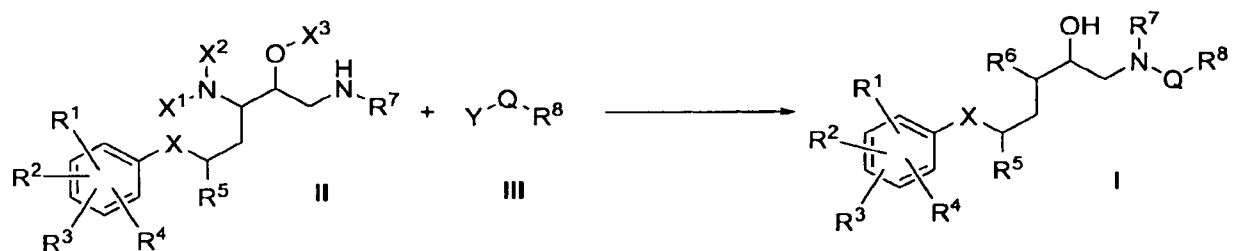
An embodiment of the invention includes administering a compound disclosed herein or composition thereof in a combination therapy with one or more additional agents for the treatment of malaria including artemisinin, chloroquine, halofantrine, hydroxychloroquine, mefloquine, primaquine, pyrimethamine, quinine, and sulfadoxine.

Combination therapy includes co-administration of the compound of the invention and said other agent, sequential administration of the compound and the other agent, administration of a composition containing the compound and the other agent, or simultaneous administration of separate compositions containing of the compound and the other agent.

The compounds of the invention have enzyme-inhibiting properties. In particular, they inhibit the action of the natural enzyme renin. The latter passes from the kidneys into the blood where it effects the cleavage of angiotensinogen, releasing the decapeptide angiotensin I which is then cleaved in the blood, lungs, the kidneys and other organs by angiotensin converting enzyme to form the octapeptide angiotensin II. The octapeptide increases blood pressure both directly by binding to its receptor, causing arterial vasoconstriction, and indirectly by liberating from the adrenal glands the sodium-ion-retaining hormone aldosterone, accompanied by an increase in extracellular fluid volume. That increase can be attributed to the action of angiotensin II. Inhibitors of the enzymatic activity of renin bring about a reduction in the formation of angiotensin I. As a result a smaller amount of angiotensin II is produced. The reduced concentration of that active peptide hormone is the direct cause of the hypotensive effect of renin inhibitors.

The first process of the invention for the preparation of compounds of formula I comprises

1) reacting a compound of formula II with a compound of formula III



wherein

X¹ is lower alkyl, lower alkanoyl, or an amino-protecting group;

X² is H or together with X³ is a bivalent protecting group;

X³ is H or a hydroxy-protecting group; and

R¹, R², R³, R⁴, X, R⁵, and R⁷ in II are as defined for formula I,

R⁸ in III has one of the meanings given for formula I, Q is a group of formula Q1 or Q2

wherein n = 1 or 2, and Y is lower alkoxy, lower alkylthio, aryloxy or chloro, and

2) removing any protecting groups present,

or, and if desired, converting the compound of formula I produced having at least one salt-forming group obtainable into its salt,

or converting an obtainable salt into the free compound or into a different salt

and/or separating mixtures of isomers that may be obtainable.

Functional groups in starting materials which are prone to participate in undesired side reactions, especially amino, carboxy, hydroxy, and mercapto groups, can be protected by suitable conventional protecting groups which are customarily used in the synthesis of peptide compounds, and also in the synthesis of cephalosporins and penicillins as well as nucleic acid derivatives and sugars. Those protecting groups may already be present in the precursors and are intended to protect the functional groups in question against undesired secondary reactions, such as acylation, etherification, esterification, oxidation, solvolysis, etc. In certain cases the protecting groups can additionally cause the reactions to proceed selectively, for example stereoselectively. It is characteristic of protecting groups that they can be removed easily, i.e. without undesired secondary reactions taking place, for example by acid treatment, fluoride treatment, solvolysis, reduction, photolysis, and also enzymatically, for example under physiological conditions. Protecting groups may also be present in the end products. Compounds of formula I having protected functional groups may have greater metabolic stability or pharmacodynamic properties that are better in some other way than the corresponding compounds having free functional groups.

The protection of functional groups by such protecting groups, the protecting groups themselves, and the reactions for their removal are described, for example, in standard works such as T.W. Greene and P. G. M. Wuts "Protective Groups in Organic Synthesis" John Wiley & Sons, Inc., New York 1999.

In compounds of formula II, amino-protecting groups X₁ are, for example, acyl groups other than lower alkanoyl, also arylmethyl, lower alkylthio, 2-acyl-lower alk-1-enyl or silyl. The group X₁-N(X₂)- can also be in the form of an azido group.

Acyl groups other than lower alkanoyl are, for example, halo-lower alkanoyl, for example 2-haloacetyl, such as 2-chloro-, 2-bromo-, 2-iodo-, 2,2,2-trifluoro- or 2,2,2-trichloro-acetyl, unsubstituted or substituted, for example halo-, lower alkoxy- or nitro-substituted, benzoyl, for example benzoyl, 4-chlorobenzoyl, 4-methoxybenzoyl or 4-nitrobenzoyl, or lower alkoxycarbonyl that is branched in the 1-position of the lower alkyl radical or suitably

substituted in the 1- or 2-position, for example tertiary lower alkoxy-carbonyl, such as tert-butoxycarbonyl, arylmethoxy-carbonyl having one or two aryl radicals which are phenyl that is unsubstituted or mono- or poly-substituted, for example, by lower alkyl, for example tertiary lower alkyl, such as tertiary butyl, lower alkoxy, such as methoxy, hydroxy, halogen, such as chlorine, and/or by nitro, for example benzyloxycarbonyl, unsubstituted or substituted benzyloxycarbonyl, such as 4-nitrobenzyl-oxycarbonyl, diphenylmethoxycarbonyl, fluorenylmethoxycarbonyl or substituted diphenylmethoxycarbonyl, such as di(4-methoxyphenyl)methoxycarbonyl, aroylmethoxycarbonyl wherein the aroyl group is preferably benzoyl that is unsubstituted or substituted, for example, by halogen, such as bromine, for example phenacyloxycarbonyl, 2-halo-lower alkoxy-carbonyl, for example 2,2,2-trichloroethoxycarbonyl, 2-bromoethoxycarbonyl or 2-iodo-ethoxycarbonyl, 2-(tri-substituted silyl)-lower alkoxy-carbonyl, for example 2-tri-lower alkylsilyl-lower alkoxy-carbonyl, for example 2-trimethylsilylethoxycarbonyl or 2-(di-n-butyl-methyl-silyl)-ethoxycarbonyl, or triarylsilyl-lower alkoxy-carbonyl, for example 2-triphenylsilylethoxycarbonyl.

In a 2-acyl-lower alk-1-enyl radical that can be used as an amino-protecting group, acyl is, for example, the corresponding radical of a lower alkanecarboxylic acid, of a benzoic acid that is unsubstituted or substituted, for example, by lower alkyl, such as methyl or tertiary butyl, lower alkoxy, such as methoxy, halogen, such as chlorine, and/or by nitro, or especially of a carbonic acid semiester, such as a carbonic acid lower alkyl semiester. Corresponding protecting groups are especially 1-lower alkanoyl-prop-1-en-2-yl, for example 1-acetyl-prop-1-en-2-yl, or lower alkoxy-carbonyl-prop-1-en-2-yl, for example 1-ethoxy-carbonyl-prop-1-en-2-yl.

Silylamino groups are, for example, tri-lower alkylsilylamino groups, for example trimethylsilylamino, triisopropylamino and t-butyl dimethylsilylamino.

An amino group can also be protected by conversion into the protonated form; suitable corresponding anions are especially those of strong inorganic acids, such as sulfuric acid, phosphoric acid or hydrohalic acids, for example the chlorine or bromine anion, or of organic sulfonic acids, such as p-toluenesulfonic acid.

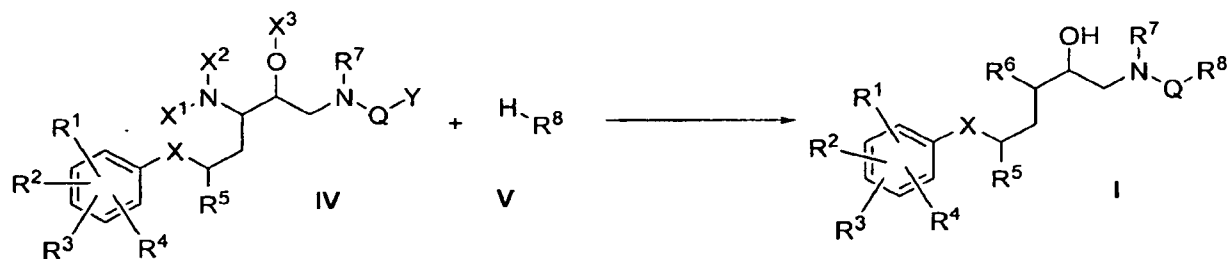
Preferred amino-protecting groups X_1 are acyl radicals of carbonic acid semiesters, such as lower alkoxy-carbonyl, especially tert-butyloxycarbonyl or fluorenylmethoxycarbonyl, unsubstituted or lower alkyl-, lower alkoxy-, nitro- and/or halo-substituted α -phenyl- or α, α -diphenyl-lower alkoxy-carbonyl, such as benzyloxycarbonyl, p-nitrobenzyloxy-carbonyl or diphenylmethoxycarbonyl, or 2-halo-lower alkoxy-carbonyl, e.g., 2,2,2-trichloroethoxycarbonyl, or 2-(trialkylsilyl)ethoxycarbonyl e.g. 2-(trimethylsilyl)ethoxycarbonyl, also trityl or formyl.

Hydroxy-protecting groups X_3 are, for example, acyl groups, for example lower alkanoyl that is substituted by halogen, such as chlorine, for example 2,2-dichloroacetyl, or especially acyl radicals of a carbonic acid semiester mentioned for protected amino groups. A preferred hydroxy-protecting group is, for example, 2,2,2-trichloroethoxycarbonyl, 4-nitrobenzyloxy-carbonyl, diphenylmethoxycarbonyl or trityl. A further suitable hydroxy-protecting group X_3 is tri-lower alkylsilyl, for example trimethylsilyl, triisopropylsilyl or dimethyl-tert-butylsilyl, a readily removable etherifying group, for example an alkyl group, such as tertiary lower alkyl, for example tertiary butyl, an oxa- or a thia-aliphatic or -cycloaliphatic, especially 2-oxa- or 2-thia-aliphatic or -cycloaliphatic, hydrocarbon radical, for example 1-lower alkoxy-lower alkyl or 1-lower alkylthio-lower alkyl, for example methoxymethyl, 1-methoxyethyl, 1-ethoxyethyl, methylthiomethyl, 1-methylthioethyl or 1-ethylthioethyl, or 2-oxa- or 2-thia-cycloalkyl having from 5 to 7 ring atoms, for example 2-tetrahydrofuryl or 2-tetrahydropyranyl, or a corresponding thia analogue, and also 1-phenyl-lower alkyl, for example benzyl, diphenylmethyl or trityl, wherein the phenyl radicals can be substituted, for example, by halogen, for example chlorine, lower alkoxy, for example methoxy, and/or by nitro.

Bivalent protecting groups formed by X_2 and X_3 together are, for example, methylene groups substituted by one or two alkyl radicals and are accordingly unsubstituted or substituted alkylidene, such as lower alkylidene, for example isopropylidene, cycloalkylidene, such as cyclohexylidene, also carbonyl or benzylidene; or dialkylsilyl groups, such as dimethylsilyl.

The second process of the invention for the preparation of compounds of formula I wherein R^8 is NR^9R^{10} comprises

1) reacting a compound of formula IV with an amine of formula V wherein R^8 is NR^9R^{10} :



wherein

X^1 is lower alkyl, lower alkanoyl, or an amino-protecting group;

X^2 is H or together with X^3 is a bivalent protecting group;

X^3 is H or a hydroxy-protecting group;

R^1 , R^2 , R^3 , R^4 , X , R^5 , and R^7 are as defined for formula I;

Q is a group of formula Q1 or Q2 as defined for formula I, wherein $n = 1$ or 2 ; and

5

Y is lower alkoxy, lower alkylthio, aryloxy or chloro,

R^8 in V is NR^9R^{10} and R^9 and R^{10} have one of the meanings given for formula I, and

2) removing any protecting groups present,

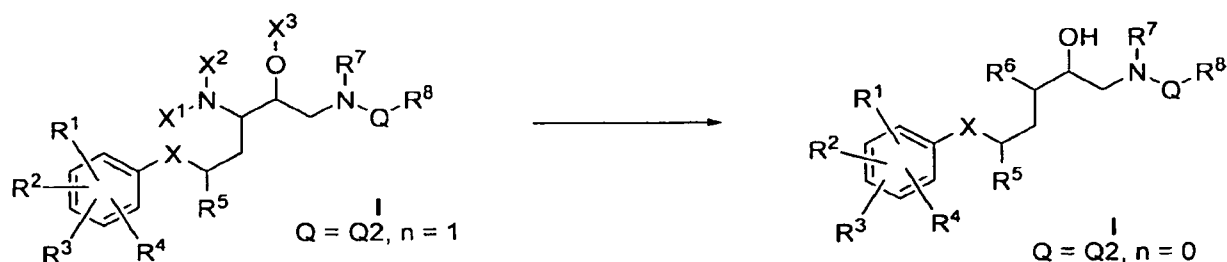
10 or, and if desired, converting the compound of formula I produced having at least one salt-forming group obtainable into its salt,

or converting an obtainable salt into the free compound or into a different salt

and/or separating mixtures of isomers that may be obtainable.

The third process of the invention for the preparation of compounds of formula I

15 wherein $Q = Q2$ and $n = 0$ comprises



1) deoxygenating a compound of formula I wherein $Q = Q2$, $n = 1$ (Arterburn, J. B.; Perry, M. C. *Tetrahedron Lett.* **1996**, 37, 7941-7944) or treating a compound of formula I wherein $Q =$

$Q2$, $n = 1$ with aqueous acid followed by N,N'-thiobisphthalimide (USP 4,440,933) and

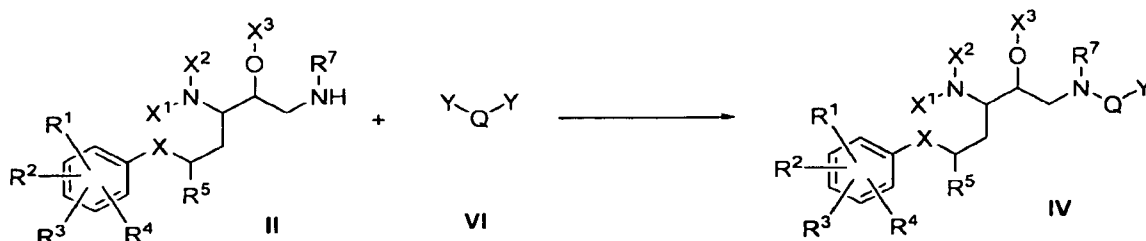
20 2) removing any protecting groups present,

or, and if desired, converting the compound of formula I produced having at least one salt-forming group obtainable into its salt,

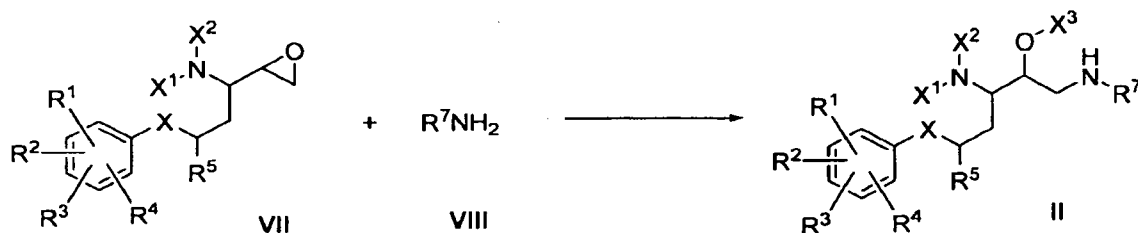
or converting an obtainable salt into the free compound or into a different salt

and/or separating mixtures of isomers that may be obtainable

25 Intermediate compounds of formula IV are prepared by reacting an amine compound of formula II with a heterocyclic compounds of formula VI bearing two leaving groups:

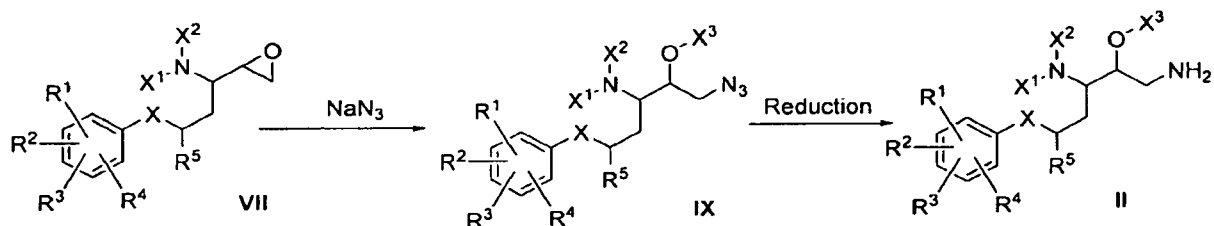


Amine compounds of formula II can be prepared, for example, by reacting an epoxide compound of formula VII with an amine of formula VIII:

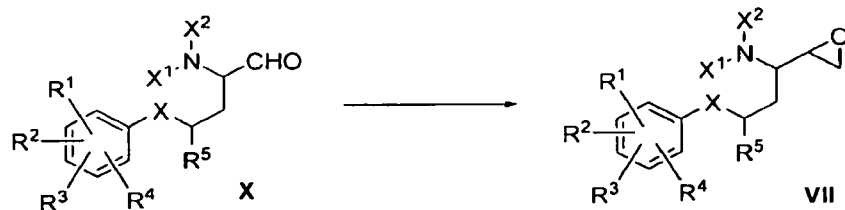


where R₇ is defined as in formula I; followed by appropriate protecting group manipulation.

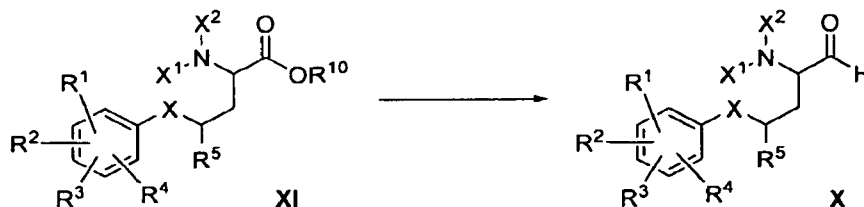
- 5 Amine compounds of formula II wherein R⁷ = H can also be prepared by reduction of azide compounds of formula IX using hydrogen gas in the presence of a transition metal catalyst, for example Raney nickel or platinum or palladium catalysts, for example platinum or palladium on active carbon, or with triphenylphosphine in the a mixed aqueous-organic solvent (Staudinger reduction). Azide compounds IX can be prepared by reacting by
- 10 reacting an epoxide compound of formula VII with nucleophilic azide source such as sodium azide in an organic solvent such as DMF or acetonitrile:



- 15 Epoxide compounds of formula VII can, in turn, be prepared in a number of ways including, for example, by reacting with aldehyde compounds of formula X with trimethylsulfoxonium iodide or trimethylsulfonium iodide (J. Aube "Epoxidation and Related Processes" Chapter 3.2 in Volume 1 of "Comprehensive Organic Synthesis" Edited by B. M. Trost, I. Fleming and Stuart L. Schreiber, Pergamon Press New York, 1992).

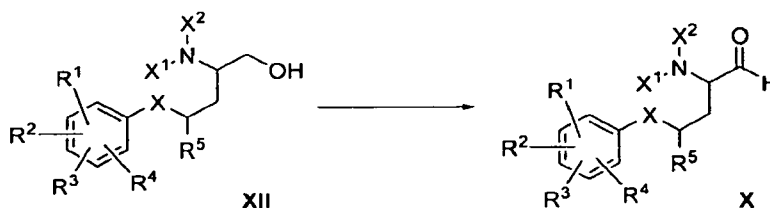


- 20 Aldehyde compounds of formula X can be prepared from compounds of formula XI, wherein R¹⁰ is lower alkyl or aryl-lower alkyl, in a number of ways. For example, compounds of formula XI can be converted to compounds of formula X:



by direct reduction from ester to aldehyde using specialized reagents and conditions known to minimize over-reduction (I. T. Harrison and S. Harrison "Compendium of Organic Synthetic Methods" Section 53, pp 152-153, John Wiley and Sons, New York 1971). One method of carrying out this transformation is by treatment with diisobutyl aluminum hydride in an organic solvent at lowered temperatures. The synthesis of compounds of Formula IX is described in USP 5,559,111 at columns 25-26.

Alternately, compounds of formula X can be prepared from alcohol compounds of formula XII:



using one of several oxidation protocols which are designed to minimize overoxidation (I. T. Harrison and S. Harrison "Compendium of Organic Synthetic Methods" Section 48, pp 137-143, John Wiley and Sons, New York 1971). Such oxidation protocols include oxalyl chloride/ dimethyl sulfoxide (Swern oxidation), (1,1,1-triacetoxy)-1,1-dihydro-1,2-dihydro-1,2-benziodoxol-3(1H)-one (Dess-Martin periodinane), sulfur trioxide/pyridine or tetrapropylammonium perruthenate (TPAP).

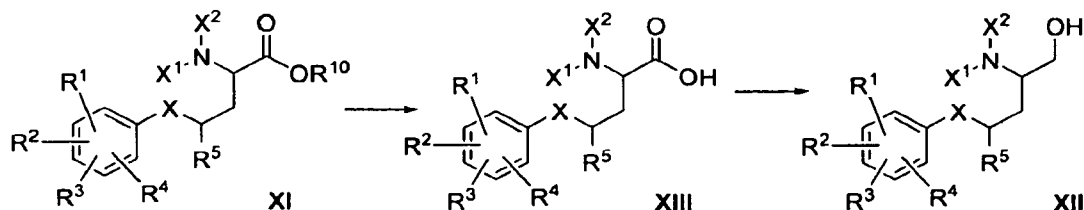
Alcohol compounds of formula XII are prepared from ester compounds of formula XI by a variety of reducing agents (I. T. Harrison and S. Harrison "Compendium of Organic Synthetic Methods" Section 38, pp 87-91, John Wiley and Sons, New York 1971) including, for example, lithium aluminum hydride.



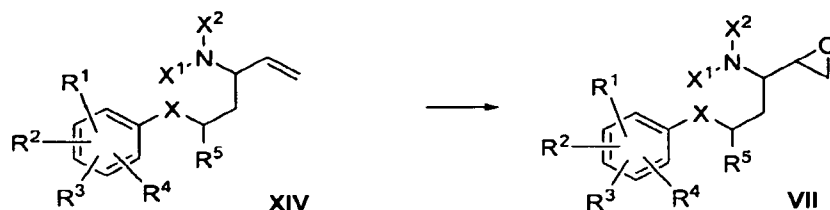
As another example, compounds of formula XI can be hydrolyzed to carboxylic acid compounds of formula XIII (I. T. Harrison and S. Harrison "Compendium of Organic Synthetic Methods" Section 23, pp 42-46, John Wiley and Sons, New York 1971).

Compounds of formula XIII can be converted to alcohol compounds of formula XII using a

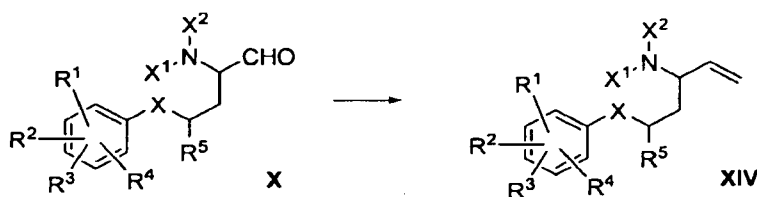
wide variety of reducing agents and conditions (I. T. Harrison and S. Harrison "Compendium of Organic Synthetic Methods" Section 32, pp 76-78, John Wiley and Sons, New York 1971).



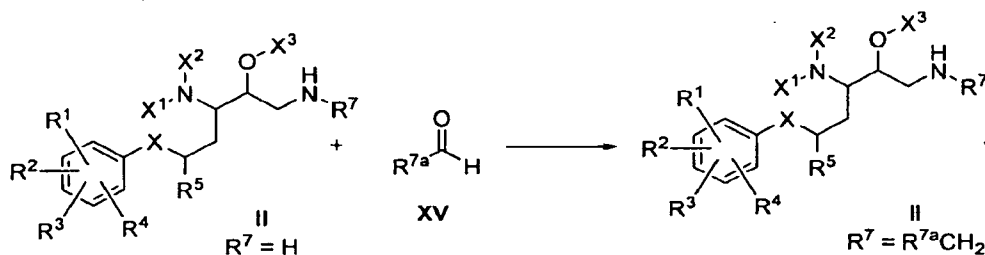
Alternately, epoxide compounds of formula VII can be prepared from alkene compounds of formula XIV by epoxidation of the alkene with for example mCPBA, monopero-phthalic acid, peracetic acid, dimethyldioxirane, H₂O₂/benzonitrile.



Alkene compounds of formula XIV are prepared from aldehyde compounds of formula X utilizing the Wittig reaction or the Tebbe reagent.



Compounds of formula II in which R⁷ is a lower alkyl, certain lower haloalkyl groups, lower cycloalkyl, certain lower alkoxyalkyl groups or certain lower lower haloalkoxy-lower alkyl groups are prepared by reductive alkylation of primary amines of formula II wherein R⁷ = H with aldehydes of formula XV wherein R^{7a} is the lower homolg of R⁷ (E. W. Baxter and A. B. Reitz "Reductive aminations of carbonyl compounds with borohydride and borane reducing agents" in Organic Reactions Volume 59 pp 1-714, Edited by L. E. Overman, John Wiley and Sons, New York, 2002).



In each of the processes mentioned above, the starting compounds may also be used in the form of salts, provided that the reaction conditions allow it.

A free amino group present in a compound of formula I obtainable in accordance with the process can be acylated or alkylated, for example to introduce a radical R^6 other than hydrogen. The acylation and the alkylation can be carried out in accordance with one of the methods mentioned for protecting groups or according to known processes.

5 Furthermore, a free hydroxy group present in a compound of formula I obtainable in accordance with the process, for example as a constituent of the radical R^8 , can be acylated. The acylation can be carried out with acylating reagents in accordance with one of the methods mentioned for protecting groups or according to known processes.

10 In compounds of formula I in which R^1 , R^2 , R^3 , and/or R^4 are hydroxy it is also possible to replace hydroxy by one of the etherified hydroxy groups mentioned under formula I by reacting the corresponding compound of formula I wherein R^1 , R^2 , R^3 , and/or R^4 is hydroxy in customary manner, for example in the presence of a basic condensation agent, with a compound of the formula(e) R^1-Y , R^2-Y , R^3-Y , and/or R^4-Y , wherein R^1 is lower alkyl or free or esterified or amidated carboxy-lower alkyl, R^2 is lower alkyl, lower alkoxy-lower alkyl, 15 lower alkoxy-lower alkoxy-lower alkyl, cycloalkoxy-lower alkyl, optionally lower alkanoylated, halogenated or sulfonylated hydroxy-lower alkyl, oxo-lower alkyl, lower alkyl, lower alkenyl, cycloalkoxy-lower alkyl, lower alkoxy-lower alkyl, lower alkoxy-lower alkenyl, lower alkenyloxy-lower alkyl, lower alkenyloxy-lower alkyl, lower alkenyloxy-lower alkyl, lower alkanoyl-lower alkyl, optionally S-oxidized lower alkyl-thio-lower alkyl, lower alkylthio- 20 (hydroxy)-lower alkyl, aryl-lower alkyl, optionally hydrogenated heteroaryl-lower alkyl, optionally hydrogenated heteroarylthio-lower alkyl, cyano-lower alkyl or free or esterified or amidated carboxy-lower alkyl, R^3 is lower alkyl, lower alkoxy-lower alkyl, hydroxy-lower alkyl, aryl-lower alkyl, halogenated lower alkyl, cyano-lower alkyl or free or esterified or amidated carboxy-lower alkyl, and R^4 is lower alkyl, and Y is reactive esterified hydroxy, 25 especially hydroxy esterified by a mineral acid, by sulfuric acid or by an organic sulfonic acid, such as halogen, preferably chlorine, bromine or iodine, lower alkanesulfonyloxy or unsubstituted or substituted benzenesulfonyloxy, especially methane-, ethane-, benzene-, p-toluene- or p-bromobenzene-sulfonyl. The reaction is preferably carried out in the presence of a basic condensation agent, such as an alkali metal carbonate, for example potassium 30 carbonate, in an inert solvent, such as a lower alkanol, such as methanol, ethanol, butanol, tert-butanol or especially amyl alcohol, advantageously at elevated temperature, for example in a temperature range of approximately from 40-140°C, if necessary with removal of the resulting water of reaction by distillation, for example by azeotropic distillation.

35 It is also possible for salts of compounds of formula I obtainable in accordance with the process to be converted in a manner known *per se* into the free compounds, for example by treatment with a base, such as an alkali metal hydroxide, a metal carbonate or metal

hydrogen carbonate, or ammonia, or another of the salt-forming bases mentioned at the beginning, or with an acid, such as a mineral acid, for example with hydrochloric acid, or another of the salt-forming acids mentioned at the beginning.

Resulting salts can be converted into different salts in a manner known *per se*: acid addition salts, for example, by treatment with a suitable metal salt, such as a sodium, barium or silver salt, of a different acid in a suitable solvent in which an inorganic salt being formed is insoluble and is therefore eliminated from the reaction equilibrium, and basic salts by freeing of the free acid and conversion into a salt again.

The compounds of formula I, including their salts, may also be obtained in the form of hydrates or may include the solvent used for crystallization.

As a result of the close relationship between the novel compounds in free form and in the form of their salts, any reference herein to the free compounds and their salts is to be understood as including also the corresponding salts and free compounds, respectively, as appropriate and expedient.

Stereoisomeric mixtures, i.e., mixtures of diastereoisomers and/or enantiomers, such as racemic mixtures, can be separated into the corresponding isomers in a manner known *per se* by suitable separating processes. For example, mixtures of diastereoisomers can be separated into the individual diastereoisomers by fractional crystallization, chromatography, solvent partition, etc. Racemates can be separated from one another, after conversion of the optical antipodes into diastereoisomers, for example by reaction with optically active compounds, for example optically active acids or bases, by chromatography on column materials charged with optically active compounds or by enzymatic methods, for example by selective reaction of only one of the two enantiomers. This separation can be carried out either at the stage of one of the starting materials or with the compounds of formula I themselves.

In a compound of formula I the configuration at individual chirality centers can be selectively reversed. For example, the configuration of asymmetric carbon atoms that carry nucleophilic substituents, such as amino or hydroxy, can be reversed by second order nucleophilic substitution, optionally after conversion of the bonded nucleophilic substituent into a suitable nucleofugal leaving group and reaction with a reagent introducing the original substituent, or the configuration at carbon atoms having hydroxy groups can be reversed by oxidation and reduction, analogously to patent application EP 236,734.

Another embodiment of the invention is those forms of the process in which a compound obtainable as an intermediate at any stage is used as a starting material and the remaining steps are carried out or the process is interrupted at any stage, or a starting material is formed under the reaction conditions or is used in the form of a reactive derivative or salt, or a compound obtained in accordance with the process of the invention is formed

under the process conditions and further processed *in situ*. It is preferable to use those starting materials which result in the compounds described above.

Representative compounds of the invention can be synthesized in accordance with the general synthetic schemes described above and are illustrated in the examples that follow. The methods for preparing the various starting materials used in the schemes and examples are well within the knowledge of persons skilled in the art

The following abbreviations have the indicated meanings:

aq	aqueous
Boc	tert-butoxy carbonyl or t-butoxy carbonyl
(Boc) ₂ O	di- <i>tert</i> -butyl dicarbonate
brine	saturated aqueous sodium chloride
CH ₂ Cl ₂	methylene chloride
CH ₃ CN or MeCN	acetonitrile
Cpd	compound
d	day
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DMAP	4-(dimethylamino)pyridine
DMF	N,N-dimethyl formamide
DMSO	dimethyl sulfoxide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
EDC.HCl	1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride
eq, equiv	equivalents
Et	ethyl
EtOAc	ethyl acetate
Fmoc	1-[[[(9H-fluoren-9-ylmethoxy)carbonyl]oxy]-
Fmoc-OSu	1-[[[(9H-fluoren-9-ylmethoxy)carbonyl]oxy]-2,5-pyrrolidinedione
h, hr	hour
HBTU	O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate
HOBt	1-hydroxybenzotriazole
KHMDS	potassium hexamethyldisilazane
LAH or LiAlH ₄	lithium aluminum hydride
LHMDS	lithium hexamethyldisilazane
Me	methyl
MeOH	methanol
MsCl	methanesulfonyl chloride
min	minute
MS	mass spectrum

NaH	sodium hydride
NaHCO ₃	sodium bicarbonate
NaN ₃	sodium azide
NaOH	sodium hydroxide
Na ₂ SO ₄	sodium sulfate
Pd ₂ (dba) ₃	tris(dibenzylideneacetone)dipalladium(0)
Ph or PH	phenyl
RT/r.t.	room temperature
satd	saturated
SOCl ₂	thionyl chloride
TEA	triethylamine or Et ₃ N
Teoc	1-[2-(trimethylsilyl)ethoxycarbonyloxy]-
Teoc-OSu	1-[2-(trimethylsilyl)ethoxycarbonyloxy]pyrrolidin-2,5-dione
TFA	trifluoroacetic acid
THF	tetrahydrofuran
tlc	thin layer chromatography
TMSCl	chlorotrimethylsilane or trimethylsilyl chloride
t _R	retention time

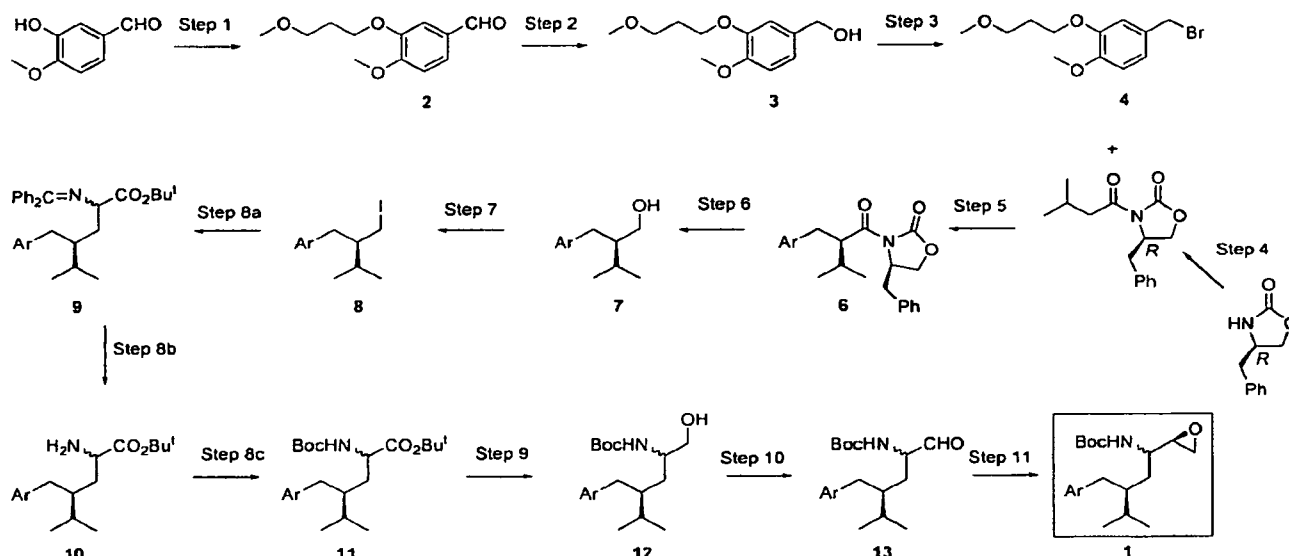
Analytical Methods

LC-MS (3 min)

5 Column: Chromolith SpeedRod, RP-18e, 50 x 4.6 mm; Mobil phase: A: 0.01%TFA/water, B: 0.01%TFA/CH₃CN; Flow rate: 1 mL/min; Gradient:

Time (min)	A%	B%
0.0	90	10
2.0	10	90
2.4	10	90
2.5	90	10
3.0	90	10

EXAMPLE 1

Tert-butyl (3S)-3-(3-(3-methoxypropoxy)-4-methoxybenzyl)-4-methyl-
1-(oxiran-2-yl)pentylcarbamate

Step 1

To a mixture of 3-hydroxy-4-methoxy-benzaldehyde (26.60 g, 0.175 mol, 1.0 equiv), triphenylphosphine (60.80 g, 1.3 equiv), and 3-methoxy-1-propanol (16.00 g, 1.0 equiv) in THF (100 mL) and toluene (300 mL) was added a solution of DIAD (47.0 g, 1.3 equiv) in toluene (100 mL) dropwise. The resulting mixture was evacuated and then stirred for 24 h at rt. The reaction mixture was concentrated *in vacuo*. The crude product was carried on to the next step without further purification. An analytical sample of 4-methoxy-3-(3-methoxypropoxy)-benzaldehyde (2) was obtained by chromatography (33% to 50% ethyl acetate in hexanes). ¹H NMR (400 MHz, CDCl₃) δ (ppm): 9.84 (s, 1H), 7.46-7.42 (m, 2H), 6.97 (d, *J* = 8.4 Hz, 1H), 4.18 (t, *J* = 6.4 Hz, 2H), 3.95 (s, 3H), 3.57 (t, *J* = 6.2 Hz, 2H), 3.35 (s, 3H), 2.13 (p, *J* = 6.3 Hz, 2H).

Step 2

A mixture of crude 4-methoxy-3-(3-methoxy-propoxy)-benzaldehyde (2) and ethanol (300 mL) was treated with a suspension of NaBH₄ (15.0 g) and ethanol (150 mL). The resulting mixture was stirred overnight at rt. The reaction mixture was concentrated *in vacuo*. The residue was treated with 10% Na₂CO₃ and extracted three times with CH₂Cl₂.

The organic phase was dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was filtered through silica gel column (33% to 75% ethyl acetate in hexanes) to give the crude 4-methoxy-3-(3-methoxy-propoxy)-benzyl alcohol (**3**). An analytical sample was obtained by further chromatography. ¹H NMR (400 MHz, CDCl₃) δ (ppm): 6.95-6.83 (m, 3H), 4.60 (s, 2H), 4.12 (t, *J* = 6.4 Hz, 2H), 3.85 (s, 3H), 3.57 (t, *J* = 6.2 Hz, 2H), 3.34 (s, 3H), 2.10 (p, *J* = 6.3 Hz, 2H), 1.75 (br s, 1H).

Step 3

To a 2-L round bottom flask of crude 4-methoxy-3-(3-methoxy-propoxy)-benzyl alcohol (**3**) was added Et₂O (400 mL) and pyridine (0.26 mL). The flask was evacuated and refilled with N₂. PBr₃ (20.93 g) was then added slowly to the stirred solution at rt. After 3 h, the reaction mixture was quenched with satd aq NaHCO₃ and extracted three times with ethyl acetate. The organic phase was dried over Na₂SO₄, filtered and concentrated *in vacuo*. A mixture of the crude product in Et₂O (100 mL) and hexane (400 mL) was vigorously stirred for 0.5 h. The mixture was filtered and the solid collected was washed with hexane. The filtrate was concentrated *in vacuo* to leave a residue which was purified on silica gel chromatography (25% to 33% ethyl acetate in hexanes) to afford 4-methoxy-3-(3-methoxy-propoxy)-benzyl bromide (**4**). ¹H NMR (400 MHz, CDCl₃) δ (ppm): 6.96-6.93 (m, 2H), 6.81 (d, *J* = 8.8 Hz, 1H), 4.49 (s, 2H), 4.12 (t, *J* = 6.4 Hz, 2H), 3.86 (s, 3H), 3.57 (t, *J* = 6.2 Hz, 2H), 3.36 (s, 3H), 2.11 (p, *J* = 6.3 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ (ppm): 149.6, 148.5, 130.2, 121.6, 113.8, 111.4, 69.2, 66.0, 58.7, 56.0, 34.4, 29.5.

Step 4

A 250-mL round bottom flask was charged with (*R*)-(+)-4-benzyl-2-oxazolidinone (7.520 g, 42.4 mmol, 1.0 equiv) and THF (100 mL). The flask was evacuated and refilled with N₂. The mixture was cooled with a dry ice-acetone bath and 1.6 M *n*-BuLi in hexanes (30 mL, 48 mmol, 1.13 equiv) was added slowly. After 0.5 h, isovaleroyl chloride (5.5 mL, 45.1 mmol, 1.06 equiv) was added. After 10 min, the dry ice-acetone bath was removed and replaced with an ice bath. After an additional 2.5 h, the reaction mixture was quenched with 10% aq Na₂CO₃ (65 mL) and vigorously stirred for 3 h. The mixture was extracted three times with ethyl acetate. The organic phase was dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (25% to 33% ethyl acetate in hexanes) to afford (4*R*)-benzyl-3-(3-methyl-butyl)-2-oxazolidinone (**5**) (10.5308 g, 95%). ¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.36-7.21 (m, 5H), 4.71-4.65 (m, 1H), 4.22-4.11 (m, 2H), 3.31 (dd, *J* = 13.3, 3.4 Hz, 1H), 2.89 (dd, *J* = 16.1, 6.7 Hz, 1H), 2.78 (dd, *J* = 16.3, 7.2 Hz, 1H), 2.75 (dd, *J* = 13.2, 9.7 Hz, 1H), 2.27-2.17 (m, 1H), 1.02 (d, *J* = 6.7 Hz, 3H), 1.00 (d, *J* = 6.7 Hz, 3H).

Step 5

To a 250-mL round bottom flask of compound (4*R*)-benzyl-3-(3-methyl-butyryl)-2-oxazolidinone (5) (5.500 g, 21.0 mmol) was added THF (60 mL). The flask was evacuated and refilled with N₂. The mixture was cooled with a dry ice-acetone bath and 1.0M LiHMDS in THF (23.5 mL, 23.5 mmol) was added dropwise. After 0.5 h, a solution of 4-methoxy-3-(3-methoxy-propoxy)-benzyl bromide (4) (5.8043 g, 20.1 mmol) in THF (30 mL) was added slowly *via* cannula. The resulting mixture was allowed to slowly warm to rt while stirring overnight. The mixture was quenched with satd aq NH₄Cl and extracted three times with ethyl acetate. The organic phase was dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (25% to 33% ethyl acetate in hexanes) to afford (R)-3-((R)-2-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-methylbutanoyl)-4-benzyloxazolidin-2-one (6) (8.349 g, 84%). LC-MS (3 min) *t*_R = 2.05 min *m/z* 492 (M+Na⁺), 470 (M+H⁺), 293, 261; ¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.24-7.20 (m, 3H), 6.93-6.91 (m, 2H), 6.85 (d, *J* = 1.8 Hz, 1H), 6.77 (dd, *J* = 8.2, 1.8 Hz, 1H), 6.73 (d, *J* = 8.2 Hz, 1H), 4.63-4.57 (m, 1H), 4.28-4.23 (m, 1H), 4.09-4.03 (m, 3H), 3.96 (dd, *J* = 8.9, 2.5 Hz, 1H), 3.78 (s, 3H), 3.55-3.49 (m, 2H), 3.31 (s, 3H), 2.97-2.80 (m, 3H), 2.19 (dd, *J* = 13.5, 9.4 Hz, 1H), 2.11-1.97 (m, 3H), 1.06 (d, *J* = 7.0 Hz, 3H), 1.03 (d, *J* = 6.7 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ (ppm): 175.9, 153.0, 148.2, 147.8, 135.2, 131.9, 129.3, 128.8, 127.1, 121.4, 114.1, 111.4, 69.4, 65.9, 65.3, 58.6, 56.0, 55.0, 50.1, 37.3, 35.4, 31.4, 29.5, 20.7, 19.5.

Step 6

To a 100-mL round bottom flask of (R)-3-((R)-2-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-methylbutanoyl)-4-benzyloxazolidin-2-one (6) (2.1475 g, 4.57 mmol) was added Et₂O (50 mL) and H₂O (0.18 mL). The flask was evacuated and refilled with N₂. The mixture was cooled with an ice bath and 2.0 M LiBH₄ in THF (5.5 mL, 11.0 mmol) was added dropwise. After 10 min, the cooling bath was removed and the mixture was stirred for an additional 0.5 h. The mixture was then cooled with an ice bath, quenched with 1 *N* aq NaOH (20 mL) and extracted three times with CH₂Cl₂. The organic phase was dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (33% to 50% ethyl acetate in hexanes) to afford (R)-2-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-methylbutan-1-ol (7) (0.7894 g, 58%). LC-MS (3 min) *t*_R = 1.60 min *m/z* 319 (MNa⁺), 297 (MH⁺), 209; ¹H NMR (400 MHz, CDCl₃) δ (ppm): 6.80-6.71 (m, 3H), 4.10 (t, *J* = 6.6 Hz, 2H), 3.84 (s, 3H), 3.59-3.55 (m, 4H), 3.36 (s, 3H), 2.65 (dd, *J* = 13.8, 5.6 Hz, 1H), 2.45 (dd, *J* = 13.8, 9.4 Hz, 1H), 2.10 (p, *J* = 6.3 Hz, 2H), 1.88-1.80 (m, 1H), 1.66-1.59 (m, 1H), 1.41 (br s, 1H), 0.97 (d, *J* = 7.0 Hz, 3H), 0.96 (d, *J* = 7.0 Hz, 3H); ¹³C NMR (100

MHz, CDCl₃) δ (ppm): 148.2, 147.5, 133.9, 121.1, 114.0, 111.6, 69.3, 65.9, 63.0, 58.7, 56.0, 48.8, 34.1, 29.5, 27.9, 19.7, 19.5.

Step 7

A 100 mL round bottom flask was charged with triphenylphosphine (1.3055 g, 4.98 mmol, 1.2 equiv) and CH₂Cl₂ (20 mL). Imidazole (0.5590 g, 8.21 mmol, 2.0 equiv) and iodine (1.4547 g, 5.73 mmol, 1.4 equiv) were added. The flask was evacuated and refilled with N₂. A solution of (R)-2-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-methylbutan-1-ol (7) (1.1992 g, 4.04 mmol, 1.0 equiv) in CH₂Cl₂ (20 mL) was added to the resulting suspension *via* cannula. After 3 h, the solvents were removed *in vacuo*. The residue was purified by chromatography on silica gel (25% to 33% ethyl acetate in hexanes) to give 2-(3-methoxypropoxy)-4-((R)-2-(iodomethyl)-3-methylbutyl)-1-methoxybenzene (8) (1.4742 g, 90%). LC-MS (3 min) t_R = 2.33 min, m/z 407 (MH⁺), 375, 177; ¹H NMR (400 MHz, CDCl₃) δ (ppm): 6.80-6.73 (m, 3H), 4.11 (t, J = 6.4 Hz, 2H), 3.84 (s, 3H), 3.58 (t, J = 6.2 Hz, 2H), 3.36 (s, 3H), 3.21 (dd, J = 10.0, 4.7 Hz, 1H), 3.09 (dd, J = 10.0, 4.4 Hz, 1H), 2.77 (dd, J = 13.9, 4.8 Hz, 1H), 2.34 (dd, J = 13.8, 9.7 Hz, 1H), 2.11 (p, J = 6.3 Hz, 2H), 1.75-1.65 (m, 1H), 1.16-1.10 (m, 1H), 1.01 (d, J = 6.8 Hz, 3H), 0.95 (d, J = 6.7 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ (ppm): 148.2, 147.7, 132.9, 121.1, 114.0, 111.7, 69.3, 65.9, 58.7, 56.0, 47.6, 36.6, 30.5, 29.5, 19.8, 19.5, 14.5.

Step 8

A flame dried 100-mL round bottom flask was charged with *N*-(diphenylmethylene)glycine *tert*-butyl ester (0.6625 g, 2.24 mmol, 1.25 equiv), THF (10 mL) and HMPA (1 mL). The flask was evacuated and refilled with N₂. The mixture was cooled with a dry ice-acetone bath and 1.0 M LiHMDS in THF (2.5 mL, 2.5 mmol) was added dropwise. After 15 min, a solution of 2-(3-methoxypropoxy)-4-((R)-2-(iodomethyl)-3-methylbutyl)-1-methoxybenzene (8) (0.7301 g, 1.80 mmol, 1.0 equiv) in THF (10 mL) was added slowly *via* cannula. The resulting mixture was allowed to slowly warm to rt while stirring overnight. The mixture was quenched with saturated brine and extracted three times with ethyl acetate. The organic phase was dried over Na₂SO₄, filtered and concentrated *in vacuo* to afford crude (4S)-*tert*-butyl 4-(3-(3-methoxypropoxy)-4-methoxybenzyl)-2-(diphenylmethyleneamino)-5-methylhexanoate (9) which was used without further purification.

A mixture of crude alkylation product 9, THF (30 mL) and 1 M aq citric acid (35 mL) was vigorously stirred overnight. The solvent was removed *in vacuo*. The aqueous phase was carefully treated with Na₂CO₃ (6.5 g) and extracted three times with CH₂Cl₂. The organic phase was dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude (4S)-

tert-butyl 4-(3-(3-methoxypropoxy)-4-methoxybenzyl)-2-amino-5-methylhexanoate (**10**) was stirred overnight with Boc_2O (1.5 g, mmol) in CH_2Cl_2 . The solvent was removed *in vacuo* and the residue was purified on silica gel chromatography (20% to 33% ethyl acetate in hexanes) to give 0.6581 g (72%) of tert-butyl (3S)-1-(tert-butoxycarbonyl)-3-(3-(3-

methoxypropoxy)-4-ethylbenzyl)-4-methylpentyl-carbamate (**11**). LC-MS (3 min) $t_R = 2.36$ m/z 532 ($\text{M}+\text{Na}^+$), 410, 354; ^1H NMR (400 MHz, CDCl_3) δ (ppm): 6.79-6.65 (m, 3H), 4.90 (d, $J = 8.5$ Hz, 1H), 4.22 (q, $J = 7.9$ Hz, 1H), 4.09 (t, $J = 6.3$ Hz, 2H), 3.82 (s, 3H), 3.57 (t, $J = 6.3$ Hz, 2H), 3.35 (s, 3H), 2.58 (dd, $J = 13.6, 6.6$ Hz, 1H), 2.45 (dd, $J = 13.3, 8.1$ Hz, 1H), 2.13-2.06 (m, 2H), 1.78-1.73 (m, 1H), 1.65 (br s, 1H), 1.52-1.47 (m, 2H), 1.44 (s, 9H), 1.43 (s, 9H), 0.86 (d, $J = 6.8$ Hz, 3H), 0.83 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ (ppm): 172.3, 155.3, 148.0, 147.3, 133.7, 121.1, 114.1, 111.4, 81.3, 79.2, 69.2, 65.7, 58.4, 55.8, 52.2, 41.9, 36.1, 33.4, 29.4, 28.1, 27.8, 27.3, 19.3, 18.3, 18.2, 17.3.

Step 9

To a -78°C solution of tert-butyl (3S)-1-(tert-butoxycarbonyl)-3-(3-(3-methoxypropoxy)-4-ethylbenzyl)-4-methylpentylcarbamate (**11**) (0.7012 g, 1.38 mmol) in THF (15 mL) was added 1.0 M diisobutylaluminum hydride in hexanes (8 mL, 8.0 mmol) dropwise. The mixture was allowed to slowly warm to rt while stirring overnight. The reaction mixture was carefully quenched with MeOH (9 mL). After 1 h, the mixture was diluted with saturated Rochelle's salt and extracted three times with ethyl acetate. The organic phase was dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (50% ethyl acetate in hexanes) to give tert-butyl (4S)-4-(3-(3-methoxypropoxy)-4-methoxybenzyl)-1-hydroxy-5-methylhexan-2-ylcarbamate (**12**) (0.5049 g, 83%).

Step 10

To a 100-mL round bottom flask of tert-butyl (4S)-4-(3-(3-methoxypropoxy)-4-methoxybenzyl)-1-hydroxy-5-methylhexan-2-ylcarbamate **12** (0.5049 g, 1.15 mmol, 1.0 equiv) were added DMSO (5 mL) and triethylamine (2 mL). The flask was cooled with an ice bath. A mixture of pyridine-sulphur trioxide complex (1.85 g, 10 equiv) in dry DMSO (5 mL) was added. After 0.5 h, the ice bath was removed. The reaction mixture was allowed to stir at rt for an additional 0.5 h. The mixture was poured into ice water and extracted three times with ethyl acetate. The combined organic phase was washed with 10% aq citric acid, sat'd aq NaHCO_3 and brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (20% to 50% ethyl acetate in hexanes) to afford tert-butyl (3S)-3-(3-(3-methoxypropoxy)-4-methoxybenzyl)-1-formyl-4-methylpentylcarbamate (**13**) (0.4909 g, 98%).

Step 11

A flame-dried 100-mL round bottom flask was charged with 60% sodium hydride in oil (0.247 g, 6.17 mmol) and trimethyloxosulfonium iodide (1.356 g, 6.16 mmol). The flask was evacuated and refilled with N₂. Dry DMSO (8 mL) was added. The mixture was stirred at rt for 1 h. When H₂ evolution had ceased, the resulting solution was clear.

A second 100-mL round bottom flask was charged with tert-butyl (3S)-3-(3-(3-methoxypropoxy)-4-methoxybenzyl)-1-formyl-4-methylpentylcarbamate (**13**) (0.4602 g, 1.05 mmol) and 6 mL of THF (6 mL). The flask was evacuated and refilled with N₂ and an aliquot of the ylid solution prepared above (2 mL, 1.5 mmol, 1.5 equiv) was added by syringe. The resulting mixture was stirred for 1 h at rt. The reaction mixture was quenched with brine and extracted three times with ethyl acetate. The organic phase was dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (33% ethyl acetate in hexanes) to afford tert-butyl (3S)-3-(3-(3-methoxypropoxy)-4-methoxybenzyl)-4-methyl-1-(oxiran-2-yl)pentylcarbamate (**1**) (0.250 g, 53%) as a mixture of four isomers, of which tert-butyl (1S,3S)-3-(3-(3-methoxypropoxy)-4-methoxybenzyl)-4-methyl-1-((R)-oxiran-2-yl)pentylcarbamate was the major isomer.

EXAMPLE 2

Halides

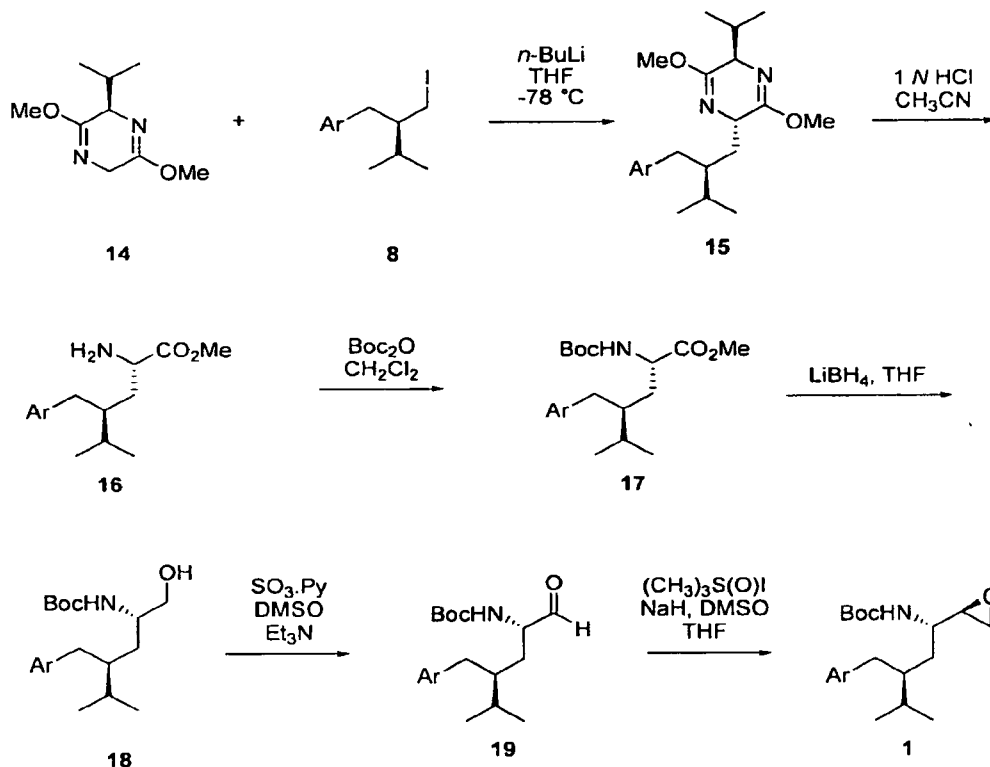
The following halides were prepared following the procedures of Example 1 Steps 5, 6, and 7:

1-(((S)-2-(bromomethyl)-3-methylbutoxy)methyl)benzene (chloromethyl benzyl ether was used in Step 5 in place of 4-methoxy-3-(3-methoxy-propoxy)-benzyl bromide)

1-((3-((R)-2-(bromomethyl)-3-methylbutyl)phenoxy)methyl)benzene (3-benzyloxybenzyl bromide was used in Step 5 in place of 4-methoxy-3-(3-methoxy-propoxy)-benzyl bromide).

EXAMPLE 3

Tert-butyl (1S,3S)-3-(3-(3-methoxypropoxy)-4-methoxybenzyl)-4-methyl-
1-((R)-oxiran-2-yl)pentylcarbamate



Ar = 4-methoxy-3-(3-methoxypropoxy)phenyl

Step 1

A flame-dried 100-mL round bottom flask was charged with (R)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (**14**) (2.4080 g, 13.07 mmol) and THF (20 mL), and evacuated and refilled with N₂. The mixture was cooled with a dry ice-acetone bath and 2.5 M *n*-BuLi in hexanes (5.2 mL, 13.00 mmol) was added dropwise over 15 min. After an additional 0.5 h, a solution of 2-(3-methoxypropoxy)-4-((R)-2-(iodomethyl)-3-methylbutyl)-1-methoxybenzene (**8**) (3.3023 g, 8.13 mmol, 0.62 equiv) from Example 1 Step 7 in THF (20 mL) was added dropwise *via* cannula over 10 min. The reaction mixture was allowed to stir at -78°C for 16 h and quenched with brine (20 mL) at -78°C. After warming to rt, the mixture was extracted three times with ethyl acetate. The organic phase was dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude (2S,5R)-2-((S)-2-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-methylbutyl)-2,5-dihydro-5-isopropyl-3,6-dimethoxypyrazine (**15**) (4.85 g, 80%) was carried on to the next step without further purification. LC-MS (3 min) *t_R* = 2.41 min *m/z* 463 (M+H⁺).

Step 2

A mixture of crude (2S,5R)-2-((S)-2-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-methylbutyl)-2,5-dihydro-5-isopropyl-3,6-dimethoxypyrazine (**15**) (4.85 g, 10.49 mmol) in acetonitrile (100 mL) and 1 N aq HCl (100 mL, 100 mmol) was vigorously stirred at rt for 3 h. The solvent was removed *in vacuo*. The aqueous phase was cooled with an ice bath, carefully treated with Na₂CO₃ (7.06 g, 66.6 mmol) and extracted three times with CH₂Cl₂. The organic phase was dried over Na₂SO₄, filtered and concentrated *in vacuo* to afford (2S,4S)-methyl 4-(3-(3-methoxypropoxy)-4-methoxybenzyl)-2-amino-5-methylhexanoate (**16**) (4.58 g), which was carried on to the next step without further purification.

Step 3

A mixture of (2S,4S)-methyl 4-(3-(3-methoxypropoxy)-4-methoxybenzyl)-2-amino-5-methylhexanoate (**16**) (4.58 g, 12.46 mmol) and Boc₂O (7.33 g, 33.58 mmol, 2.57 equiv) in CH₂Cl₂ (100 mL) was stirred at rt for 14 h. The solvent was removed *in vacuo* and the residue was purified by chromatography on silica gel (20% to 33% ethyl acetate in hexanes) to give tert-butyl (1S,3S)-1-(methoxycarbonyl)-3-(3-(3-methoxypropoxy)-4-methoxybenzyl)-4-methylpentylcarbamate (**17**) (3.3224 g, 87% from 2-(3-methoxypropoxy)-4-((R)-2-(iodomethyl)-3-methylbutyl)-1-methoxybenzene). R_f = 0.29 (30% ethyl acetate in hexanes); LC-MS (3 min) t_R = 2.07 min in 3 min chromatography, m/z 490 (MNa⁺), 368; ¹H NMR (400 MHz, CDCl₃) δ (ppm): 6.77-6.67 (m, 3H), 4.89 (d, J = 8.8 Hz, 1H), 4.36 (q, J = 7.7 Hz, 1H), 4.10 (t, J = 6.4 Hz, 2H), 3.83 (s, 3H), 3.71 (s, 3H), 3.57 (t, J = 6.2 Hz, 2H), 3.35 (s, 3H), 2.64 (dd, J = 13.8, 5.3 Hz, 1H), 2.43 (dd, J = 13.6, 8.6 Hz, 1H), 2.09 (p, J = 6.3 Hz, 2H), 1.74-1.53 (m, 4H), 1.44 (s, 9H), 0.83 (d, J = 6.5 Hz, 3H), 0.82 (d, J = 6.7 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ (ppm): 173.9, 155.5, 148.2, 147.5, 133.6, 121.3, 114.2, 111.5, 79.8, 69.4, 65.9, 58.6, 56.0, 52.2, 51.8, 41.9, 36.5, 33.2, 31.6, 29.6, 28.3, 27.7, 22.6, 20.0, 17.0, 14.1.

Step 4

To a solution of tert-butyl (1S,3S)-1-(methoxycarbonyl)-3-(3-(3-methoxypropoxy)-4-methoxybenzyl)-4-methylpentylcarbamate (**17**) (3.2926 g, 7.04 mmol) in THF (50 mL) was slowly added 2.0 M LiBH₄ in THF (11 mL, 22 mmol, 3 equiv). The mixture was allowed to stir at rt for 15 h. The reaction mixture was diluted with ethyl acetate (60 mL) and carefully quenched with 1 N aq HCl (60 mL). After the emulsion disappeared, the organic layer was separated. The aqueous layer was extracted three times with ethyl acetate. The combined organic phase was dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (50% to 66% ethyl acetate in hexanes) to afford tert-butyl (2S,4S)-4-(3-(3-methoxypropoxy)-4-methoxybenzyl)-1-hydroxy-5-methylhexan-2-

ylcarbamate (**18**) (3.1192 g, 100%). LC-MS (3 min) t_R = 1.82 min m/z 462 ($M+Na^+$), 340; 1H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.78-6.67 (m, 3H), 4.56 (br s, 1H), 4.10 (t, J = 6.6 Hz, 2H), 3.83 (s, 3H), 3.64 (br s, 1H), 3.57 (t, J = 6.3 Hz, 2H), 3.45-3.41 (m, 1H), 3.35 (s, 3H), 2.48 (d, J = 7.3 Hz, 2H), 2.09 (p, J = 6.4 Hz, 2H), 1.99 (br s, 2H), 1.77-1.69 (m, 1H), 1.58-1.52 (m, 1H), 1.47-1.40 (m, 1H), 1.44 (s, 9H), 1.27-1.21 (m, 1H), 0.88 (d, J = 6.5 Hz, 3H), 0.86 (d, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 156.4, 148.2, 147.5, 134.0, 121.2, 114.3, 111.5, 79.4, 69.4, 66.0, 60.4, 58.6, 56.0, 50.9, 42.3, 36.9, 31.4, 29.5, 28.3, 21.0, 19.7, 17.7, 14.2.

10 Step 5

To a 250-mL round bottom flask of tert-butyl (2S,4S)-4-(3-(3-methoxypropoxy)-4-methoxybenzyl)-1-hydroxy-5-methylhexan-2-ylcarbamate (**18**) (3.0542 g, 6.95 mmol, 1.0 equiv) was added DMSO (25 mL) and triethylamine (10 mL). The flask was cooled with an ice bath. A mixture of pyridine-sulphur trioxide complex (11.6 g, 72.9 mmol, 10.5 equiv) and dry DMSO (25 mL) was added. After 0.5 h, the ice bath was removed. The reaction mixture was allowed to stir at rt for an additional 0.5 h. The mixture was poured into ice water and extracted three times with ethyl acetate. The combined organic phase was washed with 10% aq citric acid, satd aq $NaHCO_3$, brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The crude tert-butyl (1S,3S)-3-(3-(3-methoxypropoxy)-4-methoxybenzyl)-1-formyl-4-methylpentyl-carbamate (**19**) (3.2205 g, 100%) was carried on to the next step without further purification. R_f = 0.27 (30% ethyl acetate in hexanes); 1H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.51 (s, 1H), 6.78-6.68 (m, 3H), 4.91 (d, J = 7.6 Hz, 1H), 4.14-4.08 (m, 3H), 3.83 (s, 3H), 3.57 (t, J = 6.2 Hz, 2H), 3.35 (s, 3H), 2.62-2.47 (m, 2H), 2.14-2.05 (m, 2H), 1.78-1.58 (m, 4H), 1.44 (s, 9H), 0.87 (d, J = 6.8 Hz, 3H), 0.84 (d, J = 6.8 Hz, 3H).

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Step 6

A flame-dried 250-mL round bottom flask was charged with 60% sodium hydride in oil (1.4483 g, 36.2 mmol) and trimethyloxosulfonium iodide (8.0500 g, 36.5 mmol). The flask was evacuated, refilled with N_2 and dry DMSO (50 mL) was added. The mixture was stirred at rt for 1 h. When H_2 evolution had ceased, the resulting ylid solution was clear.

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A second 250-mL round bottom flask was charged with crude tert-butyl (1S,3S)-3-(3-(3-methoxypropoxy)-4-methoxybenzyl)-1-formyl-4-methylpentylcarbamate (**19**) (3.2205 g, 6.97 mmol) and THF (30 mL). The flask was evacuated and refilled with N_2 . An aliquot of the ylid solution prepared above (14.5 mL, 10.5 mmol, 1.5 equiv) was added through a syringe. The resulting mixture was stirred for 1 h at rt. The reaction mixture was quenched with brine and extracted three times with ethyl acetate. The organic phase was dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified on silica gel

35

chromatography (33% ethyl acetate in hexanes) to afford *tert*-butyl (1*S*,3*S*)-3-(3-(3-methoxypropoxy)-4-methoxybenzyl)-4-methyl-1-((*R*)-oxiran-2-yl)pentylcarbamate (**1**) (1.4458 g, 46%). R_f = 0.30 (30% ethyl acetate in hexanes); LC-MS (3 min) t_R = 2.06 min m/z 474 ($M+Na^+$), 396; 1H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.79-6.66 (m, 3H), 4.31 (d, J = 9.7 Hz, 1H), 4.14-4.07 (m, 2H), 3.97 (br s, 1H), 3.83 (s, 3H), 3.59-3.55 (m, 2H), 3.35 (s, 3H), 2.93 (br s, 1H), 2.72-2.66 (m, 2H), 2.57 (dd, J = 4.8, 2.8 Hz, 1H), 2.41 (dd, J = 13.5, 9.1 Hz, 1H), 2.13-2.06 (m, 2H), 1.74-1.49 (m, 3H), 1.43 (s, 9H), 1.37-1.30 (m, 1H), 0.88-0.82 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 155.7, 148.1, 147.4, 133.8, 121.2, 114.2, 111.4, 79.2, 69.3, 65.8, 58.6, 55.9, 54.1, 53.8, 47.2, 44.3, 42.0, 36.9, 33.3, 29.5, 28.2, 20.2, 19.3, 17.9, 16.8.

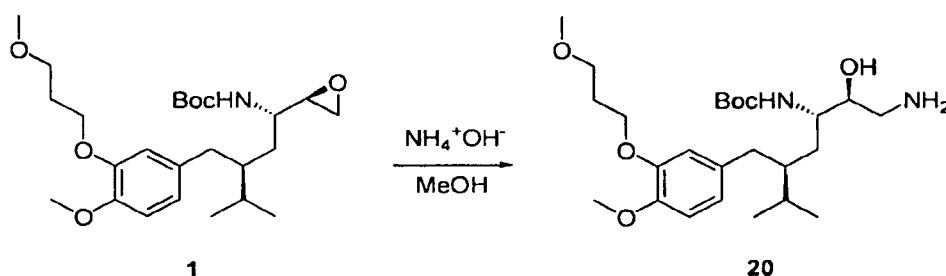
EXAMPLE 4

Epoxides

The following epoxides were prepared by following the procedures of Example 2: *tert*-butyl (1*S*,3*S*)-3-((benzyloxy)methyl)-4-methyl-1-((*R*)-oxiran-2-yl)pentylcarbamate, by using 1-(((*S*)-2-(bromomethyl)-3-methylbutoxy)methyl)benzene in place of 2-(3-methoxypropoxy)-4-((*R*)-2-(iodomethyl)-3-methylbutyl)-1-methoxybenzene in Step 1. *tert*-butyl (1*S*,3*S*)-3-(3-(benzyloxy)benzyl)-4-methyl-1-((*R*)-oxiran-2-yl)pentylcarbamate, by using 1-((3-((*R*)-2-(bromomethyl)-3-methylbutyl)phenoxy)methyl)benzene in place of 2-(3-methoxypropoxy)-4-((*R*)-2-(iodomethyl)-3-methylbutyl)-1-methoxybenzene in Step 1.

EXAMPLE 5

tert-Butyl (2*S*,3*S*,5*S*)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-1-amino-2-hydroxy-6-methylheptan-3-ylcarbamate



To a solution of *tert*-butyl (1*S*,3*S*)-3-(3-(3-methoxypropoxy)-4-methoxybenzyl)-4-methyl-1-((*R*)-oxiran-2-yl)pentylcarbamate (**1**) (0.50 g, 1.11 mmol) in methanol (10 mL) was added ammonium hydroxide solution (10 mL, excess). The resulting clear solution was stirred overnight at rt. The solvent was removed to dryness to give crude *tert*-butyl

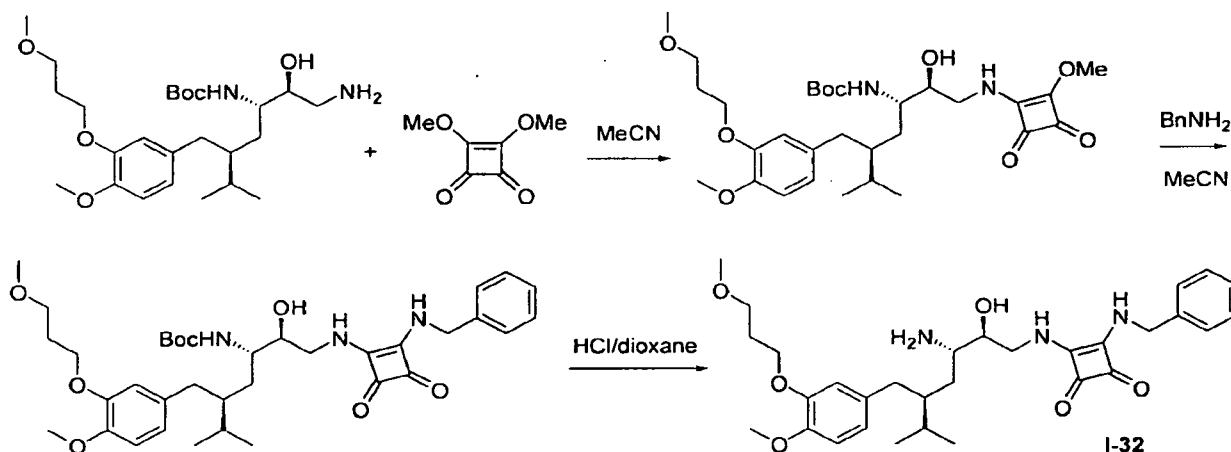
(2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-1-amino-2-hydroxy-6-methylheptan-3-ylcarbamate (**20**) (0.52 g, quant.), which was used for next step without purification. MS m/z 469 ($M+1$).

EXAMPLE 6

tert-Butyl (2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-2-hydroxy-6-methyl-1-(methylamino)heptan-3-ylcarbamate was prepared using the procedure of Example 5 replacing the ammonium hydroxide with methylamine.

EXAMPLE 7

3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(benzylamino)cyclobut-3-ene-1,2-dione (**1-32**)



Step 1

To a room-temperature solution of tert-butyl (2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-1-amino-2-hydroxy-6-methylheptan-3-ylcarbamate (23.4 mg, 0.050 mmol) in acetonitrile (1 mL) was added 3,4-dimethoxy-cyclobut-3-ene-1,2-dione (71.8 mg, 0.5 mmol, 10 eq) in one portion. The reaction was monitored by LC-MS which indicated that the formation of 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-(tert-butoxycarbonylamino)-2-hydroxy-6-methylheptylamino)-4-methoxycyclobut-3-ene-1,2-dione m/z 579 [$M+H$]⁺ was complete after 10 min.

Benzyl amine (0.1 mL, excess) was added to the reaction mixture at rt. A yellow precipitate formed immediately, and the reaction was complete after 10min. The solid was 3,4-bis(benzylamino)cyclobut-3-ene-1,2-dione, the product of double addition of benzyl amine to 3,4-dimethoxy-cyclobut-3-ene-1,2-dione. The mixture was filtered and the filtrate was submitted to preparative HPLC to give 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-

methoxybenzyl)-3-(tert-butoxycarbonylamino)-2-hydroxy-6-methylheptylamino)-4-(benzylamino)cyclobut-3-ene-1,2-dione (15.3 mg, 47%). m/z 654 $[M+H]^+$.

Step 2

3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-(tert-butoxycarbonylamino)-2-hydroxy-6-methylheptylamino)-4-(benzylamino)cyclobut-3-ene-1,2-dione (15.3 mg, 0.023 mmol) was treated with 4M HCl in dioxane (2 mL, 8 mmol) at room temperature for 1 h. The solvent was removed *in vacuo* to give 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(benzylamino)cyclobut-3-ene-1,2-dione as its HCl salt in quantitative yield. 1H NMR (CD_3OD) δ 7.36-7.32 (m, 5 H), 6.86-6.72 (m, 3 H), 4.04 (t, J = 6.4 Hz, 2 H), 3.81 (m, 1 H), 3.78 (s, 3 H), 3.73-3.62 (m, 2 H), 3.57 (t, J = 6.4 Hz, 2 H), 3.52 (m, 1 H), 3.34 (m, 1 H), 3.32 (s, 3 H), 2.93 (m; 1 H), 2.62-2.57 (m, 1 H), 2.43-2.38 (m, 1 H), 2.01 (m, 2 H), 1.72 (m, 3 H), 1.60 (m, 1 H), 0.97-0.87 (m, 6H); MS m/z 554 $[M+H]^+$.

EXAMPLE 8

The following compounds of formula I were prepared using the procedures of Example 7 substituting the appropriate amine for benzylamine in Step 1:

Cpd. No.	Name
I-1	3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-aminocyclobut-3-ene-1,2-dione
I-2	3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(methylamino)cyclobut-3-ene-1,2-dione
I-3	3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(ethylamino)cyclobut-3-ene-1,2-dione
I-4	3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(propylamino)cyclobut-3-ene-1,2-dione
I-5	3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(cyclopropylmethylamino)cyclobut-3-ene-1,2-dione
I-6	3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(butylamino)cyclobut-3-ene-1,2-dione
I-7	3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(isobutylamino)cyclobut-3-ene-1,2-dione
I-8	3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(2-methoxyethylamino)cyclobut-3-ene-1,2-dione
I-9	3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(piperidin-1-yl)cyclobut-3-ene-1,2-dione
I-10	3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(2-cyclopropylethylamino)cyclobut-3-ene-1,2-dione
I-12	3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-morpholinocyclobut-3-ene-1,2-dione
I-13	3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(neopentylamino)cyclobut-3-ene-1,2-dione
I-14	3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(pentan-2-ylamino)cyclobut-3-ene-1,2-dione
I-15	3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(tert-pentylamino)cyclobut-3-ene-1,2-dione

- I-16 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(3-methylbutan-2-ylamino)cyclobut-3-ene-1,2-dione
- I-17 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-((S)-2-methylbutylamino)cyclobut-3-ene-1,2-dione
- I-18 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(isopentylamino)cyclobut-3-ene-1,2-dione
- I-19 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(pentylamino)cyclobut-3-ene-1,2-dione
- I-21 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(N-butyl-N-methylamino)cyclobut-3-ene-1,2-dione
- I-22 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(2,2,2-trifluoroethylamino)cyclobut-3-ene-1,2-dione
- I-23 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(4-methylpiperazin-1-yl)cyclobut-3-ene-1,2-dione
- I-24 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(dipropylamino)cyclobut-3-ene-1,2-dione
- I-25 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(2-methylpentan-2-ylamino)cyclobut-3-ene-1,2-dione
- I-26 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(hexan-2-ylamino)cyclobut-3-ene-1,2-dione
- I-27 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(hexylamino)cyclobut-3-ene-1,2-dione
- I-28 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(N-methyl-N-pentylamino)cyclobut-3-ene-1,2-dione
- I-29 3-((2R,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(N-methyl-N-pentylamino)cyclobut-3-ene-1,2-dione
- I-30 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(2-methylpentan-2-ylamino)cyclobut-3-ene-1,2-dione
- I-31 3-((2R,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(2-methylpentan-2-ylamino)cyclobut-3-ene-1,2-dione
- I-34 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(cyclohexylmethylamino)cyclobut-3-ene-1,2-dione
- I-35 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(2-ethylpiperidin-1-yl)cyclobut-3-ene-1,2-dione
- I-36 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(heptylamino)cyclobut-3-ene-1,2-dione
- I-37 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(heptan-2-ylamino)cyclobut-3-ene-1,2-dione
- I-38 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(2-methylhexan-2-ylamino)cyclobut-3-ene-1,2-dione
- I-40 3-(2-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-3,4-dioxocyclobut-1-enylamino)-2,2-dimethylpropanamide
- I-41 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(phenethylamino)cyclobut-3-ene-1,2-dione
- I-43 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(2-cyclohexylethylamino)cyclobut-3-ene-1,2-dione
- I-44 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(octan-2-ylamino)cyclobut-3-ene-1,2-dione
- I-45 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(2,4,4-trimethylpentan-2-ylamino)cyclobut-3-ene-1,2-dione
- I-47 3-((1S,2R)-2-phenylcyclopropylamino)-4-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)cyclobut-3-ene-1,2-dione
- I-48 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(2,3-dihydro-1H-inden-2-ylamino)cyclobut-3-ene-1,2-dione
- I-49 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(3-phenylpropylamino)cyclobut-3-ene-1,2-dione
- I-51 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(N-methyl-N-phenethylamino)cyclobut-3-ene-1,2-dione
- I-52 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-((2-methyl)phenethylamino)cyclobut-3-ene-1,2-dione
- I-53 N-(3-(2-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-3,4-dioxocyclobut-1-enylamino)-2,2-dimethylpropyl)acetamide
- I-54 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(3-phenylpyrrolidin-1-yl)cyclobut-3-ene-1,2-dione
- I-55 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(4-phenylbutylamino)cyclobut-3-ene-1,2-dione
- I-56 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-

	(2,4-dimethylphenethylamino)cyclobut-3-ene-1,2-dione
I-57	3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(2-chlorophenethylamino)cyclobut-3-ene-1,2-dione
I-58	3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(3-chlorophenethylamino)cyclobut-3-ene-1,2-dione
I-59	3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(4-chlorophenethylamino)cyclobut-3-ene-1,2-dione
I-61	3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(4-phenylpiperidin-1-yl)cyclobut-3-ene-1,2-dione
I-62	3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(4-nitrophenethylamino)cyclobut-3-ene-1,2-dione
I-63	3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(3-benzylpiperidin-1-yl)cyclobut-3-ene-1,2-dione
I-64	3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(2,5-dimethoxyphenethylamino)cyclobut-3-ene-1,2-dione
I-65	3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(2,3-dimethoxyphenethylamino)cyclobut-3-ene-1,2-dione
I-66	3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(2,2,3,3,4,4,4-heptafluorobutylamino)cyclobut-3-ene-1,2-dione
I-67	3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(2-morpholino-2-(pyridin-3-yl)ethylamino)cyclobut-3-ene-1,2-dione

EXAMPLE 9

The following compounds of formula I were prepared using the procedures of

- 5 Example 7 by substituting in Step 1 (a) tert-Butyl (2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-2-hydroxy-6-methyl-1-(methylamino)heptan-3-ylcarbamate for tert-butyl (2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-1-amino-2-hydroxy-6-methylheptan-3-ylcarbamate and (b) the appropriate amine for benzylamine:

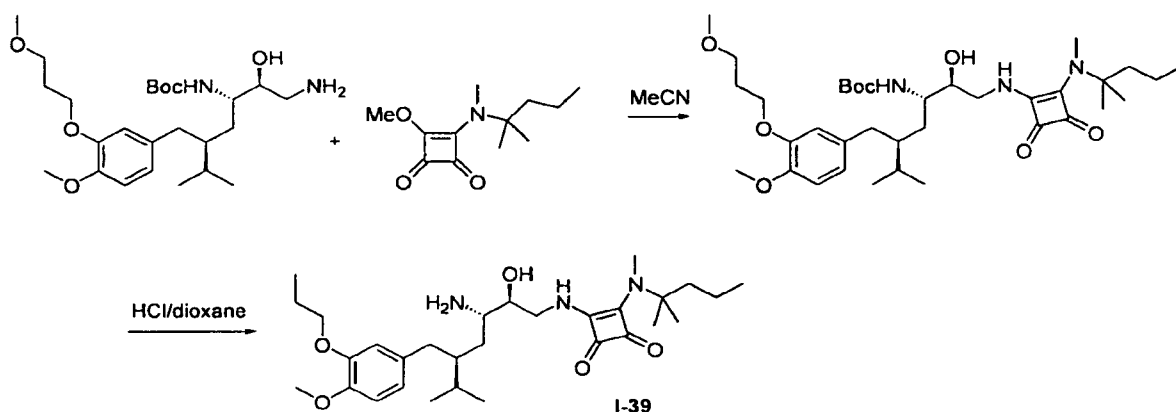
10

Cpd. No.	Name
I-20	3-(N-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptyl)-N-methylamino)-4-(butylamino)cyclobut-3-ene-1,2-dione
I-50	3-(N-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptyl)-N-methylamino)-4-(phenethylamino)cyclobut-3-ene-1,2-dione

EXAMPLE 10

3-((2S,3S,5S)-5-(4-methoxy-3-propoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(N-methyl-N-(2-methylpentan-2-yl)amino)cyclobut-3-ene-1,2-dione (**I-39**)

5



Step 1

To a solution of tert-butyl (2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-1-amino-2-hydroxy-6-methylheptan-3-ylcarbamate (94.4 mg, 0.2 mmol) in i-PrOH (1 mL) and diisopropylethylamine (0.1 mL) at rt, was added in one portion 3-(N-methyl-N-(2-methylpentan-2-yl)amino)-4-methoxycyclobut-3-ene-1,2-dione (22.7 mg, 0.1 mmol). The resulting solution was heated at 55°C until no starting material remained (~1 h) and submitted to purification by preparative HPLC to afford 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-(tert-butoxycarbonylamino)-2-hydroxy-6-methylheptylamino)-4-(N-methyl-N-(2-methylpentan-2-yl)amino)cyclobut-3-ene-1,2-dione (18.0 mg, 27%). MS m/z 662 $[M+H]^+$.

Step 2

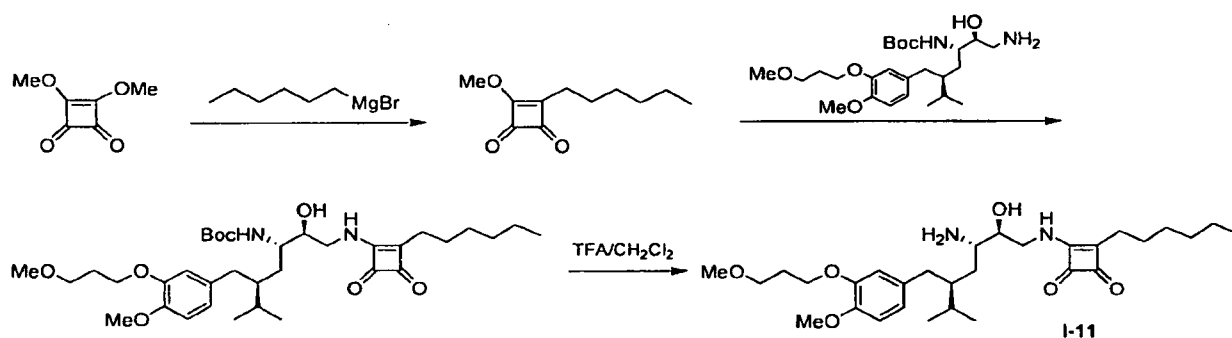
3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-(tert-butoxycarbonylamino)-2-hydroxy-6-methylheptylamino)-4-(N-methyl-N-(2-methylpentan-2-yl)amino)cyclobut-3-ene-1,2-dione (18.0 mg, 0.027 mmol) was dissolved in 4 M HCl in dioxane (2 mL, 8 mmol) and stirred at rt for 1 h. Solvent was removed *in vacuo* to give 3-((2S,3S,5S)-5-(4-methoxy-3-propoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(N-methyl-N-(2-methylpentan-2-yl)amino)cyclobut-3-ene-1,2-dione as its HCl salt in quantitative yield. 1H NMR (CD_3OD) δ 0.92 (m), 1.42 (s), 2.02 (m), 3.20 (s), 3.36 (s), 3.60 (t), 3.80 (s), 4.06 (t), 6.7-6.9 (m); MS m/z 562 $[M+H]^+$.

EXAMPLE 11

3-((2S,3S,5S)-5-(4-methoxy-3-propoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(N-methyl-N-(2-methylhexan-2-yl)amino)cyclobut-3-ene-1,2-dione (I-46) was prepared following the procedure of Example 10 substituting 3-(N-methyl-N-(2-methylhexan-2-yl)amino)-4-methoxycyclobut-3-ene-1,2-dione for 3-(N-methyl-N-(2-methylpentan-2-yl)amino)-4-methoxycyclobut-3-ene-1,2-dione in Step 1.

EXAMPLE 12

3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-hexylcyclobut-3-ene-1,2-dione (I-11)



Step 1

To a solution of 3,4-dimethoxycyclobut-3-ene-1,2-dione (170 mg, 1 mmol) in ether (4.2 mL) was added dropwise a solution of the Grignard reagent derived from 1-bromohexane in THF (4.2 mL of 0.36 M, 1.5 mmol) at 0°C. After the addition was complete, the reaction mixture was allowed to warm to rt, stirred for 1 h, and quenched with 18% aq HCl (5 mL). The mixture was extracted with ether (2 x 10 mL). The combined organic extracts were washed with water (10 mL), dried over Na₂SO₄, concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel eluting with hexane:ethyl acetate (2:1) to give 3-hexyl-4-methoxy-cyclobut-3-ene-1,2-dione (34.5 mg, 15%). ¹H NMR (400 MHz, CDCl₃) δ 4.41 (3H, s), 2.58 (t, J=7.6Hz, 2H), 1.66 (m, 2H), 1.32 (m, 6H), 0.87 (t, J=7.2Hz, 3H); MS m/z 197 (M+1)⁺.

Step 2

A solution of 3-hexyl-4-methoxy-cyclobut-3-ene-1,2-dione (21 mg, 0.1 mmol) and Et₃N (51 mg, 0.5 mmol) in ethanol (6 mL) was added dropwise to a stirred solution of (2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-1,3-diamino-6-methylheptan-2-ol

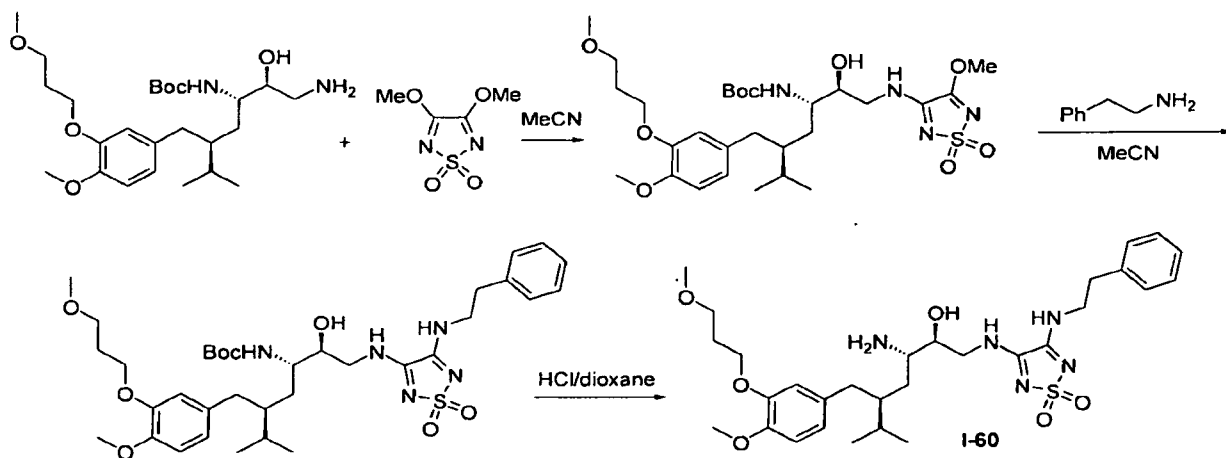
(51.5 mg, 0.11 mmol). The reaction mixture was stirred at rt for overnight and concentrated to leave a residue which was purified by preparative tlc to afford 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-(tert-butoxycarbonylamino)-2-hydroxy-6-methylheptylamino)-4-hexylcyclobut-3-ene-1,2-dione (8.6 mg, 12%). MS m/z 633 (M+1)⁺.

Step 3

A solution of 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-(tert-butoxycarbonylamino)-2-hydroxy-6-methylheptylamino)-4-hexylcyclobut-3-ene-1,2-dione (8.6 mg) in TFA/CH₂Cl₂ (6 mL, 1:1 v/v) was stirred for 3 h and concentrated. The residue was purified by preparative HPLC to give 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-hexylcyclobut-3-ene-1,2-dione (4.3 mg) as its trifluoroacetic acid salt. ¹H NMR (400 MHz, CDCl₃) δ 6.86 (3H, m), 4.06 (m, 2H), 3.80 (s, 3H), 3.58 (m, 4H), 3.31 (m, 3H), 2.72-2.556 (m, 3H), 2.43 (m, 1H), 2.02 (t, J=6.4Hz, 2H), 1.80-1.658 (m, 6H), 1.55-1.28(m, 7H), 1.0-0.85(m, 9H); MS(M⁺+1): 533

EXAMPLE 13

(2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-1-(1,1-dioxo-4-(phenethylamino)-1,2,5-thiadiazol-3-ylamino)-3-amino-6-methylheptan-2-ol (**I-60**)



Step 1

To a solution of tert-butyl (2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-1-amino-2-hydroxy-6-methylheptan-3-ylcarbamate (21.1 mg, 0.045 mmol) in MeCN (1 mL) at rt was added 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide (24 mg, 0.13 mmol). The resulting solution was heated at 90°C for 20 min in a CEM microwave synthesizer to give a solution of crude tert-butyl (2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-1-(1,1-dioxo-4-methoxy-1,2,5-thiadiazol-3-ylamino)-2-hydroxy-6-methylheptan-3-ylcarbamate. MS m/z 615 [M+H]⁺. Phenethylamine (0.1 mL, excess) was added and the mixture was heated in a CEM

microwave synthesizer at 90°C for 20 min. The crude product solution was submitted directly to preparative HPLC to give tert-butyl (2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-1-(1,1-dioxo-4-(phenethylamino)-1,2,5-thiadiazol-3-ylamino)-2-hydroxy-6-methylheptan-3-ylcarbamate (15.6 mg, 49%). MS m/z 704 [M+H]⁺.

5

Step 2

tert-Butyl (2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-1-(1,1-dioxo-4-(phenethylamino)-1,2,5-thiadiazol-3-ylamino)-2-hydroxy-6-methylheptan-3-ylcarbamate (15.6 mg, 0.022 mmol) was dissolved in 4 M HCl in dioxane (8 mmol) and the solution was stirred at rt for 1 h. The solvent was removed *in vacuo* to afford (2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-1-(1,1-dioxo-4-(phenethylamino)-1,2,5-thiadiazol-3-ylamino)-3-amino-6-methylheptan-2-ol as its HCl salt in quantitative yield. ¹H NMR (CD₃OD) δ (ppm): 7.31-7.21 (m, 5 H), 6.89-6.57 (m, 3 H), 4.06 (t, *J* = 6.4 Hz, 2 H), 3.80 (s, 3 H), 3.68 (dt, *J* = 7.2, 2.4 Hz, 2 H), 3.58 (t, *J* = 6.4 Hz, 2 H), 3.55-3.51 (m, 2 H), 3.36-3.26 (m, 1 H), 3.34 (s, 3 H), 3.11 (m, 1 H), 2.97 (t, *J* = 7.2 Hz, 2 H), 2.85 (dd, *J* = 11.6, 6.4 Hz, 1 H), 2.64 (dd, *J* = 13.6, 6.4 Hz, 1 H), 2.41 (dd, *J* = 13.6, 8.0 Hz, 1 H), 2.02 (m, 2 H), 1.74 (m, 3 H), 1.60 (m, 1 H), 0.93 (m, 6 H); MS m/z 604 [M+H]⁺.

15

EXAMPLE 14

20

The following compounds of formula I were prepared following the procedures of Example 13 substituting butylamine and pentylamine for phenethylamine in Step 1.

Cpd. No.	Name
I-33	(2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-1-(4-(butylamino)-1,1-dioxo-1,2,5-thiadiazol-3-ylamino)-3-amino-6-methylheptan-2-ol
I-42	(2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-1-(4-(pentylamino)-1,1-dioxo-1,2,5-thiadiazol-3-ylamino)-3-amino-6-methylheptan-2-ol

25

The following are compounds of the invention:

Table of Compounds

Cpd. No.	LC-MS (3min) t _R (min)	Mass Observed	¹ H NMR solvent	Selected ¹ H NMR resonances
I-1	1.03	464		not determined
I-2	1.05	478	CDCl ₃	6.77-6.64 (m, 3H), 4.08 (t, <i>J</i> = 6.4 Hz, 2H), 3.81 (s, 3H), 3.57 (t, <i>J</i> = 6.2 Hz, 2H), 3.46 (br s, 1H), 3.34 (s, 3H), 3.25 (br s, 3H), 2.65-1.25 (m, 15H), 0.85 (d, <i>J</i> = 6.4 Hz, 6H)
I-3	1.11	492	CD ₃ OD	0.9 (m), 1.26 (t), 1.4-1.9 (m), 2.02 (m), 2.42 (m), 2.60 (m), 3.00 (m), 3.36 (s), 3.60 (t), 3.64 (m), 3.80 (s), 4.04 (t), 6.7-6.9 (m)
I-4	1.16	506	CD ₃ OD	0.9 (m), 1.3-1.9 (m), 2.02 (m), 2.42 (m), 2.60 (m), 3.00 (m), 3.36 (s), 3.60 (t), 3.64 (m), 3.80 (s), 4.04 (t), 6.7-6.9 (m)

I-5	1.17	518	CD ₃ OD	0.28 (m), 0.56 (m), 0.9 (m), 1.04 (m), 1.3-1.9 (m), 2.02 (m), 2.40 (m), 2.60 (m), 2.98 (m), 3.36 (s), 3.54 (m), 3.60 (t), 3.7 (m), 3.80 (s), 4.04 (m), 6.7-6.9 (m) 6.75 (d, J = 8.4 Hz, 1H), 6.70 (s, 1H), 6.63 (d, J = 8.0 Hz, 1H), 3.94 (t, J = 6.2 Hz, 2H), 3.68 (s, 3H), 3.64-3.42 (m, 12H), 3.23 (s, 3H), 2.88 (br s, 1H), 2.49 (dd, J = 13.4, 6.2 Hz, 1H), 2.32 (dd, J = 13.6, 7.6 Hz, 1H), 1.91 (p, J = 6.2 Hz, 2H), 1.65-1.61 (m, 2H), 1.53-1.44 (m, 4H), 1.33-1.24 (m, 2H), 0.84-0.81 (m, 9H)
I-6	1.21	520	CD ₃ OD	0.9 (m), 1.4-1.9 (m), 2.02 (m), 2.40 (m), 2.60 (m), 3.36 (s), 3.46 (m), 3.60 (t), 3.70 (m), 3.80 (s), 4.04 (t), 6.76 (d), 6.80 (s), 6.84 (d) 6.74-6.60 (m, 3H), 3.95-3.89 (m, 2H), 3.66 (s, 3H), 3.63-3.31 (m, 8H), 3.22 (s, 3H), 3.19 (s, 3H), 2.88-2.79 (m, 1H), 2.55-2.24 (m, 2H), 1.92-1.47 (m, 8H), 0.87-0.76 (m, 6H)
I-7	1.20	520	CD ₃ OD	0.94(m,6H),3.58(t,2H),4.05(m,2H)
I-8	1.1	536	CD ₃ OD	0.02 (m), 0.42 (m), 0.84 (m), 0.9 (m), 1.50 (q), 1.60 (m), 1.7 (m), 2.02 (m), 2.40 (m), 2.60 (m), 3.0 (m), 3.36 (s), 3.60 (t), 3.7 (m), 3.80 (s), 4.06 (t), 6.7-6.9 (m)
I-9		532	CD ₃ OD	1.32(m, 6H), 1.62(m,2H), 1.75(m,2H), 2.02(m,2H), 2.42(m, 1H), 2.56(t, 2H), 3.31(m, 3H), 3.58(m, 2H), 3.80(s, 3H), 4.05(m, 2H)
I-10	1.24	532	CD ₃ OD	0.95(m,6H),3.58(t,2H),3.78(t,4H),4.05(m,2H)
I-11		533	CD ₃ OD	0.9 (m), 1.4-1.9 (m), 2.02 (m), 2.42 (m), 2.60 (m), 2.98 (m), 3.36 (s), 3.44 (m), 3.60 (t), 3.7 (m), 3.80 (s), 4.04 (t), 6.74(d), 6.80 (s), 6.84 (d)
I-12		534	CD ₃ OD	0.9 (m), 1.24 (t), 1.3-1.9 (m), 2.02 (m), 2.42 (m), 2.60 (m), 3.00 (m), 3.36 (s), 3.60 (t), 3.70 (m), 3.80 (s), 4.04 (t), 4.18 (m), 6.7-6.9 (m)
I-13	1.28	534	CD ₃ OD	0.9 (m), 1.40 (s), 1.6-1.8 (m), 2.02 (m), 2.42 (m), 2.60 (m), 2.98 (m), 3.36 (s), 3.60 (t), 3.7 (m), 3.80 (s), 4.04 (m), 6.7-6.9 (m)
I-14	1.24	534	CD ₃ OD	0.9 (m), 1.22 (t), 1.4-1.9 (m), 2.02 (m), 2.42 (m), 2.60 (m), 3.02 (m), 3.36 (s), 3.56 (m), 3.60 (t), 3.70 (m), 3.80 (s), 4.04 (t), 6.7-6.9 (m)
I-15	1.24	534	CD ₃ OD	0.9 (m), 1.20 (m), 1.4-1.9 (m), 2.02 (m), 2.42 (m), 2.60 (m), 3.02 (m), 3.36 (s), 3.52 (m), 3.60 (mt), 3.74 (m), 4.04 (t), 6.7-6.9 (m)
I-16	1.24	534	CD ₃ OD	0.9 (m), 1.3-1.9 (m), 2.02 (m), 2.42 (m), 2.60 (m), 3.02 (m), 3.36 (s), 3.60 (t), 3.64 (m), 3.80 (s), 4.04 (t) 6.76 (d), 6.82 (s), 6.84 (d)
I-17	1.28	534	CD ₃ OD	0.9 (m), 1.36 (m), 1.6-1.8 (m), 2.02 (m), 2.42 (m), 2.60 (m), 3.02 (m), 3.36 (s), 3.60 (t), 3.62 (m), 3.80 (s), 4.04 (t), 6.7-6.9 (m)
I-18	1.29	534	CD ₃ OD	0.9 (m), 1.40 (m), 1.6-1.8 (m), 2.02 (m), 2.40 (m), 2.64 (m), 2.84 (m), 3.20 (s), 3.36 (s), 3.42 (m), 3.60 (t), 3.7 (m), 3.80 (s), 4.04 (t), 6.7-6.9 (m)
I-19	1.29	534	CD ₃ OD	0.9 (m), 1.38 (m), 1.4-1.8 (m), 2.02 (m), 2.40 (m), 2.62 (m), 2.96 (m), 3.22 (m), 3.36 (s), 3.46 (m), 3.60 (t), 3.70 (m), 3.80 (s), 4.06 (t), 6.7-6.9 (m)
I-20	1.26	534	CD ₃ OD	0.9 (m), 1.3-1.9 (m), 2.02 (m), 2.40 (m), 2.62 (m), 2.96 (m), 3.36 (s), 3.54 (m), 3.60 (t), 3.70 (m), 3.80 (s), 4.04 (t), 4.36 (m), 6.7-6.9 (m)
I-21	1.28	534	CD ₃ OD	0.95(m,6H),2.94(s,3H),3.58(m,2H),4.05(m,2H)
I-22	1.21	546	CD ₃ OD	0.9 (m), 1.6-1.8 (m), 2.02 (m), 2.40 (m), 2.60 (m), 3.02 (m), 3.36 (s), 3.52 (m), 3.60 (t), 3.78 (m), 3.80 (s), 4.04 (t), 6.7-6.9 (m)
I-23		547	CD ₃ OD	0.9 (m), 1.32 (m), 1.40 (s), 1.5-1.8 (m), 2.02 (m), 2.40 (m), 2.60 (m), 3.02 (m), 3.36 (s), 3.60 (t), 3.70 (m), 3.80 (t), 4.06 (t), 6.7-6.9 (m)
I-24	1.30	548	CD ₃ OD	0.9 (m), 1.2-1.9 (m), 2.02 (m), 2.40 (m), 2.60 (m), 3.04 (m), 3.36 (s), 3.60 (t), 3.70 (m), 3.80 (s), 4.04 (t), 4.16 (m), 6.7-6.9 (m)
I-25	1.34	548	CD ₃ OD	0.9 (m), 1.38 (m), 1.6-1.8 (m), 2.02 (m), 2.40 (m), 2.60 (m), 2.96 (m), 3.36 (s), 3.60 (t), 3.64 (m), 3.80 (s), 4.04 (t), 6.7-6.9 (m)
I-26	1.36	548	CD ₃ OD	0.9 (m), 1.38 (m), 1.6-1.8 (m), 2.02 (m), 2.40 (m), 2.60 (m), 2.92 (m), 3.20 (m), 3.36 (s), 3.40 (m), 3.60 (t), 3.62 (m), 3.80 (s), 4.06 (t), 6.7-6.9 (m)
I-27	1.36	548	CD ₃ OD	0.9 (m), 1.3 (m), 1.40 (s), 1.6-1.8 (m), 2.44 (m), 2.56 (m), 3.06 (m), 3.34 (s), 3.58 (t), 3.7 (m), 3.80 (s), 4.06 (t), 6.76 (d), 6.84 (m)
I-28	1.36	548	CD ₃ OD	0.9 (m), 1.40 (s), 1.72 (m), 2.02 (m), 2.40 (m), 2.60 (m), 3.04 (m), 3.34 (s), 3.58 (t), 3.80 (s), 4.04 (t), 6.72 (m), 6.80 (s), 6.84 (d)
I-29	1.34	548	CD ₃ OD	0.9 (m), 1.3-1.9 (m), 2.02 (m), 2.40 (m), 2.60 (m), 2.94 (m), 3.36
I-30	1.35	548	CD ₃ OD	
I-31	1.36	548	CD ₃ OD	
I-32	1.28	554	CD ₃ OD	

				(s), 3.54 (m), 3.60 (t), 3.64 (m), 3.80 (s), 4.04 (t), 6.7-6.9 (m), 7.36 (m)
I-33	1.32	556	CD ₃ OD	0.9 (m), 1.40 (m), 1.6-1.9 (m), 2.02 (m), 2.40 (m), 2.62 (m), 2.94 (m), 3.36 (s), 3.42 (t), 3.60 (t), 3.7 (m), 3.80 (s), 4.06 (t), 6.7-6.9 (m)
I-34	1.37	560	CD ₃ OD	0.9 (m), 1.2-1.8 (m), 2.02 (m), 2.40 (m), 2.60 (m), 2.98 (m), 3.36 (s), 3.52 (m), 3.60 (t), 3.7 (m), 3.80 (s), 4.04 (t), 6.7-6.9 (m)
I-35	1.32	560	CD ₃ OD	0.9 (m), 1.3-1.8 (m), 2.02 (m), 2.40 (m), 2.60 (m), 3.0 (m), 3.36 (s), 3.60 (t), 3.80 (s), 4.06 (t), 6.7-6.9 (m)
I-36	1.48	562	CD ₃ OD	0.9 (m), 1.2-1.4 (m), 1.6-1.8 (m), 2.02 (m), 2.40 (m), 2.60 (m), 2.98 (m), 3.36 (s), 3.60 (t), 3.76 (t), 3.80 (s), 4.06 (t), 6.7-6.9 (m)
I-37	1.44	562	CD ₃ OD	0.9 (m), 1.24 (m), 1.30 (m), 1.5-1.8 (m), 2.02 (m), 2.40 (m), 2.60 (m), 2.98 (m), 3.36 (s), 3.60 (t), 3.70 (m), 3.80 (s), 4.04 (t), 4.16 (m), 6.7-6.9 (m)
I-38	1.41	562	CD ₃ OD	0.9 (m), 1.30 (m), 1.40 (s), 1.6-1.8 (m), 2.02 (m), 2.40 (m), 2.60 (m), 3.0 (m), 3.36 (s), 3.60 (t), 3.80 (s), 4.06 (t), 6.7-6.9 (m)
I-39	1.41	562	CD ₃ OD	0.92 (m), 1.42 (s), 2.02 (m), 3.20 (s), 3.36 (s), 3.60 (t), 3.80 (s), 4.06 (t), 6.7-6.9 (m)
I-40	1.06	563	CD ₃ OD	0.9 (m), 1.22 (s), 1.4-1.9 (m), 2.02 (m), 2.40 (m), 2.60 (m), 2.98 (m), 3.36 (s), 3.60 (t), 3.64 (m), 3.76 (m), 3.80 (s), 4.04 (m), 6.74 (d), 6.80 (s), 6.84 (d)
I-41	1.26	568	CD ₃ OD	0.9 (m), 1.3-1.9 (m), 2.02 (m), 2.42 (m), 2.60 (m), 2.93 (m), 3.36 (s), 3.58 (t), 3.80 (s), 3.86 (m), 4.06 (t), 6.7-6.9 (m), 7.24 (m)
I-42	1.38	570	CD ₃ OD	0.9 (m), 1.38 (m), 1.6-1.9 (m), 2.02 (m), 2.42 (m), 2.64 (m), 2.96 (m), 3.36 (s), 3.40 (t), 3.58 (m), 3.60 (t), 3.7 (m), 3.80 (s), 4.06 (t), 6.7-6.9 (m)
I-43	1.45	574	CD ₃ OD	0.9 (m), 1.2-1.8 (m), 2.02 (m), 2.40 (m), 2.60 (m), 3.02 (m), 3.36 (s), 3.60 (t), 3.80 (s), 4.06 (t), 6.7-6.9 (m)
I-44	1.53	576	CD ₃ OD	0.9 (m), 1.2-1.8 (m), 2.02 (m), 2.40 (m), 2.60 (m), 3.04 (m), 3.36 (s), 3.60 (t), 3.7 (m), 3.80 (s), 4.04 (t), 4.16 (m), 6.7-6.9 (m)
I-45	1.44	576	CD ₃ OD	0.94 (d), 0.96 (ds), 1.46 (s), 1.6-1.9 (m), 2.02 (m), 2.42 (m), 2.32 (m), 3.06 (m), 3.36 (s), 3.60 (t), 3.70 (m), 3.80 (s), 4.04 (t), 6.7-6.9 (m)
I-46	1.49	576	CD ₃ OD	0.94 (m), 1.26 (m), 1.42 (s), 1.62 (m), 2.02 (m), 2.40 (m), 2.60 (m), 3.00 (m), 3.20 (s), 3.34 (m), 3.60 (t), 3.80 (s), 4.06 (t), 6.76 (d), 6.80 (s), 6.84 (d)
I-47	1.38	580	CD ₃ OD	0.9 (m), 1.3-1.9 (m), 2.02 (m), 2.40 (m), 2.62 (m), 2.88 (m), 3.36 (s), 3.60 (t), 3.7 (m), 3.80 (s), 4.06 (t), 6.7-6.9 (m), 7.2-7.4 (m)
I-48	1.32	580	CD ₃ OD	7.13-7.02 (m, 4H), 6.75-6.60 (m, 3H), 3.93 (t, J = 6.0 Hz, 2H), 3.67 (s, 3H), 3.62-3.38 (m, 5H), 3.22 (s, 3H), 3.26-3.16 (m, 2H), 2.92-2.79 (m, 3H), 2.54-2.44 (m, 1H), 2.32-2.25 (m, 1H), 1.90 (p, J = 6.3 Hz, 2H), 1.80-1.25 (m, 5H), 0.86-0.76 (m, 6H)
I-49	1.36	582	CD ₃ OD	0.9 (m), 1.3-2.0 (m), 2.02 (m), 2.42 (m), 2.60 (m), 2.66 (t), 3.02 (m), 3.36 (s), 3.60 (t), 3.7 (m), 3.80 (s), 4.04 (t), 6.7-6.9 (m), 7.1-7.3 (m)
I-50	1.35	582	CD ₃ OD	0.9 (m), 1.3-1.8 (m), 2.02 (m), 2.40 (m), 2.64 (m), 2.82 (m), 2.94 (t), 3.20 (s), 3.36 (s), 3.38 (m), 3.60 (t), 3.7 (m), 3.80 (s), 3.84 (m), 4.04 (t), 6.7-6.9 (m), 7.20 (m), 7.24 (m)
I-51	1.33	582	CD ₃ OD	0.9 (m), 1.4-1.8 (m), 2.02 (m), 2.40 (m), 2.62 (m), 2.88 (m), 2.94 (t), 3.22 (m), 3.36 (s), 3.60 (t), 3.70 (m), 3.80 (s), 4.04 (t), 6.7-6.9 (m), 7.20 (m), 7.24 (m)
I-52	1.37	582	CD ₃ OD	0.9 (m), 1.4-1.9 (m), 2.02 (m), 2.26 (s), 2.40 (m), 2.60 (m), 2.84 (t), 2.96 (m), 3.36 (s), 3.54 (m), 3.60 (t), 3.64 (m), 3.80 (s), 3.84 (m), 4.06 (t), 6.7-6.9 (m), 7.10 (m)
I-53	1.10	591	CD ₃ OD	0.9 (m), 1.4-1.9 (m), 1.98 (s), 2.02 (m), 2.40 (m), 2.60 (m), 3.02 (m), 3.36 (s), 3.40 (m), 3.60 (t), 3.66 (m), 3.80 (s), 4.06 (t), 6.7-6.9 (m)
I-54		594	CD ₃ OD	0.95(m,6H),3.58(m,2H),4.05(m,2H),7.25(m,1H),7.32(m,4H)
I-55	1.41	596	CD ₃ OD	0.9 (m), 1.4-1.9 (m), 2.02 (m), 2.42 (m), 2.60 (mt), 3.02 (m), 3.36 (s), 3.60 (t), 3.7 (m), 3.80 (s), 4.04 (t), 6.7-6.9 (m), 7.1-7.3 (m)
I-56	1.44	596	CD ₃ OD	0.9 (m), 1.4-1.9 (m), 2.02 (m), 2.22 (s), 2.28 (s), 2.40 (m), 2.60 (m), 2.88 (t), 2.98 (m), 3.36 (s), 3.54 (m), 3.60 (t), 3.64 (m), 3.80 (s), 3.82 (m), 4.06 (t), 6.7-7.1 (m)
I-57	1.36	602	CD ₃ OD	0.9 (m), 1.3-1.9 (m), 2.02 (m), 2.42 (m), 2.60 (m), 2.98 (m), 3.06 (t), 3.36 (s), 3.60 (t), 3.7 (m), 3.80 (s), 3.88 (m), 4.06 (t), 6.7-6.9 (m), 7.22 (m), 7.36 (m)
I-58	1.40	602	CD ₃ OD	0.9 (m), 1.3-1.9 (m), 2.02 (m), 2.42 (m), 2.60 (m), 2.94 (t), 2.98

				(m), 3.36 (s), 3.60 (t), 3.7 (m), 3.80 (s), 3.86 (m), 4.06 (t), 6.7-6.9 (m), 7.2-7.3 (m)
I-59	1.40	603	CD ₃ OD	0.9 (m), 1.60 (m), 1.7 (m), 2.02 (m), 2.40 (m), 2.60 (m), 2.88 (t), 2.94 (m), 3.36 (s), 3.60 (t), 3.80 (s), 3.84 (m), 4.06 (t), 6.7-6.9 (m), 7.24 (m)
I-60	1.36	604	CD ₃ OD	0.9 (m), 1.4-1.9 (m), 2.02 (m), 2.42 (m), 2.64 (m), 2.84 (m), 2.98 (t), 3.36 (s), 3.58 (m), 3.60 (t), 3.68 (m), 3.80 (s), 4.06 (t), 6.7-6.9 (m), 7.2-7.3 (m)
I-61		608	CD ₃ OD	0.95(m,6H),3.58(t,2H),4.05(m,2H),7.21(m,3H),7.29(m,2H)
I-62	1.30	613	CD ₃ OD	0.9 (m), 1.40 (m), 1.60 (m), 1.7 (m), 2.02 (m), 2.40 (m), 2.60 (m), 2.96 (m), 3.04 (t), 3.36 (s), 3.52 (m), 3.60 (t), 3.64 (m), 3.80 (s), 3.96 (m), 4.06 (t), 6.7-6.9 (m), 7.48 (m), 8.18(m)
I-63		622	CD ₃ OD	0.94(m,6H),3.58(t,2H),4.05(m,2H),7.18(m,3H),7.26(m,2H)
I-64	1.29	628	CD ₃ OD	0.9 (m), 1.4-1.9 (m), 2.02 (m), 2.40 (m), 2.60 (m), 2.88 (t), 2.92 (m), 3.36 (s), 3.60 (t), 3.72 (s), 3.78 (s), 3.80 (s), 3.82 (m), 4.04 (t), 6.7-7.0 (m)
I-65	1.30	628	CD ₃ OD	0.9 (m), 1.4-1.9 (m), 2.02 (m), 2.40 (m), 2.60 (m), 2.96 (m), 3.36 (s), 3.60 (t), 3.62 (m), 3.80 (m), 4.04 (t), 6.7-7.0 (m)
I-66	1.37	646	CD ₃ OD	6.76-6.61 (m, 3H), 4.35 (t, <i>J</i> = 15.6 Hz, 2H), 3.92 (t, <i>J</i> = 6.0 Hz, 2H), 3.67 (s, 3H), 3.62-3.49 (m, 2H), 3.46 (t, <i>J</i> = 6.2 Hz, 2H), 3.43-3.39 (m, 1H), 3.22 (s, 3H), 2.85-2.80 (m, 1H), 2.57-2.46 (m, 1H), 2.32-2.25 (m, 1H), 1.90 (p, <i>J</i> = 6.2 Hz, 2H), 1.73-1.47 (m, 5H), 0.87-0.76 (m, 6H)
I-67	1.03	654	CD ₃ OD	0.9 (m), 1.3-1.9 (m), 2.02 (m), 2.5 (m), 3.02 (m), 3.18 (m), 3.36 (s), 3.60 (t), 3.80 (s), 3.98 (m), 4.04 (t), 4.46 (m), 4.78 (m), 6.7-6.9 (m), 8.14 (m), 8.90 (m), 9.22 (m)

EXAMPLE 15

IN VITRO ACTIVITY STUDIES – IC₅₀ VALUES FOR RENIN INHIBITION

The action of renin inhibitors was demonstrated experimentally by means of an *in vitro* test which measures the increase in fluorescence of an internally quenched peptide substrate. The sequence of this peptide corresponds to the sequence of human angiotensinogen. The following test protocol was used:

All reactions were carried out in a flat bottom white opaque microtiter plate. A 4 µL aliquot of 400 µM renin substrate (DABCYL-γ-Abu-Ile-His-Pro-Phe-His-Leu-Val-Ile-His-Thr-EDANS) in 192 µL assay buffer (50 mM BES, 150 mM NaCl, 0.25 mg/mL bovine serum albumin, pH7.0) was added to 4 µL of test compound in DMSO at various concentrations ranging from 10 µM to 1 nM final concentrations. Next, 100 µL of trypsin-activated recombinant human renin (final enzyme concentration of 0.2-2 nM) in assay buffer was added, and the solution was mixed by pipetting. The increase in fluorescence at 495 nm (excitation at 340 nm) was measured for 60-360 minutes at room temperature using a Perkin-Elmer Fusion microplate reader. The slope of a linear portion of the plot of fluorescence increase as a function of time was then determined, and the rate was used for calculating percent inhibition in relation to uninhibited control. The percent inhibition values were plotted as a function of inhibitor concentration, and the IC₅₀ was determined from a fit of this data to a four parameter equation. The IC₅₀ was defined as the concentration of a particular inhibitor that reduces the formation of product by 50% relative to a control sample containing no inhibitor.

In the *in vitro* systems the compounds of the invention exhibited inhibiting activities at minimum concentrations of from approximately 5×10^{-5} M to approximately 10^{-12} M.

Preferred compounds of the invention exhibited inhibiting activities at minimum concentrations of from approximately 5×10^{-8} M to approximately 10^{-12} M. (Wang G. T. et al. *Anal. Biochem.* **1993**, *210*, 351; Nakamura, N. et al. *J. Biochem. (Tokyo)* **1991**, *109*, 741; Murakami, K. et al. *Anal Biochem.* **1981**, *110*, 232).

EXAMPLE 16

INHIBITION IN HUMAN PLASMA

The action of renin inhibitors *in vitro* in human plasma can also be demonstrated experimentally by the decrease in plasma renin activity (PRA) levels observed in the presence of the compounds. Incubations mixtures contain in the final volume of 250 μ L 95.5 mM N,N-bis(2-hydroxyethyl)-2-aminoethanesulfonic acid, pH 7.0, 8 mM EDTA, 0.1 mM neomycin sulfate, 1 mg/mL sodium azide, 1 mM phenylmethanesulfonyl fluoride, 2% DMSO and 87.3% of pooled mixed-gender human plasma stabilized with EDTA. For plasma batches with low PRA (less than 1 ng/ml/hr) ~ 2 pM of recombinant human renin is added to achieve PRA of 3-4 ng/ml/hr. The cleavage of endogenous angiotensinogen in plasma is carried out at 37°C for 90 min and the product angiotensin I is measured by competitive radioimmunoassay using DiaSorin PRA kit. Uninhibited incubations containing 2% DMSO and fully inhibited controls with 2 μ M of isovaleryl-Phe-Nle-Sta-Ala-Sta-OH are then used for deriving percent of inhibition for each concentration of inhibitors and fitting dose-response data into a four parametric model from which IC_{50} values, defined as concentrations of inhibitors at which 50% inhibition occurs, are determined.

EXAMPLE 17

IN VIVO ACTIVITY

The cardiac and systemic hemodynamic efficacy of selective renin inhibitors can be evaluated *in vivo* in sodium-depleted, normotensive cynomolgus monkeys and in sodium-depleted, normotensive beagle dogs following a single oral and intravenous administration of the test compound. Arterial blood pressure is monitored by telemetry in freely moving, conscious animals.

Cynomolgus Monkey: Six male naïve cynomolgus monkeys weighing between 2.5 and 3.5 kg can be used in the studies. At least 4 weeks before the experiment, the monkeys are anesthetized with ketamine hydrochloride (15 mg/kg, i.m.) and xylazine hydrochloride (0.7 mg/kg, i.m.), and are implanted into the abdominal cavity with a transmitter (Model #TL11M2-D70-PCT, Data Sciences, St. Paul, MN). The pressure catheter is inserted into

the lower abdominal aorta *via* the femoral artery. The bipotential leads are placed in Lead II configuration. The animals are housed under constant temperature (19-25°C), humidity (>40%) and lighting conditions (12 h light and dark cycle), are fed once daily, and are allowed free access to water. The animals are sodium depleted by placing them on a low sodium diet (0.026%, Expanded Primate Diet 829552 MP-VENaCl (P), Special Diet Services, Ltd., UK) 7 days before the experiment and furosemide (3 mg/kg, intramuscularly i.m., Aventis Pharmaceuticals) is administered at -40 h and -16 h prior to administration of test compound.

For oral dosing, the renin inhibitors are formulated in 0.5% methylcellulose at dose levels of 10 and 30 mg/kg (5 mL/kg) by infant feeding tubes. For intravenous delivery, a silastic catheter is implanted into posterior vena cava *via* a femoral vein. The catheter is attached to the delivery pump *via* a tether system and a swivel joint. Test compound (dose levels of 0.1 to 10 mg/kg, formulated at 5% dextrose) is administered by continuous infusion (1.67 mL/kg/h) or by bolus injection (3.33 mL/kg in 2 min).

Arterial blood pressures (systolic, diastolic and mean) and body temperature are recorded continuously at 500 Hz and 50 Hz, respectively, using the Dataquest™ A.R.T. (Advanced Research Technology) software. Heart rate is derived from the phasic blood pressure tracing. During the recording period, the monkeys are kept in a separate room without human presence to avoid pressure changes secondary to stress. All data are expressed as mean $\pm$ SEM. Effects of the renin inhibitors on blood pressure are assessed by ANOVA, taking into account the factors dose and time compared with the vehicle group.

Beagle Dogs: Non-naive Beagle dogs (2 per sex) weighing between 9 and 11 kg can be used in the studies. Each animal is implanted subcutaneously with a telemetry transmitter (Data Sciences) and the blood pressure catheter is inserted into the left femoral artery. The electrocardiogram leads are also tunneled subcutaneously to the appropriate anatomical regions. The animals are housed under constant temperature and lighting conditions, are fed once daily, and are allowed free access to water. A sodium depleted state is produced by placing them on a low-sodium diet (<4 meq/day, a combination of canned Prescription Diet canine h/d, from Hill's Pet Products and dry pellets from Bio-Serv Inc., Frenchtown, NJ) beginning 10 days before the experiment, and furosemide (3 mg/kg i.m.; Aventis Pharmaceuticals) is administered at -40 and -16 h prior to administration of test compound.

A renin inhibitor is orally administered by orogastric gavage to all overnight fasted animals at a dose level of 30 mg/kg (4 mL/kg formulated in 0.5% methylcellulose). Food is given 4 h postdose. In some experiments, the renin inhibitor is administered by bolus *i.v.* at

increasing dose levels of 1, 3 and 6 mg/kg (2, 6 and 20 mg/mL formulated in sterile saline). Cardiovascular parameters are collected continuously at least 80 min predose and 3 h postdose, followed by every 10 min for 5 h and every 30 min for 16 h postdose. The Dataquest™ ART (version 2.2) software package from DSI (Data Sciences International) is used to collect telemetered cardiovascular data.

EXAMPLE 18

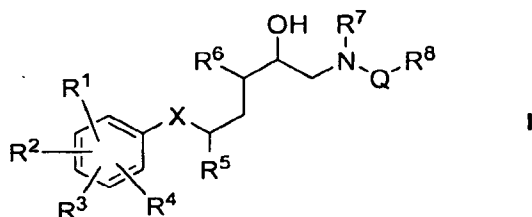
The efficacy of the renin inhibitors can also be evaluated *in vivo* in double transgenic rats engineered to express human renin and human angiotensinogen (Bohlender J, Fukamizu A, Lippoldt A, Nomura T, Dietz R, Menard J, Murakami K, Luft FC, Ganten D. High human renin hypertension in transgenic rats. *Hypertension* 1997, 29, 428–434).

Experiments are conducted in 6-week-old double transgenic rats (dTGRs). The model has been described in detail earlier. Briefly, the human renin construct used to generate transgenic animals made up the entire genomic human renin gene (10 exons and 9 introns), with 3.0 kB of the 5'-promoter region and 1.2 kB of 3' additional sequences. The human angiotensinogen construct made up the entire human angiotensinogen gene (5 exons and 4 introns), with 1.3 kB of 5'-flanking and 2.4 kB of 3'-flanking sequences. The rats can be purchased from RCC Ltd (Füllinsdorf, Switzerland). Radio telemetry transmitters can be surgically implanted at 4 weeks of age. The telemetry system provides 24-h recordings of systolic, mean, diastolic arterial pressure (SAP, MAP, DAP, respectively) and heart rate (HR). Beginning on day 42, animals are transferred to telemetry cages. A 24 h telemetry reading is obtained. Rats are then dosed orally on the following 4 consecutive days (days 43–46). The rats are monitored continuously and allowed free access to standard 0.3%-sodium rat chow and drinking water.

While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

WHAT IS CLAIMED IS

1. A compound of formula I



wherein

- 5 R¹ is hydrogen, halogen, cyano, carbamoyl, lower alkyl, lower haloalkyl, cycloalkyl, hydroxy, lower alkoxy, cycloalkoxy, lower alkoxy-lower alkoxy, lower alkylthio-lower alkoxy, cyano-lower alkoxy, hydroxy-lower alkoxy, carboxy-lower alkoxy, lower alkoxycarbonyl-lower alkoxy, carbamoyl-lower alkoxy, N-mono- or N,N-di-lower alkylcarbamoyl-lower alkoxy, or aryl;
- 10 R² is 1) hydrogen or 2) (C₁-C₁₂)alkyl, (C₂-C₁₂)alkenyl, (C₂-C₁₂)alkynyl, (C₁-C₁₂)alkoxy, (C₁-C₁₂)alkylthio, (C₁-C₁₂)alkylamino, oxo(C₁-C₁₂)alkyl, oxo(C₂-C₁₂)alkenyl, oxo(C₂-C₁₂)alkynyl, oxo(C₁-C₁₂)alkoxy, oxo(C₁-C₁₂)alkylthio, oxo(C₁-C₁₂)alkylamino, (C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₁-C₆)alkylthio(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, (C₁-C₆)alkoxy(C₁-C₆)alkoxy, (C₁-C₆)alkoxy(C₁-C₆)alkylthio, (C₁-C₆)alkoxy(C₁-C₆)alkylamino, (C₁-C₆)alkylthio(C₁-C₆)alkoxy, (C₁-C₆)alkylthio(C₁-C₆)alkylamino, (C₁-C₆)alkylthio(C₁-C₆)alkylthio, (C₁-C₆)alkylamino(C₁-C₆)alkoxy, (C₁-C₆)alkylamino(C₁-C₆)alkylthio, (C₁-C₆)alkylamino(C₁-C₆)alkylamino, (C₁-C₄)alkoxy(C₁-C₄)alkoxy(C₁-C₄)alkyl, aminocarbonylamino(C₁-C₁₂)alkyl, aminocarbonylamino(C₁-C₁₂)alkoxy, aminocarbonylamino(C₁-C₁₂)alkylthio,
- 20 aminocarbonylamino(C₁-C₁₂)alkylamino, (C₁-C₆)-alkanoylamino(C₁-C₆)alkyl, (C₁-C₆)alkanoylamino(C₁-C₆)alkoxy, (C₁-C₆)alkanoylamino(C₁-C₆)alkylthio, (C₁-C₆)alkanoylamino(C₁-C₆)alkylamino, (C₁-C₆)alkoxycarbonyl(C₁-C₆)alkyl, (C₁-C₆)alkoxycarbonyl(C₁-C₆)alkoxy, (C₁-C₆)alkoxycarbonyl(C₁-C₆)alkylthio, (C₁-C₆)alkoxycarbonyl-(C₁-C₆)alkylamino, (C₁-C₆)acyloxy(C₁-C₆)alkyl, (C₁-C₆)acyloxy(C₁-C₆)alkoxy, (C₁-C₆)acyloxy(C₁-C₆)alkylthio, (C₁-C₆)acyloxy(C₁-C₆)alkylamino,
- 25 aminosulfonylamino(C₁-C₁₂)alkyl, aminosulfonylamino(C₁-C₁₂)alkoxy, aminosulfonylamino(C₁-C₁₂)alkylthio, aminosulfonylamino(C₁-C₁₂)alkylamino, (C₁-C₆)alkanesulfonylamino(C₁-C₆)alkyl, (C₁-C₆)alkanesulfonylamino(C₁-C₆)alkoxy, (C₁-C₆)alkanesulfonylamino(C₁-C₆)alkylthio, (C₁-C₆)-alkanesulfonylamino(C₁-C₆)alkylamino,
- 30 formylamino(C₁-C₆)alkyl, formylamino(C₁-C₆)alkoxy, formylamino(C₁-C₆)alkylthio, formylamino(C₁-C₆)alkylamino, (C₁-C₆)alkoxycarbonylamino(C₁-C₆)alkyl, (C₁-C₆)alkoxycarbonylamino(C₁-C₆)alkoxy, (C₁-C₆)alkoxycarbonylamino(C₁-C₆)alkylthio, (C₁-C₆)alkoxycarbonylamino(C₁-C₆)alkylamino, (C₁-C₆)alkylaminocarbonyl-amino(C₁-C₆)alkyl,

(C₁-C₆)alkylaminocarbonylamino(C₁-C₆)alkoxy, (C₁-C₆)alkylaminocarbonyl-amino(C₁-C₆)alkylthio, (C₁-C₆)alkylaminocarbonylamino(C₁-C₆)alkylamino, aminocarbonyl(C₁-C₆)alkyl, aminocarbonyl(C₁-C₆)alkoxy, aminocarbonyl(C₁-C₆)alkylthio, aminocarbonyl(C₁-C₆)alkylamino, (C₁-C₆)alkylaminocarbonyl(C₁-C₆)alkyl, (C₁-C₆)alkylaminocarbonyl(C₁-C₆)alkoxy, (C₁-C₆)alkyl-aminocarbonyl(C₁-C₆)alkylthio, (C₁-C₆)alkylaminocarbonyl(C₁-C₆)alkylamino, aminocarboxy(C₁-C₆)alkyl, aminocarboxy(C₁-C₆)alkoxy, aminocarboxy(C₁-C₆)alkylthio, aminocarboxy(C₁-C₆)-alkylamino, (C₁-C₆)alkylaminocarboxy(C₁-C₆)alkyl, (C₁-C₆)alkylaminocarboxy(C₁-C₆)alkoxy, (C₁-C₆)alkylaminocarboxy(C₁-C₆)alkylthio, (C₁-C₆)alkylaminocarboxy(C₁-C₆)alkylamino, (C₁-C₁₂)alkoxycarbonylamino, (C₁-C₁₂)-alkylaminocarbonylamino, or (C₁-C₁₂)alkanoylamino,

wherein (1) hydrogen atoms in these groups are optionally substituted by (a) 1 to 5 halogen atoms and (b) by 1 group selected from cyano, hydroxyl, (C₁-C₃)alkyl, (C₁-C₃)alkoxy, (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkoxy, halo(C₁-C₃)alkyl, halo(C₁-C₃)alkoxy, halo(C₃-C₆)cycloalkyl, and halo(C₃-C₆)cycloalkoxy; and

(2) divalent sulfur atoms are optionally oxidized to sulfoxide or sulfone, and

(3) a carbonyl group is optionally replaced by a thiocarbonyl group,

R³ is hydrogen, halogen, cyano, carbamoyl, lower alkyl, lower haloalkyl, lower alkoxy-lower alkyl, cycloalkoxy-lower alkyl, hydroxy-lower alkyl, lower alkylthio-lower alkyl, lower alkanesulfonyl-lower alkyl, optionally partially hydrogenated or N-oxidized pyridyl-lower alkyl, thiazolyl-thio-lower alkyl or thiazolylthio-lower alkyl, imidazolylthio-lower alkyl, optionally N-oxidized pyridylthio-lower alkyl, pyrimidinylthio-lower alkyl, amino-lower alkyl, lower alkylamino-lower alkyl, di-lower alkylamino-lower alkyl, lower alkanoyl-amino-lower alkyl, lower alkanesulfonylamino-lower alkyl, polyhalo-lower alkane-sulfonylamino-lower alkyl, pyrrolidino-lower alkyl, piperidino-lower alkyl, piperazino-lower alkyl, N'-lower alkylpiperazino-lower alkyl or N'-lower alkanoylpiperazino-lower alkyl, morpholino-lower alkyl, thiomorpholino-lower alkyl, S-oxothiomorpholino-lower alkyl or S,S-dioxothio-morpholino-lower alkyl, cyano-lower alkyl, carboxy-lower alkyl, lower alkoxy-carbonyl-lower alkyl, carbamoyl-lower alkyl, N-mono- or N,N-di-lower alkyl-carbamoyl-lower alkyl, cycloalkyl; phenyl or naphthyl that is unsubstituted or substituted with one to three groups independently selected from lower alkyl, lower alkoxy, hydroxy, lower alkylamino, di-lower alkylamino, halogen, trifluoromethyl, trifluoromethoxy, and cyano; hydroxy, lower alkoxy, cycloalkoxy, lower alkoxy-lower alkoxy, cycloalkoxy-lower alkoxy, hydroxy-lower alkoxy, aryl, lower haloalkoxy, lower alkylthio-lower alkoxy, lower haloalkylthio-lower alkoxy, lower alkanesulfonyl-lower alkoxy, lower haloalkanesulfonyl-lower alkoxy, optionally hydrogenated heteroaryl-lower alkoxy, heterocyclyl-lower alkoxy, optionally partially or fully hydrogenated heteroarylthio-lower alkoxy, imidazolylthio-lower alkoxy, optionally N-oxidized

pyridylthio-lower alkoxy, pyrimidinylthio-lower alkoxy, amino-lower alkoxy, lower
alkylamino-lower alkoxy, di-lower alkylamino-lower alkoxy, lower alkanoylamino-lower
alkoxy, lower alkanesulfonylamino-lower alkoxy, polyhalo-lower alkanesulfonylamino-lower
alkoxy, pyrrolidino-lower alkoxy, piperidino-lower alkoxy, piperazino-lower alkoxy, N'-
5 lower alkylpiperazino-lower alkoxy or N'-lower alkanoylpiperazino-lower alkoxy, morpholino-
lower alkoxy, thiomorpholino-lower alkoxy, S-oxothiomorpholino-lower alkoxy or S,S-
dioxothiomorpholino-lower alkoxy, cyano-lower alkoxy, carboxy-lower alkoxy, lower
alkoxycarbonyl-lower alkoxy, carbamoyl-lower alkoxy, N-mono- or N,N-di-lower
alkylcarbamoyl-lower alkoxy, carboxy-lower alkyl, lower alkoxycarbonyl-lower alkyl,
10 carbamoyl-lower alkyl, or N-mono- or N,N-di-lower alkylcarbamoyl-lower alkyl; or

R² and R³ taken together with the atoms through which they are attached form a fused
dioxolane, dioxane, benzene, or cyclohexene ring, wherein said ring is substituted with up to
2 substituents independently selected from lower alkyl and lower alkoxy-lower alkyl;

R⁴ is hydrogen, lower alkyl, hydroxy, lower alkoxy, cycloalkoxy, lower alkoxy-lower alkoxy, or
cycloalkyl-lower alkoxy; or

R³ and R⁴ taken together with the atoms through which they are attached form a fused
dioxolane, dioxane, benzene, or cyclohexene ring, wherein said ring is substituted with up to
2 substituents independently selected from lower alkyl and lower alkoxy-lower alkyl; provided
that R³ does not form a ring with R²;

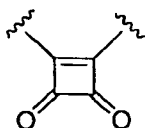
X is methylene or hydroxymethylene;

R⁵ is lower alkyl, lower haloalkyl, cycloalkyl, halocycloalkyl, lower alkyl-cycloalkyl, lower
haloalkyl-cycloalkyl, cycloalkyl-lower alkyl, aryl, aryl-lower alkyl, heterocyclyl, or heterocyclyl-
lower alkyl;

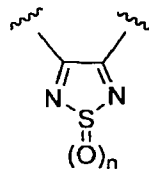
R⁶ is amino, lower alkylamino, di-lower alkylamino, or lower alkanoylamino;

R⁷ is hydrogen, lower alkyl, lower haloalkyl, cycloalkyl, lower alkoxy-lower alkyl, or lower
haloalkoxy-lower alkyl;

Q is a group of formula Q1 or Q2, wherein n = 0, 1 or 2;



Q1



Q2

R^8 is lower alkyl, lower haloalkyl, (C_8-C_{15}) alkyl, (C_8-C_{15}) haloalkyl, cycloalkyl, halocycloalkyl, lower alkyl-cycloalkyl, cycloalkyl-lower alkyl, halocycloalkyl-lower alkyl,
 5 lower alkoxy-loweralkyl, lower haloalkoxy-lower alkyl, cycloalkoxy-lower alkyl, cycloalkoxy-cycloalkyl, lower alkylthio-lower alkyl, lower haloalkylthio-lower alkyl, lower alkanesulfonyl-lower alkyl, lower haloalkanesulfonyl-lower alkyl, lower alkylthio-cycloalkyl, lower haloalkylthio-cycloalkyl, lower alkanesulfonyl-cycloalkyl, lower haloalkanesulfonyl-cycloalkyl, aryl, aryl-lower alkyl, aryl-lower hydroxyalkyl, arylcycloalkyl, aryloxy-lower alkyl,
 10 aryloxy cycloalkyl, arylthio-lower alkyl, arylsulfonyl-lower alkyl, arylthio-cycloalkyl, arylsulfonyl-cycloalkyl, or NR^9R^{10} ;

R^9 and R^{10} are independently selected from 1) hydrogen, lower alkyl, lower haloalkyl, (C_8-C_{15}) alkyl, (C_8-C_{15}) haloalkyl, cycloalkyl, halocycloalkyl, lower alkyl-cycloalkyl, lower
 15 haloalkyl-cycloalkyl, cycloalkyl-lower alkyl, halocycloalkyl-lower alkyl, lower alkoxy-loweralkyl, lower haloalkoxy-lower alkyl, cycloalkoxy-lower alkyl, cycloalkoxy-cycloalkyl, lower alkylthio-lower alkyl, lower haloalkylthio-lower alkyl, lower alkanesulfonyl-lower alkyl, lower haloalkanesulfonyl-lower alkyl, lower alkylthio-cycloalkyl, lower haloalkylthio-cycloalkyl, lower alkanesulfonyl-cycloalkyl, lower haloalkanesulfonyl-cycloalkyl,
 20 aminocarbonyl-lower alkyl, lower alkylaminocarbonyl-lower alkyl, di-lower alkylaminocarbonyl-lower alkyl, or lower acylamino-lower alkyl, or 2) aryl, aryl-lower alkyl, aryl-lower hydroxyalkyl, arylcycloalkyl, arene fused-cycloalkyl, aryloxy-lower alkyl, aryloxy cycloalkyl, arylthio-lower alkyl, arylsulfonyl-lower alkyl, arylthio-cycloalkyl, or arylsulfonyl-cycloalkyl

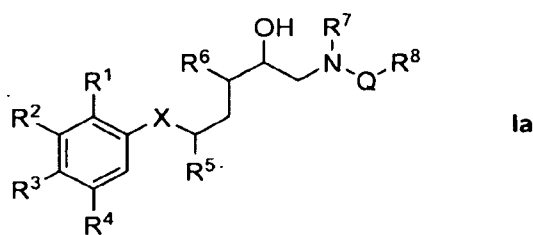
25 wherein the aryl groups are optionally substituted with up to four groups independently selected from halo, cyano, optionally halogenated lower alkyl, optionally halogenated lower alkoxy, optionally halogenated lower alkylthio, optionally halogenated lower alkanesulfonyl, morpholino, and lower alkoxy-carbonyl;

30 or R^9 and R^{10} taken together with the nitrogen to which they are attached form a 4-, 5-, 6- or 7-membered heterocyclic ring composed of carbon atoms and 0 or 1 hetero atoms in addition to the nitrogen atom to which R^9 and R^{10} are attached, said hetero atoms being

selected from 0 or 1 nitrogen atoms, 0 or 1 oxygen atoms, and 0 or 1 sulfur atoms, said ring atoms being substituted with the appropriate number of hydrogen atoms, said ring being optionally substituted with up to four groups independently selected from halogen, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl, aryl, aryl-lower alkyl and oxo, such that substitution of one oxo group on a carbon atom forms a carbonyl group and substitution of one or two oxo groups on sulfur forms a sulfoxide or a sulfone group respectively; wherein the aryl and arylalkyl groups are substituted with up to four groups independently selected from halo, cyano, optionally halogenated lower alkyl, optionally halogenated lower alkoxy, optionally halogenated lower alkylthio, optionally halogenated lower alkanesulfonyl, and lower alkoxycarbonyl;

or an enantiomer, diastereomer, or pharmaceutically acceptable salt thereof.

2. A compound of claim 1 of the formula Ia



or an enantiomer, diastereomer, or pharmaceutically acceptable salt thereof.

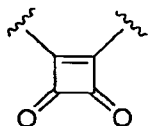
3. A compound of claim 2,

wherein

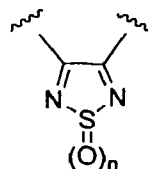
R¹ is hydrogen or aryl;

R² is hydrogen, (C₁-C₈)alkyl, (C₄-C₈)cycloalkylalkyl, fluoro(C₁-C₈)alkyl, fluoro(C₄-C₈)cycloalkylalkyl, (C₁-C₈)alkoxy, (C₄-C₈)cycloalkylalkoxy, fluoro(C₁-C₈)alkoxy, hydroxy(C₁-C₈)alkyl, (C₁-C₅)alkoxy(C₁-C₅)alkyl, halo(C₁-C₅)alkylamino(C₁-C₅)alkyl, (C₁-C₅)alkoxy(C₁-C₅)hydroxyalkyl, (C₃-C₄)cycloalkoxy(C₁-C₅)alkyl, fluoro(C₁-C₅)alkoxy(C₁-C₅)alkyl, fluoro(C₃-C₄)cycloalkoxy(C₁-C₅)alkyl, (C₁-C₅)alkylthio(C₁-C₅)alkyl, (C₁-C₅)alkoxy(C₁-C₅)alkoxy, hydroxy(C₁-C₈)alkoxy, (C₃-C₄)cycloalkoxy(C₁-C₅)alkoxy, fluoro(C₁-C₅)alkoxy(C₁-C₅)alkoxy, fluoro(C₃-C₄)cycloalkoxy(C₁-C₅)alkoxy, (C₁-C₃)alkoxy(C₁-C₃)alkoxy(C₁-C₃)alkyl, fluoro(C₁-C₃)alkoxy(C₁-C₃)alkoxy(C₁-C₃)alkyl, aminocarbonylamino(C₁-C₈)alkyl, aminocarbonylamino(C₁-C₈)alkoxy, (C₁-C₅)alkanoylamino(C₁-C₅)alkyl, (C₁-C₅)alkanoylamino(C₁-C₅)alkoxy, fluoro(C₁-C₅)alkanoyl-amino(C₁-C₅)alkyl, fluoro(C₁-C₅)alkanoylamino(C₁-C₅)alkoxy, (C₁-C₃)alkoxy(C₁-C₅)alkanoyl-amino(C₁-C₅)alkyl, (C₁-

- C₃)alkoxy(C₁-C₅)alkanoylamino(C₁-C₅)alkoxy, (C₃-C₄)cycloalkane-carbonyllamino(C₁-C₅)alkyl,
 (C₃-C₄)cycloalkanecarbonyllamino(C₁-C₅)alkoxy, aminosulfonylamino(C₁-C₈)alkyl,
 aminosulfonylamino(C₁-C₈)alkoxy, (C₁-C₅)alkanesulfonyl-amino(C₁-C₅)alkyl, (C₁-
 C₅)alkanesulfonylamino(C₁-C₅)alkoxy, formylamino(C₁-C₅)alkyl, formylamino(C₁-C₅)alkoxy,
 5 (C₁-C₅)alkoxycarbonylamino(C₁-C₅)alkyl, (C₁-C₅)alkoxycarbonyl-amino(C₁-C₅)alkoxy, (C₁-
 C₅)alkylaminocarbonylamino(C₁-C₅)alkyl, (C₁-C₅)alkylaminocarbonyl-amino(C₁-C₅)alkyl,
 di(C₁-C₅)alkylaminocarbonylamino(C₁-C₅)alkoxy, aminocarbonyl(C₁-C₅)alkyl,
 aminocarbonyl(C₁-C₅)alkoxy, (C₁-C₅)alkylaminocarbonyl(C₁-C₅)alkyl, (C₁-
 C₅)alkylaminocarbonyl-(C₁-C₅)alkoxy, aminocarboxy(C₁-C₅)alkyl, aminocarboxy(C₁-C₅)alkoxy,
 10 (C₁-C₅)alkylamino-carboxy(C₁-C₅)alkyl, (C₁-C₅)alkylaminocarboxy(C₁-C₅)alkoxy, (C₁-
 C₈)alkoxycarbonylamino, (C₁-C₈)alkylaminocarbonylamino, (C₁-C₈)alkanoylamino, fluoro(C₁-
 C₈)alkoxycarbonylamino, fluoro(C₁-C₈)alkylaminocarbonylamino, or fluoro(C₁-
 C₈)alkanoylamino;
- 15 R³ is hydrogen, halogen, cyano, lower alkyl, lower haloalkyl, aryl, hydroxy, lower alkoxy, or
 polyhalo-lower alkoxy; or
- R² and R³ taken together with the atoms through which they are attached form a fused
 dioxolane ring, wherein said ring is substituted with up to 2 substituents independently
 20 selected from lower alkyl and lower alkoxy-lower alkyl;
- R⁴ is hydrogen, lower alkoxy-lower alkoxy, lower alkoxy-lower alkyl, or cyloalkyl-lower alkoxy;
 or
- 25 R³ and R⁴ taken together with the atoms through which they are attached form a fused
 dioxolane ring, wherein said ring is substituted with up to 2 substituents independently
 selected from lower alkyl and lower alkoxy-lower alkyl; provided that R³ does not form a ring
 with R²;
- 30 X is methylene or hydroxymethylene;
- R⁵ is lower alkyl or cycloalkyl;
- R⁶ is amino, lower alkylamino, di-lower alkylamino, or lower alkanoylamino;
- 35 R⁷ is hydrogen or methyl;
- Q is a group of formula Q1, or formula Q2 wherein n = 2;



Q1



Q2

R^8 is lower alkyl, lower haloalkyl, (C_8-C_{15}) alkyl, (C_8-C_{15}) haloalkyl, cycloalkyl, halocycloalkyl, lower alkyl-cycloalkyl, cycloalkyl-lower alkyl, halocycloalkyl-lower alkyl, lower alkoxy-lower alkyl, lower haloalkoxy-lower alkyl, cycloalkoxy-lower alkyl, cycloalkoxy-cycloalkyl, aryl, aryl-lower alkyl, aryloxy-lower alkyl, or is NR^9R^{10} ;

R^9 is selected from 1) hydrogen, lower alkyl, lower haloalkyl, (C_8-C_{15}) alkyl, (C_8-C_{15}) haloalkyl, cycloalkyl, halocycloalkyl, lower alkyl-cycloalkyl, lower haloalkyl-cycloalkyl, cycloalkyl-lower alkyl, halocycloalkyl-lower alkyl, lower alkoxy-loweralkyl, lower haloalkoxy-lower alkyl, cycloalkoxy-lower alkyl, cycloalkoxy-cycloalkyl, lower alkylthio-lower alkyl, lower haloalkylthio-lower alkyl, lower alkanesulfonyl-lower alkyl, lower haloalkanesulfonyl-lower alkyl, lower alkylthio-cycloalkyl, lower haloalkylthio-cycloalkyl, lower alkanesulfonyl-cycloalkyl, lower haloalkanesulfonyl-cycloalkyl, aminocarbonyl-lower alkyl, lower alkylaminocarbonyl-lower alkyl, di-lower alkylaminocarbonyl-lower alkyl, or lower acylamino-lower alkyl, or 2) aryl, aryl-lower alkyl, arene fused-cycloalkyl, heteroaryl-lower alkyl, arylcycloalkyl, aryloxy-lower alkyl, aryloxy cycloalkyl, arylthio-lower alkyl, arylsulfonyl-lower alkyl, arylthio-cycloalkyl, or arylsulfonyl-cycloalkyl

wherein the aryl groups are optionally substituted with up to four groups

independently selected from halo, cyano, nitro, optionally halogenated lower alkyl, optionally halogenated lower alkoxy, optionally halogenated lower alkylthio, optionally halogenated lower alkanesulfonyl, morpholino, and lower alkoxycarbonyl;

R^{10} is selected from 1) hydrogen, lower alkyl, lower haloalkyl, C_8-C_{15} alkyl, C_8-C_{15} haloalkyl, cycloalkyl, halocycloalkyl, lower alkyl-cycloalkyl, cycloalkyl-lower alkyl, halocycloalkyl-lower alkyl, lower alkoxy-loweralkyl, or lower haloalkoxy-lower alkyl, or 2) aryl, aryl-lower alkyl, or aryloxy-lower alkyl, wherein the aryl and aryloxy groups are optionally substituted with up to four groups independently selected from halo, cyano, optionally halogenated lower alkyl, optionally halogenated lower alkoxy, optionally halogenated lower alkylthio, optionally halogenated lower alkanesulfonyl, and lower alkoxycarbonyl;

or R^9 and R^{10} taken together with the nitrogen to which they are attached form a 4-, 5-, 6- or 7-membered heterocyclic ring composed of carbon atoms and 0 or 1 hetero atom in addition

to the nitrogen atom to which R⁹ and R¹⁰ are attached, said hetero atom being selected from 0 or 1 nitrogen atoms, 0 or 1 oxygen atoms, and 0 or 1 sulfur atoms, said ring atoms being substituted with the appropriate number of hydrogen atoms, said ring being optionally substituted with up to four groups independently selected from halogen, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl, aryl, aryl-lower alkyl or oxo, such that substitution of one oxo group on a carbon atom forms a carbonyl group and substitution of one or two oxo groups on sulfur forms a sulfoxide or a sulfone group respectively; wherein the aryl and arylalkyl groups are substituted with up to four groups independently selected from halo, cyano, optionally halogenated lower alkyl, optionally halogenated lower alkoxy, optionally halogenated lower alkylthio, optionally halogenated lower alkanesulfonyl, and lower alkoxycarbonyl;

or an enantiomer, diastereomer, or pharmaceutically acceptable salt thereof.

4. A compound of claim 2,

wherein:

R¹ is hydrogen;

R² is (C₃-C₄)cycloalkyl(C₁-C₄)alkyl, fluoro(C₃-C₄)cycloalkyl(C₁-C₄)alkyl, (C₁-C₈)alkoxy, (C₃-C₄)cycloalkyl(C₁-C₄)alkoxy, hydroxy(C₁-C₈)alkyl, (C₁-C₄)alkoxy(C₁-C₄)alkoxy, (C₁-C₄)alkoxy-(C₁-C₄)alkyl, (C₁-C₄)alkoxy(C₁-C₄)hydroxyalkyl, (C₃-C₄)cycloalkoxy(C₁-C₄)alkyl, hydroxy(C₁-C₈)alkoxy, (C₃-C₄)cycloalkoxy(C₁-C₄)alkoxy, (C₁-C₃)alkoxy(C₁-C₃)alkoxy(C₁-C₃)alkyl, aminocarbonylamino(C₁-C₄)alkyl, aminocarbonylamino(C₁-C₄)alkoxy, (C₁-C₄)alkanoylamino(C₁-C₄)alkyl, (C₁-C₄)alkanoylamino(C₁-C₄)alkoxy, (C₃-C₄)cycloalkanecarbonylamino(C₁-C₄)alkyl, (C₃-C₄)cycloalkanecarbonylamino(C₁-C₄)alkoxy, aminosulfonylamino(C₁-C₄)alkyl, aminosulfonylamino(C₁-C₄)alkoxy, (C₁-C₄)alkanesulfonylamino(C₁-C₄)alkyl, (C₁-C₄)alkanesulfonylamino(C₁-C₄)alkoxy, formylamino(C₁-C₄)alkyl, formylamino(C₁-C₄)alkoxy, (C₁-C₄)alkoxycarbonylamino(C₁-C₄)alkyl, (C₁-C₄)alkoxycarbonylamino(C₁-C₄)alkoxy, (C₁-C₄)alkylaminocarbonylamino(C₁-C₄)alkyl, aminocarbonyl(C₁-C₄)alkyl, aminocarbonyl(C₁-C₄)alkoxy, (C₁-C₄)alkylaminocarbonyl(C₁-C₄)alkyl, (C₁-C₄)alkylaminocarbonyl-(C₁-C₄)alkoxy, aminocarboxy(C₁-C₄)alkyl, aminocarboxy(C₁-C₄)alkoxy, (C₁-C₄)alkylamino-carboxy(C₁-C₄)alkyl, or (C₁-C₄)alkylaminocarboxy(C₁-C₄)alkoxy;

R³ is fluoro, chloro, bromo, cyano, (C₁-C₄)alkyl, (C₁-C₄) haloalkyl, aryl, (C₁-C₄)alkoxy, or (C₁-C₄)haloalkoxy;

R⁴ is hydrogen;

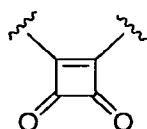
X is methylene;

R^5 is (C₃-C₅)alkyl;

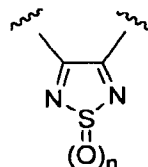
R^6 is amino;

5 R^7 is hydrogen or methyl;

Q is a group of formula Q1, or formula Q2 wherein $n = 2$;



Q1



Q2

10 R^8 is (C₁-C₁₂)alkyl, (C₁-C₁₂)haloalkyl, or NR^9R^{10} ;

R^9 is 1) hydrogen, (C₁-C₁₂)alkyl, halo(C₁-C₁₂)alkyl, (C₃-C₇)cycloalkyl, (C₃-C₇)cycloalkyl(C₅-C₉)alkyl, halo(C₃-C₇)cycloalkyl(C₅-C₉)alkyl, (C₅-C₉)alkyl(C₃-C₇)cycloalkyl, halo(C₅-C₉)alkyl(C₃-C₇)cycloalkyl, (C₁-C₆)alkoxy(C₁-C₆)alkyl, or halo(C₁-C₆)alkoxy(C₁-C₆)alkyl or 2) aryl(C₁-C₆)alkyl, aryl(C₃-C₇)cycloalkyl, arene fused-cycloalkyl, aminocarbonyl(C₁-C₆)alkyl, (C₁-C₆)acylamino(C₁-C₆)alkyl, or heteroaryl(C₁-C₆)alkyl each optionally substituted with up to four substituents independently selected from fluorine, chlorine, cyano, nitro, (C₁-C₃)alkyl, halo(C₁-C₃)alkyl, (C₁-C₃)alkoxy, halo(C₁-C₃)alkoxy, (C₁-C₃)alkanesulfonyl, and morpholino;

20 R^{10} is hydrogen, (C₁-C₆)alkyl, or halo(C₁-C₆)alkyl; or

R^9 and R^{10} taken together with the nitrogen to which they are attached form a 5- or 6-membered heterocyclic ring composed of carbon atoms and 0 or 1 hetero atom in addition to the nitrogen atom to which R^9 and R^{10} are attached, said hetero atom being selected from 0 or 1 nitrogen atoms, 0 or 1 oxygen atoms, said ring atoms being substituted with the appropriate number of hydrogen atoms, said ring being optionally substituted with up to four groups independently selected from halogen, (C₁-C₃)alkyl, halo(C₁-C₃)alkyl, aryl, aryl-lower alkyl, and oxo, such that substitution of one oxo group on a carbon atom forms a carbonyl group; wherein the aryl and arylalkyl groups are substituted with up to two groups independently selected from halo, cyano, optionally halogenated lower alkyl, optionally halogenated lower alkoxy, optionally halogenated lower alkylthio, optionally halogenated lower alkanesulfonyl, and lower alkoxy carbonyl;

or an enantiomer, diastereomer, or pharmaceutically acceptable salt thereof.

5. A compound of claim 2,

wherein:

R¹ is hydrogen;

- 5 R² is 3-(cyclopropyl)propyl, 4-(cyclopropyl)butyl, 3-hydroxypropyl, 4-hydroxybutyl, 4-hydroxypentyl, 4-hydroxyhexyl, 3-ethoxypropyl, 4-methoxybutyl, 4-ethoxybutyl, 3-methoxypropoxy, 3-ethoxypropoxy, 3-propoxypropoxy, 2-cyclopropylethoxy, 3-cyclopropylpropoxy, 3-(acetylamino)propyl, 3-(propionylamino)propyl, 3-(butanoylamino)propyl, 2-(acetylamino)ethoxy, 2-(propionylamino)ethoxy, 2-(butanoylamino)ethoxy, 3-(methoxycarbonylamino)propyl, 3-(ethoxycarbonylamino)propyl, 2-(methoxycarbonylamino)ethoxy, 2-(ethoxycarbonylamino)ethoxy, 2-(methylaminocarbonyl)ethyl, 2-(ethylaminocarbonyl)ethyl, (methylaminocarbonyl)methoxy, or (ethylaminocarbonyl)methoxy;
- 10 R³ is fluoro, chloro, bromo, cyano, methyl, ethyl, isopropyl, tert-butyl, trifluoromethyl, pentafluoroethyl, phenyl, methoxy, difluoromethoxy, or trifluoromethoxy;

R⁴ is hydrogen;

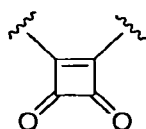
- 20 X is methylene;

R⁵ is branched (C₃-C₅)alkyl;

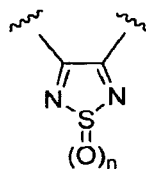
R⁶ is amino;

- 25 R⁷ is hydrogen;

Q is a group of formula Q1 or Q2 wherein n = 2



Q1



Q2

- 30 R⁸ is hexyl or NR⁹R¹⁰

R⁹ is H, methyl, ethyl, propyl, butyl, 2-methyl-1-propyl, 1-pentyl, 2,2-dimethyl-1-propyl, 2-methyl-2-butyl, 3-methyl-2-butyl, 2-methylbutyl, 3-methylbutyl, 2-pentyl, 2-methyl-2-pentyl, 2,4,4-trimethylthyl-2-pentyl, 1-hexyl, 2-hexyl, 2-heptyl, 2-methyl-2-hexyl, 2-octyl, cyclopropylmethyl, cyclopropylethyl, cyclohexylmethyl, cyclohexylethyl, 2,2,2-trifluoroethyl,

35

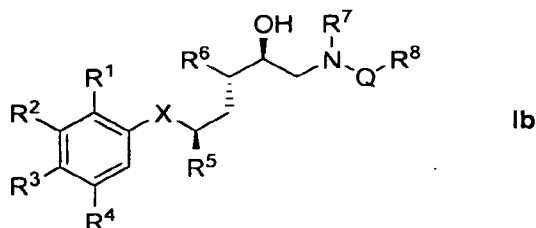
2,2,3,3,4,4,4-heptafluorobutyl, 2-methoxyethyl, benzyl, 2-phenylethyl, 2-(2-chlorophenyl)ethyl, 2-(3-chlorophenyl)ethyl, 2-(4-chlorophenyl)ethyl, 2-(2-methylphenyl)ethyl, 2-(2,4-dimethylphenyl)ethyl, 2-(2,3-dimethoxyphenyl)ethyl, 2-(2,5-dimethoxyphenyl)ethyl, 2-(4-nitrophenyl)ethyl, 3-phenylpropyl, 4-phenylbutyl, 2-phenylcyclopropyl, 2-indanyl, 2-(aminocarbonyl)-2-methylthyl-1-propyl, 3-(acetylamino)-2,2-dimethylthylpropyl, or 2-(4-morpholino)-2-(3-pyridyl)-ethyl;

R¹⁰ is H, methyl, ethyl, or propyl; or

R⁹ and R¹⁰ taken together are -(CH₂)₅-, -(CH₂)₂O(CH₂)₂-, -(CH₂)₂NMe(CH₂)₂-, -(CH₂)₄CHEt-, -(CH₂)CHPhCH₂CH₂-, -(CH₂)₂CHPh(CH₂)₂-, or -CH₂CHBn(CH₂)₃-;

or an enantiomer, diastereomer, or pharmaceutically salt thereof.

6. A compound of claim 2, wherein at least one, two, or preferably all three of the asymmetric carbon atoms of the main chain have the stereochemical configuration shown in formula Ib



or a pharmaceutically acceptable salt thereof.

7. A compound of claim 1, wherein X is methylene and R⁵ is isopropyl or a pharmaceutically acceptable salt thereof.

8. A compound of claim 2, wherein X is methylene and R⁵ is isopropyl or a pharmaceutically acceptable salt thereof.

9. A compound of claim 6, wherein X is methylene and R⁵ is isopropyl or a pharmaceutically acceptable.

10. A compound of claim 1 which is:

Cpd. No.	Name
I-1	3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-aminocyclobut-3-ene-1,2-dione
I-2	3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(methylamino)cyclobut-3-ene-1,2-dione

- I-3 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(ethylamino)cyclobut-3-ene-1,2-dione
- I-4 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(propylamino)cyclobut-3-ene-1,2-dione
- I-5 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(cyclopropylmethylamino)cyclobut-3-ene-1,2-dione
- I-6 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(butylamino)cyclobut-3-ene-1,2-dione
- I-7 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(isobutylamino)cyclobut-3-ene-1,2-dione
- I-8 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(2-methoxyethylamino)cyclobut-3-ene-1,2-dione
- I-9 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(piperidin-1-yl)cyclobut-3-ene-1,2-dione
- I-10 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(2-cyclopropylethylamino)cyclobut-3-ene-1,2-dione
- I-11 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-hexylcyclobut-3-ene-1,2-dione
- I-12 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-morpholinocyclobut-3-ene-1,2-dione
- I-13 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(neopentylamino)cyclobut-3-ene-1,2-dione
- I-14 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(pentan-2-ylamino)cyclobut-3-ene-1,2-dione
- I-15 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(tert-pentylamino)cyclobut-3-ene-1,2-dione
- I-16 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(3-methylbutan-2-ylamino)cyclobut-3-ene-1,2-dione
- I-17 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-((S)-2-methylbutylamino)cyclobut-3-ene-1,2-dione
- I-18 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(isopentylamino)cyclobut-3-ene-1,2-dione
- I-19 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(pentylamino)cyclobut-3-ene-1,2-dione
- I-20 3-(N-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptyl)-N-methylamino)-4-(butylamino)cyclobut-3-ene-1,2-dione
- I-21 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(N-butyl-N-methylamino)cyclobut-3-ene-1,2-dione
- I-22 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(2,2,2-trifluoroethylamino)cyclobut-3-ene-1,2-dione
- I-23 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(4-methylpiperazin-1-yl)cyclobut-3-ene-1,2-dione
- I-24 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(dipropylamino)cyclobut-3-ene-1,2-dione
- I-25 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(2-methylpentan-2-ylamino)cyclobut-3-ene-1,2-dione
- I-26 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(hexan-2-ylamino)cyclobut-3-ene-1,2-dione
- I-27 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(hexylamino)cyclobut-3-ene-1,2-dione
- I-28 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(N-methyl-N-pentylamino)cyclobut-3-ene-1,2-dione
- I-29 3-((2R,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(N-methyl-N-pentylamino)cyclobut-3-ene-1,2-dione
- I-30 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(2-methylpentan-2-ylamino)cyclobut-3-ene-1,2-dione
- I-31 3-((2R,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(2-methylpentan-2-ylamino)cyclobut-3-ene-1,2-dione
- I-32 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(benzylamino)cyclobut-3-ene-1,2-dione
- I-33 (2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-1-(4-(butylamino)-1,1-dioxo-1,2,5-thiadiazol-3-ylamino)-3-amino-6-methylheptan-2-ol
- I-34 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(cyclohexylmethylamino)cyclobut-3-ene-1,2-dione
- I-35 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(2-ethylpiperidin-1-yl)cyclobut-3-ene-1,2-dione
- I-36 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-

- methylheptylamino)-4-(heptylamino)cyclobut-3-ene-1,2-dione
- I-37 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(heptan-2-ylamino)cyclobut-3-ene-1,2-dione
- I-38 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(2-methylhexan-2-ylamino)cyclobut-3-ene-1,2-dione
- I-39 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(N-methyl-N-(2-methylpentan-2-yl)amino)cyclobut-3-ene-1,2-dione
- I-40 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-3,4-dioxocyclobut-1-enylamino)-2,2-dimethylpropanamide
- I-41 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(phenethylamino)cyclobut-3-ene-1,2-dione
- I-42 (2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-1-(4-(pentylamino)-1,1-dioxo-1,2,5-thiadiazol-3-ylamino)-3-amino-6-methylheptan-2-ol
- I-43 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(2-cyclohexylethylamino)cyclobut-3-ene-1,2-dione
- I-44 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(octan-2-ylamino)cyclobut-3-ene-1,2-dione
- I-45 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(2,4,4-trimethylpentan-2-ylamino)cyclobut-3-ene-1,2-dione
- I-46 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(N-methyl-N-(2-methylhexan-2-yl)amino)cyclobut-3-ene-1,2-dione
- I-47 3-((1S,2R)-2-phenylcyclopropylamino)-4-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)cyclobut-3-ene-1,2-dione
- I-48 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(2,3-dihydro-1H-inden-2-ylamino)cyclobut-3-ene-1,2-dione
- I-49 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(3-phenylpropylamino)cyclobut-3-ene-1,2-dione
- I-50 3-(N-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptyl)-N-methylamino)-4-(phenethylamino)cyclobut-3-ene-1,2-dione
- I-51 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(N-methyl-N-phenethylamino)cyclobut-3-ene-1,2-dione
- I-52 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-((2-methyl)phenethylamino)cyclobut-3-ene-1,2-dione
- I-53 N-(3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-3,4-dioxocyclobut-1-enylamino)-2,2-dimethylpropylacetamide
- I-54 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(3-phenylpyrrolidin-1-yl)cyclobut-3-ene-1,2-dione
- I-55 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(4-phenylbutylamino)cyclobut-3-ene-1,2-dione
- I-56 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(2,4-dimethylphenethylamino)cyclobut-3-ene-1,2-dione
- I-57 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(2-chlorophenethylamino)cyclobut-3-ene-1,2-dione
- I-58 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(3-chlorophenethylamino)cyclobut-3-ene-1,2-dione
- I-59 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(4-chlorophenethylamino)cyclobut-3-ene-1,2-dione
- I-60 (2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-1-(4-(phenethylamino)-1,1-dioxo-1,2,5-thiadiazol-3-ylamino)-3-amino-6-methylheptan-2-ol
- I-61 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(4-phenylpiperidin-1-yl)cyclobut-3-ene-1,2-dione
- I-62 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(4-nitrophenethylamino)cyclobut-3-ene-1,2-dione
- I-63 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(3-benzylpiperidin-1-yl)cyclobut-3-ene-1,2-dione
- I-64 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(2,5-dimethoxyphenethylamino)cyclobut-3-ene-1,2-dione
- I-65 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(2,3-dimethoxyphenethylamino)cyclobut-3-ene-1,2-dione
- I-66 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(2,2,3,3,4,4,4-heptafluorobutylamino)cyclobut-3-ene-1,2-dione or
- I-67 3-((2S,3S,5S)-5-(3-(3-methoxypropoxy)-4-methoxybenzyl)-3-amino-2-hydroxy-6-methylheptylamino)-4-(2-morpholino-2-(pyridin-3-yl)ethylamino)cyclobut-3-ene-1,2-dione

or an enantiomer, diastereomer, or pharmaceutically acceptable salt thereof.

11. A composition comprising an effective amount of a compound of claim 1 or enantiomer, diastereomer, or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier therefor.

12. A composition of claim 11 further comprising α -blockers, β -blockers, calcium channel blockers, diuretics, angiotensin converting enzyme (ACE) inhibitors, dual ACE and neutral endopeptidase (NEP) inhibitors, angiotensin-receptor blockers (ARBs), aldosterone synthase inhibitors, aldosterone-receptor antagonists, or endothelin receptor antagonists.

13. A composition of claim 11 comprising compounds having a mean inhibition constant (IC_{50}) against renin of between about 50,000 nM to about 0.001 nM; preferably between about 100 nM to about 0.001 nM; and more preferably between about 10 nM to about 0.01 nM.

14. A method of antagonizing renin inhibitors which comprises administering to a subject in need thereof a therapeutically effective amount of a compound of claim 1 or enantiomer, diastereomer, or pharmaceutically acceptable salt thereof.

15. A method of claim 14 which comprises administering compounds having an IC_{50} for renin of between about 50,000 nM to about 0.001 nM; preferably between about 100 nM to about 0.001 nM; and more preferably between about 10 nM to about 0.01 nM.

16. A method for treating or ameliorating a renin mediated disorder in a subject in need thereof comprising administering to said subject a therapeutically effective amount of a compound of claim 1, or enantiomer, diastereomer, or pharmaceutically acceptable salt thereof or composition thereof.

17.. A method of claim 16, wherein said disorder is hypertension, congestive heart failure, cardiac hypertrophy, cardiac fibrosis, cardiomyopathy post-infarction, nephropathy, vasculopathy and neuropathy, diseases of the coronary vessels, post-surgical hypertension, restenosis following angioplasty, raised intra-ocular pressure, glaucoma, abnormal vascular growth, hyperaldosteronism, anxiety states, or cognitive disorders.

18. A method of claim 16 further comprising administering said compound of claim 1 or enantiomer, diastereomer, or pharmaceutically acceptable salt thereof or composition thereof in combination with one or more additional agents selected from the group consisting of α -blockers, β -blockers, calcium channel blockers, diuretics, angiotensin converting enzyme (ACE) inhibitors, dual ACE and neutral endopeptidase (NEP) inhibitors, angiotensin-

receptor blockers (ARBs), aldosterone synthase inhibitors, aldosterone-receptor antagonists, and endothelin receptor antagonist.

19. A method of claim 18 wherein:

- 5 α -blockers include doxazosin, prazosin, tamsulosin, and terazosin;
 β -blockers include atenolol, bisoprol, metoprolol, acetutolol, esmolol, celiprolol, taliprolol, acebutolol, oxprenolol, pindolol, propanolol, bupranolol, penbutolol, mepindolol, carteolol, nadolol, carvedilol, and their pharmaceutically acceptable salts;
 calcium channel blockers include dihydropyridines (DHPs) and non-DHPs, wherein the
10 DHPs are selected from the group consisting of amlodipine, felodipine, ryosidine, isradipine, lacidipine, nicardipine, nifedipine, nigulpidine, niludipine, nimodipine, nisoldipine, nitrendipine, and nivaldipine and their pharmaceutically acceptable salts and the non-DHPs are selected from the group consisting of flunarizine, prenylamine, diltiazem, fendiline, gallopamil, mibefradil, anipamil, tiapamil, and verampimil, and their pharmaceutically
15 acceptable salts;
 the diuretics include a thiazide derivative selected from amiloride, chlorothiazide, hydrochlorothiazide, methylchlorothiazide, and chlorothalidon;
 ACE inhibitors include alacepril, benazepril, benazaprilat, captopril, ceronapril, cilazapril, delapril, enalapril, enalaprilat, fosinopril, lisinopril, moexipiril, moveltopril, perindopril,
20 quinapril, quinaprilat, ramipril, ramiprilat, spirapril, temocapril, trandolapril, and zofenopril;
 dual ACE/NEP inhibitors include omapatrilat, fasidotril, and fasidotrilat;
 ARBs include candesartan, eprosartan, irbesartan, losartan, olmesartan, tasosartan, telmisartan, and valsartan;
 aldosterone synthase inhibitors include anastrozole, fadrozole, and exemestane;
25 aldosterone-receptor antagonists include spironolactone and eplerenone; and
 endothelin antagonists include bosentan, enrasentan, atrasentan, darusentan, sitaxentan, and tezosentan, and their pharmaceutically acceptable salts.

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2007/007961

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07C225/20 C07C233/36 C07D295/12 C07D211/14 C07D285/10
 A61K31/137 A61K31/433 A61K31/445 A61K31/5377 A61K31/165
 A61P9/12 C07D213/38

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)

C07C C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2005/070877 A (SPEEDEL EXPERIMENTA AG [CH]; HEROLD PETER [CH]; STUTZ STEFAN [CH]; STO) 4 August 2005 (2005-08-04) page 19 - page 21; compounds 24,28,55 claims 1,8 -----	1-19



Further documents are listed in the continuation of Box C.



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 document but published on or after the international filing date
 L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
 O document referring to an oral disclosure, use, exhibition or other means
 P document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
 X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
 Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
 & document member of the same patent family

Date of the actual completion of the international search

21 September 2007

Date of mailing of the international search report

28/09/2007

Name and mailing address of the ISA/

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Authorized officer

Fitz, Wolfgang

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2007/007961

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of 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. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 14-19 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
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:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box 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 an additional fee, this Authority did not invite payment of any additional fee.
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 claims 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 claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2007/007961

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