The present invention relates to certain novel 1,3-oxazolidine compounds of formula (I), to processes for making such compounds and to their utility as renin inhibitors or prodrugs of renin inhibitors.
Title: NOVEL 1,3-OXAZOLIDINE COMPOUNDS AND THEIR USE AS RENIN INHIBITORS

Abstract: The present invention relates to certain novel 1,3-oxazolidine compounds of formula (I), to processes for making such compounds and to their utility as renin inhibitors or prodrugs of renin inhibitors.
Novel 1,3-oxazolidine compounds and their use as renin inhibitors

Field of the Invention

The present invention relates to certain novel 1,3-oxazolidine compounds, to processes for making such compounds and to their utility as renin inhibitors, precursors of renin inhibitors or prodrugs of renin inhibitors.

Background of the Invention

Hypertension is one of the major cardiovascular diseases, which are responsible for the millions death worldwide each year. The renin-angiotensin system (RAS) plays a key role in the maintenance of hemodynamic integrity via modulating regulator of blood pressure and body fluid volume in response to a broad range of physiological and environmental variations.

Renin is a proteolytic enzyme that metabolizes angiotensinogen to angiotensin I. Angiotensin I can be subsequently cleaved by Angiotensin-converting enzyme (ACE), producing angiotensin II, which is the effector of the RAS system and mediates its physiological function via the interaction with its receptors. The blockade of RAS is an effective therapeutic approach in the treatment of hypertension and the intervention of other pathogenesis of cardiovascular and renal disorder.

Direct renin inhibition has long been suggested as one of the means for the inhibition of the RAS. Renin (EC 3.4.99.19) was first discovered in 19th century and its functions in the RAS was established thereafter. Renin controls the first step of the renin-angiotension system and catalyzes the cleavage of angiotensinogen at a unique site, releasing the decapeptide angiotensin. Renin is a highly specific protease and its only known natural substrate is angiotensinogen. Due to the high specificity and its rate-limiting nature in the RAS cascade, renin is regarded as one of the most attractive targets for the inhibition of the RAS, and enormous efforts have been made to develop potent and safe renin inhibitors.

The compound (2S,4S,5S,7S)-N-(2-Carbamoyl-2-methylpropyl)-5-amino-4-hydroxy-2,7-diisopropyl-8-[4-methoxy-3-(3-methoxypropoxy)phenyl]-octanamide, which is disclosed in EP-A-678503, more commonly known under the name aliskiren, is one of the most
important renin inhibitors, and the first renin inhibitor that has been approved for clinical use in the treatment of hypertension and related diseases. The chemical structure of aliskiren is shown in Figure 1.

![Chemical Structure of Aliskiren](image)

**Figure 1**

Aliskiren is being used in monotherapy for hypertension, and studies for the combination therapies such as with diuretics, ACE inhibitors and angiotensin receptor blockers are under way. Aliskiren is a potent inhibitor of renin with a Ki in the sub-nanomolar level. Aliskiren has a very good safety profile.

However, the renin inhibitors are known to have unfavorable properties such as an unfavorable pharmacokinetic profile. For instance, they exhibit low oral bioavailability, interaction with efflux system and so on.

In the journal Clinical Pharmacokinetics, 2008, 47, 515-531, it is disclosed that aliskiren has a low oral bioavailability of about 2.6 %. Many other renin inhibitors were also reported to have bad pharmacokinetic properties.

It is an object of the present invention to overcome or at least mitigate some of the disadvantages associated with renin inhibitors mentioned above.

**Description of the Invention**

Thus, the present invention relates to a compound of formula (I)
wherein

\[ \text{R}^1 \text{ and } \text{R}^2 \text{ independently represent} \]

\[ \text{H, C}_1\text{-C}_6\text{alkyl, C}_3\text{-C}_6\text{cycloalkyl or C}_3\text{-C}_6\text{cycloalkyl-C}_1\text{-C}_3\text{alkyl, wherein said C}_1\text{-C}_6\text{alkyl, C}_3\text{-C}_6\text{cycloalkyl or C}_3\text{-C}_6\text{cycloalkyl-C}_1\text{-C}_3\text{alkyl is optionally substituted by one or more substituents independently selected from halogen, CN, NH(C}_1\text{-C}_6\text{alkyl), N(C}_1\text{-C}_6\text{alkyl)}_2, C}_1\text{-C}_6\text{alkyl and C}_1\text{-C}_6\text{alkoxy;}} \]

or \text{R}^1 \text{ and } \text{R}^2 \text{ together with the carbon to which they are bonded form a C}_3\text{-C}_6\text{cycloalkyl or a 4-6 membered heterocyclyl, wherein said C}_3\text{-C}_6\text{cycloalkyl or 4-6 membered heterocyclyl is optionally substituted by one or more substituents independently selected from halogen, CN, NH(C}_1\text{-C}_6\text{alkyl), N(C}_1\text{-C}_6\text{alkyl)}_2, C}_1\text{-C}_6\text{alkyl and C}_1\text{-C}_6\text{alkoxy;}}

\[ \text{R}^3 \text{ and } \text{R}^4 \text{ independently represent} \]

\[ \text{H, C}_1\text{-C}_8\text{alkyl, C}_2\text{-C}_8\text{alkenyl, C}_2\text{-C}_8\text{alkynyl, C}_3\text{-C}_6\text{cycloalkyl, C}_3\text{-C}_6\text{cycloalkyl-C}_1\text{-C}_6\text{alkyl, C}_1\text{-C}_3\text{alkoxy, C}_1\text{-C}_3\text{alkoxy-C}_1\text{-C}_6\text{alkyl, aryl-C}_1\text{-C}_6\text{alkyl, heterocyclyl-C}_1\text{-C}_6\text{alkyl, aryl, aryloxy, heterocyclyl or heterocyclyloxy, wherein said C}_1\text{-C}_8\text{alkyl, C}_2\text{-C}_8\text{alkenyl, C}_2\text{-C}_8\text{alkynyl, C}_3\text{-C}_6\text{cycloalkyl, C}_3\text{-C}_6\text{cycloalkyl-C}_1\text{-C}_6\text{alkyl, C}_1\text{-C}_3\text{alkoxy, C}_1\text{-C}_3\text{alkoxy-C}_1\text{-C}_6\text{alkyl, aryl-C}_1\text{-C}_6\text{alkyl, heterocyclyl-C}_1\text{-C}_6\text{alkyl, aryl, aryloxy, heterocyclyl or heterocyclyloxy is optionally substituted by one or more substituents independently selected from halogen, OH, CN, NO}_2, \text{NH}_2, \text{NH(C}_1\text{-C}_6\text{alkyl), N(C}_1\text{-C}_6\text{alkyl)}_2, C}_1\text{-C}_6\text{alkyl, C}_1\text{-C}_6\text{alkoxy and C}_3\text{-C}_6\text{cycloalkyl;}} \]

or \text{R}^3 \text{ and } \text{R}^4 \text{ together with the carbon to which they are bonded form}
a C₃-C₈ cycloalkyl or a 4-8 membered heterocycyl, wherein said C₃-C₈ cycloalkyl or 4-8 membered heterocycyl is optionally substituted by one or more substituents independently selected from halogen, OH, CN, NO₂, NH₂, NH(C₁-C₃ alkyl), N(C₁-C₃ alkyl)₂, C₁-C₃ alkyl, C₃-C₆ cycloalkyl and C₁-C₃ alkoxy;

X¹ represents
O or S;

X² represents
O or S;

W represents
H, R⁶ X¹⁻, C₂-C₆ alkyl, halogen, (OH)₂ P(O)O, [R₈ C(O)OCH₂ O]₂ P(O)O, or [R₈ C(O)OCH(C₁-C₃ alkyl) O]₂ P(O)O, [R₈ C(O)SCH₂ CH₂ O]₂ P(O)O;

R⁶ represents
C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₂-C₆ alkenyl, heterocycyl or aryl, wherein said C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₂-C₆ alkenyl, heterocycyl or aryl is optionally substituted by one or more substituents independently selected from halogen, OH, NH₂, NH(C₁-C₃ alkyl), N(C₁-C₃ alkyl)₂, C₁-C₃ alkyl, C₁-C₃ alkoxy, aryl and heterocycyl;

R⁶ is –C(=X¹)TZ ;

T represents
O, S, NH, N(C₁-C₃ alkyl) or a single bond;

Z represents
C₁-C₁₈ alkyl, C₂-C₁₈ alkenyl, C₂-C₁₈ alkynyl, C₃-C₈ cycloalkenyl, C₄-C₈ cycloalkynyl, aryl, heterocycyl, C₃-C₈ cycloalkyl, C₁-C₁₈ alkyl-heterocycyl, tetrazolyl-biphenyl-methyl-heterocycyl, tetrazolyl-biphenyl-methyl-heterocyclylmethyl, tetrazolyl-biphenyl-methyl-amino-C₁-C₆ alkyl, oxadiazolyl-biphenyl-methyl-heterocycyl,
5 heterocyclmethyaryl, C₁-C₆alkyl-aryl or C₁-C₆alkyl-C₃-C₈cycloalkyl, wherein said C₁-C₈alkyl, C₂-C₁₈alkenyl, C₂-C₁₈alkynyl, C₃-C₈cycloalkenyl, C₄-C₈cycloalkynyl, aryl, heterocyclyl, C₃-C₈cycloalkyl, C₁-C₁₈alkyl-heterocyclyl, tetrazolyl-biphenylmethyl-heterocyclyl, tetrazolyl-biphenylmethyl-heterocyclylmethyl, tetrazolyl-biphenylmethyl-amino-C₁-C₆alkyl, oxadiazolylbiphenyl-methyl-heterocyclyl, heterocyclmethyaryl, C₁-C₆alkyl-aryl or C₁-C₆alkyl-C₃-C₈cycloalkyl is optionally substituted by one or more substituents independently selected from halogen, OH, CN, oxo, N₃, NO₂, NH₂, NH(C₁-C₆alkyl), N(C₁-C₆alkyl)₂, C₁-C₆alkanoylNH, C₂-C₆alkoxy carbonylNH, C₁-C₆alkanoyl, C₁-C₆alkanoyloxy, COOH, (OH)₂P(O)O, [R²C(O)OCH₂O]₂P(O)O, [R³C(O)OCH(C₁-C₆alkyl)O]₂P(O)O, [R³C(O)SCH₂CH₂O]₂P(O)O, NH₂C(O), C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆alkoxy, C₁-C₆alkoxy carbonyl, C₁-C₆alkoxycarbonyl, NH₂C₁-C₆alkyl, C₁-C₆alkoxycarbonylNH, C₁-C₆alkoxycarbonylNH, C₁-C₆alkoxycarbonylNH, C₁-C₆alkoxycarbonyl, C₁-C₆cycloalkyl, C₁-C₆cycloalkenyl, C₂-C₆cycloalkoxy, C₂-C₆cycloalkenyl, aryl, arloxy, heterocyclyloxy and heterocyclyl;

M represents

\[ \text{O, S, SO}_2, \text{N}(\text{R}^7) \text{ or } \]

20 \[ \text{R}^7 \text{ represents } \]

H, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₈cycloalkyl, aryl, heterocyclyl or aryl(C₁-C₆alkyl, wherein said C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₈cycloalkyl, aryl, heterocyclyl or aryl(C₁-C₆alkyl is optionally substituted by one or more substituents independently selected from halogen, C₂-C₆cycloalkyl or C₁-C₆alkyl, wherein said C₂-C₆cycloalkyl or C₁-C₆alkyl is optionally substituted by one or more substituents selected from halogen, aryl and heterocyclyl;

R⁸ represents

30 H, OH, halogen, C₁-C₆alkyl or C₁-C₆alkoxy;
or \( R^7 \) and \( R^8 \) together with the carbon atom to which they are bonded form a \( C_3^- \)
\( C_9 \)cycloalkyl;

\( Y \) represents

- a single bond, \( \text{CH}_2 \), \( \text{C}_2^- \text{C}_6 \)alkanoyloxymethylene, \( \text{O}, \text{S}, \text{SO}, \text{SO}_2 \), \( \text{NH}, \text{N(C}_1^- \text{C}_4 \)alkyl), \( \text{C(O)}, \text{or CH(OH)} \);

\( U \) represents

- a single bond, \( \text{CH}_2 \), \( \text{C(O)} \), \( \text{C(O)NH}, \text{NHC(O)}, \) \( \text{NH} \) or \( \text{N(C}_1^- \text{C}_4 \)alkyl);  

\( V \) represents

- a 3-18-membered saturated, partially unsaturated or aromatic mono-, bi- or tricyclic
system, said system is a carbocyclic ring system or a heterocyclic ring system
selected from \( \text{C}_3^- \text{C}_4 \)cycloalkyl, \( \text{C}_3^- \text{C}_4 \)cycloalkenyl, \( \text{C}_4^- \text{C}_4 \)cycloalkynyl,
heterocyclyl and aryl, wherein said system is optionally substituted with one, two,
three or four substituents independently selected from halogen, \( \text{OH}, \text{CN}, \text{oxo}, \)
\( \text{COOH}, \text{CF}_3 \), \( \text{NO}_2 \), \( \text{NH}_2 \), \( \text{NH} \text{(C}_1^- \text{C}_6 \)alkyl), \( \text{N(C}_1^- \text{C}_6 \)alkyl)\)_2, \( \text{C}_1^- \text{C}_6 \)alkoxy, \( \text{C}_1^- \text{C}_6 \)alkoxy-C_1^-C_6 \)alkoxy, \( \text{NH}_2 \text{C(O)}, \text{C}_3^- \text{C}_6 \)cycloalkyl, \( \text{C}_2^- \text{C}_6 \)alkenyl, \( \text{C}_3^- \text{C}_6 \)cycloalkoxy-C_1^-C_6 \)alkoxy, \( \text{C}_3^- \text{C}_6 \)cycloalkyl-C_1^-C_6 \)alkoxy, \( \text{dioxalanyl}, \text{hydroxyl-C}_2^-\text{C}_7 \)alkoxy, \( \text{haloC}_2^-\text{C}_7 \)alkoxy, \( \text{carbamoyloxy-C}_2^-\text{C}_7 \)alkoxy, [(\( \text{C}_3^5 \)\text{N}NHC(O))]C_1^-\text{C}_7 \)alkoxy, \( \text{C}_3^-\text{C}_6 \)cycloalkoxy, \( \text{C}_2^-\text{C}_7 \)alkenyloxy, \( \text{C}_1^-\text{C}_6 \)alkanoyloxy, \( \text{C}_1^-\text{C}_6 \)alkoxy carbonyl, \( \text{C}_1^-\text{C}_6 \)alkoxy carbonyl, \( \text{C}_1^-\text{C}_6 \)alkylenedioxy, aryl, phenoxy,
phenylthio, pyridyl and \( \text{C}_1^-\text{C}_6 \)alkyl, wherein said \( \text{C}_1^-\text{C}_6 \)alkyl is optionally substituted
by \( \text{C}_3^-\text{C}_6 \)cycloalkoxy, \( \text{C}_1^-\text{C}_6 \)alkoxy, \( \text{C}_5^5 \)N\text{C(O)NH}, \text{NH}_2 \text{C(O)}, \text{NH} \text{(C}_1^- \text{C}_6 \)alkyl)\)_2, \( \text{C}_3^5 \)alkyl)\text{C(O)}, \( \text{N(C}_1^- \text{C}_3 \)\text{C}_2 \)\text{C(O)}, \( \text{NH}_2 \text{C(O)C}_1^-\text{C}_3 \)alkoxy, \( \text{NH} \text{(C}_1^- \text{C}_3 \)alkyl)\text{C(O)C}_1^-\text{C}_3 \)alkoxy, \( \text{N(C}_1^- \text{C}_3 \)alkyl)_2 \text{C(O)C}_1^-\text{C}_3 \)alkoxy or phenyl;

\( A \) represents

- \( \text{CH} \) or \( \text{N} \);

\( R^9 \) represents
H, C₃₋C₆alkyl, C₂₋C₆alkenyl, C₂₋C₆alkynyl, C₃₋C₆cycloalkyl or C₁₋C₆alkoxy, wherein said C₁₋C₆alkyl, C₂₋C₆alkenyl, C₂₋C₆alkynyl, C₃₋C₆cycloalkyl or C₁₋C₆alkoxy is optionally substituted by one or more of substituents independently selected from halogen, OH, C₃₋C₆cycloalkyl, C₁₋C₆alkoxy and aryl;

Q represents
C₁₋C₆alkyl, C₃₋C₆cycloalkyl, NH(C₁₋C₆alkyl)C(O)C₁₋C₆alkyl, N(C₁₋C₆alkyl)₂C(O)C₁₋C₆alkyl, aryl, heterocyclyl or heterocyclyl-C₁₋C₆alkyl;

or Q is selected from the group of partial structures consisting of E1 and E2

![E1](image1.png)  ![E2](image2.png)

G represents

![G](image3.png)

or N(R⁹);

R¹¹ represents
H or C₁₋C₆alkyl;

or R⁵, Q and A, wherein A is N, form a 3-18-membered saturated, partially unsaturated or aromatic mono-, bi- or tricyclic ring system, wherein said system is optionally substituted by one, two, three or four substituents independently selected from halogen, OH, oxo, CN, C₁₋C₆alkyl, C₃₋C₆cycloalkyl, C₃₋C₆cycloalkanoyl, C₁₋C₆alkanoyl, aryl-C₁₋C₆alkanoyl, C₁₋C₆alkoxy carbonyl, C₁₋C₆alkyl-SO₂, heterocyclyl-SO₂, aryl and heterocyclyl;

R⁹ represents
H, C₁-C₆alkyl, C₃-C₉cycloalkyl, C₂-C₆alkenyl or C₁-C₆alkoxy, wherein said C₁-C₆alkyl, C₃-C₉cycloalkyl, C₂-C₆alkenyl or C₁-C₆alkoxy is optionally substituted by one or more halogen;

R²⁰ represents

H, C₁-C₁₂alkyl, C₂-C₁₂alkenyl, C₃-C₁₂cycloalkyl, C₃-C₁₂cycloalkenyl, heterocyclyl or aryl, wherein said C₁-C₁₂alkyl, C₂-C₁₂alkenyl, C₃-C₁₂cycloalkyl, C₃-C₁₂cycloalkenyl, heterocyclyl or aryl is optionally substituted by one or more substituents independently selected from halogen, OH, CN, NO₂, C₁-C₆alkoxy, C₃-C₆cycloalkyl, aryloxy, heterocycloxy, NH₂C(O), NH(C₁-C₈alkyl), NH(aryl), NH(heterocyclyl), NH(aryl)C(O), NH(heterocyclyl)C(O), C₁-C₈alkyl-C(O)NH, arylC(O)NH, C₁-C₈alkanoyl, C₁-C₆alkoxyC(O), C₁-C₈alkylSO₂, aryl-SO₂, aryl and heterocyclyl;

or R²⁰ is

C₁-C₈alkyl or C₁-C₈alkenyl, wherein said C₁-C₈alkyl or C₁-C₈alkenyl is optionally substituted by NH₂C(O), NH(C₁-C₈alkyl)C(O), NH(C₃-C₈cycloalkyl)C(O), NH(C₃-C₆-alkenyl)C(O), N(C₁-C₆alkyl)₂C(O), C₁-C₆alkoxy carbonylNHC(O), N(C₃-C₈cycloalkyl)₂C(O), N(C₃-C₆cycloalkyl)(C₁-C₆alkyl)C(O), N(heterocyclyl)(C₁-C₆alkyl)C(O), NH₂C(S) or NH(C₁-C₈alkyl)C(S);

or R²⁰ is

C₁-C₆alkyl or C₂-C₆alkenyl, wherein said C₁-C₆alkyl or C₂-C₆alkenyl is optionally substituted with NH₂C(O)C₃-C₆cycloalkyl;

or R⁹ and R¹⁰ together with the atom of G to which R⁹ and R¹⁰ are bonded form

a 3-18-membered saturated, partially unsaturated or aromatic mono-, bi- or tricyclic system, said system is a carbocyclic ring system or a heterocyclic ring system, wherein said system is optionally substituted by one, two, three or four substituents independently selected from halogen, Oxo, C₁-C₆alkyl, C₃-C₆cycloalkyl, C₁-C₆alkoxy, C₃-C₆cycloalkoxy, C₁-C₈alkanoyl, C₁-C₈alkanoyloxy, aryl-C₁-C₆alkanoyl, C₁-C₈alkoxy carbonyl, C₁-C₈alkyl-SO₂-, heterocyclyl-SO₂, aryl and heterocyclyl;
with the proviso that R^4 is not aryl when R^3 and W are H;
and with the proviso that R^3 is not aryl when R^4 and W are H;
or a pharmaceutically acceptable salt thereof.

5

In one embodiment of the present invention, there is provided a compound of formula (I) wherein
Z represents
C_1-C_{18}alkyl, C_2-C_{18}alkenyl, C_2-C_{18}alkynyl, C_{3-8}cycloalkenyl, C_{4-8}cycloalkynyl,
aryl, heterocyclyl or C_{3-8}cycloalkyl, wherein said C_1-C_{18}alkyl, C_2-C_{18}alkenyl, C_2-
C_{18}alkynyl, C_{3-8}cycloalkenyl, C_{4-8}cycloalkynyl, aryl, heterocyclyl or C_{3-}
C_{8}cycloalkyl is optionally substituted by one or more of the substituents independently selected from: halogen, OH, CN, oxo, N_3, NO_2, NH_2, NH(C_{1-}
C_{8}alkyl), N(C_{1-6}alkyl)_2, C_{1-6}alkanoylNH, C_{2-6}alkoxycarbonylNH, C_{1-6}-
alkanoyl, C_{1-6}alkanoyloxy, COOH, (OH)_2P(O)O, [R^3C(O)OCH_2O]_2P(O)O,
[R^3C(O)OCH(C_{1-6}alkyl)O]_2P(O)O, [R^3C(O)SCH_2CH_2O]_2P(O)O, NH_2C(O), C_{1-}
C_{6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkoxycarbonyl, C_{3-}
C_{6}cycloalkyl, C_{3-6}cycloalkenyl, C_{3-6}cycloalkoxy, C_{3-6}cycloalkenylOxy, C_{1-}
C_{3}alkoxy-C_{1-6}alkoxy, aryl, aryloxy, heterocyclyloxy and heterocyclyl.

10

In one embodiment of the present invention, there is provided a compound of formula (I) wherein
X^1 is O;
X^2 is O or S; and
W is R^6O-.

15

In another embodiment of the present invention, there is provided a compound of formula (I) wherein
X^2 is O.
In one embodiment of the present invention, there is provided a compound of formula (I) wherein

$X^1$ is O;
$X^2$ is O;

$\begin{array}{c}
\text{R}^7 \\
\text{R}^8 \\
\end{array}$

5 M is ; and

U is a single bond.

In one embodiment of the present invention, there is provided a compound of formula (I) wherein

10 $X^1$ is O;
$X^2$ is O;
$W$ is $R^6$O-;

$\begin{array}{c}
\text{R}^7 \\
\text{R}^8 \\
\end{array}$

M is ;

U is a single bond;

15 A is CH and
Q is EI.

In one embodiment of the present invention, there is provided a compound of formula (I) wherein

20 $R^5$ is C$_1$-C$_6$alkyl or C$_3$-C$_6$cycloalkyl.

In one embodiment of the present invention, there is provided a compound of formula (I) wherein

V-Y-U-M is:
$R^5$ is isopropyl;

$Q$ is E1, wherein $G$ is $N(R^9)$; and

$R^9$ is H.

In one embodiment of the present invention, there is provided a compound of formula (I) wherein

$V$-U-Y-M is

$A(R^5)Q$ is

$R^{10}$ is

$C_1$-$C_6$alkyl, $NH_2$C(O)C$_2$-$C_6$alkyl, $NH(C_1$-$C_6$alkyl)C(O)C$_2$-$C_5$alkyl, $N(C_1$-$C_6$alkyl)$_2$C(O)C$_2$-$C_5$alkyl, $C_1$-$C_6$alkyloxycarbonylNHCO(O)C$_2$-$C_6$alkyl, aryl-$C_1$-$C_3$alkyl, $C_3$-$C_6$cycloalkyl-$C_1$-$C_2$alkyl, $NH_2$C(O)cyclopropyl, $C_2$-$C_6$cycloalkyl or aryl.
In one embodiment of the present invention, there is provided a compound of formula (I) wherein

V-U-Y-M is

\[ \text{structure image} \]

; and

5 \( A(R^5)Q \) is

\[ \text{structure image} \]

In one embodiment of the present invention, there is provided a compound of formula (I) wherein

10 \( X^1 \) is O;
\( X^2 \) is O;
\( W \) is \( R^6 \) O-;
V-U-Y-M is

\[ \text{structure image} \]

; and

15
A(R₅)Q is

In one embodiment of the present invention, there is provided a compound of formula (I) wherein

V-U-Y-M is

A(R₅)Q is

R¹ and R² independently represent
H, methyl or ethyl;
or R¹ and R² together with the carbon to which they are bonded form
a C₃-C₆ cycloalkyl or a 4-6 membered heterocyclyl, wherein said C₃-C₆ cycloalkyl or 4-6 membered heterocyclyl is optionally substituted by one or more substituents independently selected from halogen, CN, NH(C₁-C₃ alkyl), N(C₁-C₃ alkyl)₂, C₁-C₃ alkyl and C₁-C₃ alkoxy;
R³ and R⁴ independently represent
H or methyl;
or R³ and R⁴ together with the carbon to which they are bonded form a
C₃-C₈ cycloalkyl or a 4-8 membered heterocycl, wherein said C₃-C₈ cycloalkyl or 4-8 membered heterocycl is optionally substituted by one or more substituents independently selected from halogen, OH, NH₂, NH(C₁-C₃alkyl), N(C₁-C₃alkyl)₂, C₁-C₃alkyl or C₁-C₃alkoxy;

X¹ is O;
X² is O;
W is R⁶O⁻;
R⁶ is −C(=X¹)TZ
T is a single bond or O;

Z represents
C₁-C₁₈alkyl, C₂-C₁₈alkenyl, C₂-C₁₈alkynyl, C₃-C₈ cycloalkenyl, C₄-C₈ cycloalkynyl, aryl, heterocycl, or C₃-C₈ cycloalkyl, wherein said C₁-C₁₈alkyl, C₂-C₁₈alkenyl, C₂-C₁₈alkynyl, C₃-C₈ cycloalkenyl, C₄-C₈ cycloalkynyl, aryl, heterocycl or C₃-C₈ cycloalkyl is optionally substituted by one or more of the substituents independently selected from: halogen, OH, CN, oxo, N₃, NO₂, NH₂, NH(C₁-C₆alkyl), N(C₁-C₆alkyl)₂, C₁-C₆ alkanoylNH, C₂-C₆ alkoxy carbonyl NH, C₁-C₆ alkanoyl, C₁-C₆ alkanoyloxy, COOH, (OH)₂P(O)O, [R⁸C(O)OCH₂O]₂P(O)O, [R⁸C(O)OCH(C₁-
C₃alkyl)O]₂P(O)O, [R⁸C(O)SCH₂CH₂O]₃P(O)O, NH₂C(O)⁻, C₁-C₆alkyl, C₂-
C₆alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₁-C₆ alkoxy carbonyl, C₃-C₆ cycloalkyl, C₃-
C₆ cycloalkenyl, C₃-C₆ cycloalkoxy, C₃-C₆ cycloalkenyl oxy, C₁-C₃ alkoxy-C₁-
C₆ alkoxy⁻, aryl, aryloxy, heterocyclyoxy and heterocycl.

In one embodiment of the present invention, there is provided a compound of formula (I) wherein

R¹ and R² independently represent
H or C₁-C₂ alky;
R³ and R⁴ independently represent H or C₁-C₃ alky;
X¹ represents O;
X² represents O;
W represents R⁶ X¹⁻ or H;
R⁶ represents −C(=X¹)TZ;
T represents O or a single bond;
Z represents
C₁⁻C₈alkyl, C₂⁻C₁₈alkenyl, C₃⁻C₈cycloalkyl, aryl, heterocyclyl, or C₁⁻C₆alkyl-C₃⁻C₈cycloalkyl, wherein said C₁⁻C₈alkyl, C₂⁻C₁₈alkenyl, C₃⁻C₈cycloalkyl, aryl, heterocyclyl, C₁⁻C₆alkyl-aryl or C₁⁻C₆alkyl-C₃⁻C₈cycloalkyl is optionally substituted by one or two substituents independently selected from halogen, OH, oxo, NH₂, N(C₁⁻C₆alkyl)₂, C₂⁻C₄alkoxy Carbonyl NH, C₁⁻C₆alkyl, C₁⁻C₆alkoxy, C₁⁻C₆alkoxycarbonyl NH, C₁⁻C₆alkoxy carbonyl NH, C₁⁻C₆alkoxycarbonyl, C₃⁻C₈cycloalkyl, C₁⁻C₃alkoxy-C₁⁻C₃alkoxy-, heterocyclyloxy, heterocyclyl, NH₂C₁⁻C₆alkyl, C₁⁻C₆alkoxycarbonyl NH₃C₁⁻C₃alkyl and arylC₁⁻C₄alkyl carbonyl NH;

A(R⁵)Q is

R¹⁰ represents C₁⁻C₄alkyl, said C₁⁻C₄alkyl is optionally substituted by one NH₂C(O).

In one embodiment of the present invention, there is provided a compound of formula (I) wherein
R¹ and R² independently represent
H or C₁⁻C₃alkyl;
R² and R⁴ independently represent H or C₁⁻C₃alkyl;
X¹ represents O;
X² represents O;
W represents $R^6 X^1$;
$R^6$ represents $-C(=X^1)TZ$;
T represents O or a single bond;
Z represents

\[ C_1-C_18 \text{ alkyl-heterocyclyl}, [2^-(1H-tetrazol-5-yl)biphenyl-4-yl] \text{ methyl-heterocyclyl}, [2^-(1H-tetrazol-5-yl)biphenyl-4-yl] \text{ methyl-heterocyclyl-methyl}, [2^-(1H-tetrazol-5-yl)biphenyl-4-yl] \text{ methylamino-C}_1-C_6 \text{ alkyl}, \text{ oxadiazolyl-biphenyl-methyl-heterocyclyl or heterocyclylmethyl-biphenyl}, \text{ wherein said C}_1-C_18 \text{ alkyl-heterocyclyl}, [2^-(1H-tetrazol-5-yl)biphenyl-4-yl] \text{ methyl-heterocyclyl}, [2^-(1H-tetrazol-5-yl)biphenyl-4-yl] \text{ methyl-heterocyclyl-methyl}, [2^-(1H-tetrazol-5-yl)biphenyl-4-yl] \text{ methylamino-C}_1-C_6 \text{ alkyl}, \text{ oxadiazolyl-biphenyl-methyl-heterocyclyl or heterocyclylmethyl-biphenyl is optionally substituted by one or more substituents independently selected from halogen, OH, C}_2-C_6 \text{ alkanoyl, C}_1-C_6 \text{ alkyl, C}_1-C_6 \text{ alkoxy, heterocyclxyloxy, hydroxyc}_1-C_4 \text{ alkyl and heterocyclyl}; \]

V-U-Y-M is

\[ \text{ and} \]

A($R^5$)Q is

\[ . \]
Specific compounds of the present invention are one or more of the following:

(4S,5S)-1-((isobutyryloxy)ethyl 5-[(S)-2-(3-amino-2,2-dimethyl-3-oxopropylcarbamoyl)-3-methylbutyl]-4-[(S)-2-[4-methoxy-3-(methoxypropoxy)benzyl]-3-methylbutyl] oxazolidine-3-carboxylate;

(4S,5S)-pivaloyloxymethyl 5-[(S)-2-(3-amino-2,2-dimethyl-3-oxopropylcarbamoyl)-3-methylbutyl]-4-[(S)-2-[4-methoxy-3-(methoxypropoxy)benzyl]-3-methylbutyl] oxazolidine-3-carboxylate;

(4S,5S)-isobutyl 5-[(S)-2-(3-amino-2,2-dimethyl-3-oxopropylcarbamoyl)-3-methylbutyl]-4-[(S)-2-[4-methoxy-3-(methoxypropoxy)benzyl]-3-methylbutyl] oxazolidine-3-carboxylate;

(4S,5S)-valyloxymethyl 5-[(S)-2-(3-amino-2,2-dimethyl-3-oxopropylcarbamoyl)-3-methylbutyl]-4-[(S)-2-[4-methoxy-3-(methoxypropoxy)benzyl]-3-methylbutyl] oxazolidine-3-carboxylate, trifluoroacetic acid salt;

(4S,5S)-(ethoxycarbonyloxy)methyl 5-[(S)-2-(3-amino-2,2-dimethyl-3-oxopropylcarbamoyl)-3-methylbutyl]-4-[(S)-2-[4-methoxy-3-(methoxypropoxy)benzyl]-3-methylbutyl] oxazolidine-3-carboxylate;

(4S,5S)-(isopropoxycarbonyloxy)methyl 5-[(S)-2-(3-amino-2,2-dimethyl-3-oxopropylcarbamoyl)-3-methylbutyl]-4-[(S)-2-[4-methoxy-3-(methoxypropoxy)benzyl]-3-methylbutyl] oxazolidine-3-carboxylate;

[[2S)-2-hydroxypropanoyl]oxy]methyl (4S,5S)-5-[(2S)-2-(3-amino-2,2-dimethyl-3-oxopropylaminocarbonyl)-3-methylbutyl]-4-[(2S)-2-[4-methoxy-3-(methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate;

[[2S)-2-(ethoxycarbonyloxy)propanoyl]oxy]methyl (4S,5S)-5-[(2S)-2-[3-amino-2,2-dimethyl-3-oxopropylcarbamoyl]-3-methylbutyl]-4-[(2S)-2-[4-methoxy-3-(methoxypropoxy)benzyl]-3-methylbutyl] oxazolidine-3-carboxylate;

(4S,5S)-5-[(2S)-2-(3-amino-2,2-dimethyl-3-oxopropylaminocarbonyl)-3-methylbutyl]-4-[(2S)-2-[4-methoxy-3-(methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidin-3-yl carbonyloxy]methyl morpholine-4-carboxylate;

(4S,5S) [[pyridine-3-yl]carbonyloxy]methyl 5-[(S)-2-(3-amino-2,2-dimethyl-3-oxopropylcarbamoyl)-3-methylbutyl]-4-[(S)-2-[4-methoxy-3-(methoxypropoxy)benzyl]-3-methylbutyl] oxazolidine-3-carboxylate;
(4S,5S) [(pyridine-2-yl)carbonyloxy]methyl 5-[(S)-2-(3-amino-2,2-dimethyl-3-oxopropyl)carbamoyl]-3-methylbutyl]-4-{(S)-2-[4-methoxy-3-(methoxypropoxy)benzyl]-3-methylbutyl}oxazolidine-3-carboxylate;
[(2-methylpropoxycarbonyloxy)methyl (4S,5S)-5-{(2S)-2-[(3-amino-2,2-dimethyl-3-oxopropyl)carbamoyl]-3-methylbutyl}]-4-{(2S)-2-[4-methoxy-3-(methoxypropoxy)benzyl]-3-methylbutyl}-1,3-oxazolidine-3-carboxylate;
{{(pyridin-3-yl)methoxy}carbonyl}oxy)methyl (4S,5S)-5-{(2S)-2-[(3-amino-2,2-dimethyl-3-oxopropyl)carbamoyl]-3-methylbutyl}]-4-{(2S)-2-[4-methoxy-3-(methoxypropoxy)benzyl]-3-methylbutyl}-1,3-oxazolidine-3-carboxylate;
[(2-methyl-3-morpholin-4-ylpropanoyloxy)methyl (4S,5S)-5-{(2S)-2-[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl]-3-methylbutyl}]-4-{(2S)-2-[4-methoxy-3-(methoxypropoxy)benzyl]-3-methylbutyl}-1,3-oxazolidine-3-carboxylate;
(1-methylpiperidine-4-carbonyloxy)methyl (4S,5S)-5-{(2S)-2-[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl]-3-methylbutyl}]-4-{(2S)-2-[4-methoxy-3-(methoxypropoxy)benzyl]-3-methylbutyl}-1,3-oxazolidine-3-carboxylate;
{{(1,3-dioxan-5-yl-ox)carbonyl}oxy}methyl (4S,5S)-5-{(2S)-2-[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl]-3-methylbutyl}]-4-{(2S)-2-[4-methoxy-3-(methoxypropoxy)benzyl]-3-methylbutyl}-1,3-oxazolidine-3-carboxylate;
{{(1,3-dioxolan-4-ylmethoxy)carbonyl}oxy}methyl (4S,5S)-5-{(2S)-2-[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl]-3-methylbutyl}]-4-{(2S)-2-[4-methoxy-3-(methoxypropoxy)benzyl]-3-methylbutyl}-1,3-oxazolidine-3-carboxylate;
[(3-hydroxy-2,2-dimethylpropanoyloxy)methyl (4S,5S)-5-{(2S)-2-[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl]-3-methylbutyl}]-4-{(2S)-2-[4-methoxy-3-(methoxypropoxy)benzyl]-3-methylbutyl}-1,3-oxazolidine-3-carboxylate;
{(4-methoxybenzyloxy)carbonyl}oxy)methyl (4S,5S)-5-{(2S)-2-[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl]-3-methylbutyl}]-4-{(2S)-2-[4-methoxy-3-(methoxypropoxy)benzyl]-3-methylbutyl}-1,3-oxazolidine-3-carboxylate;
{(benzyloxy)carbonyl}oxy)methyl (4S,5S)-5-{(2S)-2-[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl]-3-methylbutyl}]-4-{(2S)-2-[4-methoxy-3-(methoxypropoxy)benzyl]-3-methylbutyl}-1,3-oxazolidine-3-carboxylate;
[(pyridine-4-yl)carbonyloxy]methyl (4S,5S)-5-[(2S)-2-[(3-amino-2,2-dimethyl-3-oxopropyl)carbamoyl]-3-methylbutyl]-4-[(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate;

(((1-methyl-1H-imidazol-4-yl)carbonyloxy)methyl (4S,5S)-5-[(2S)-2-[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl]-3-methylbutyl]-4-[(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate;

[(1,3-dioxan-5-yl)carbonyl]oxy)methyl (4S,5S)-5-[(2S)-2-[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl]-3-methylbutyl]-4-[(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate;

(((1-methyl-1H-imidazol-5-yl)carbonyl]oxy)methyl (4S,5S)-5-[(2S)-2-[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl]-3-methylbutyl]-4-[(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate;

(((1-methyl-1H-imidazol-4-yl)methoxy]carbonyl]oxy)methyl (4S,5S)-5-[(2S)-2-[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl]-3-methylbutyl]-4-[(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate;

[(1-methylpiperidin-4-yl)oxy]methyl (4S,5S)-5-[(2S)-2-[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl]-3-methylbutyl]-4-[(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate;

[(1,3-dioxan-5-ylmethoxy]carbonyl]oxy)methyl (4S,5S)-5-[(2S)-2-[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl]-3-methylbutyl]-4-[(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate;

((Pyridin-3-yl)oxy)methyl (4S,5S)-5-[(2S)-2-[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl]-3-methylbutyl]-4-[(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate;
20
{[(dimethylamino)carbonyl]oxy}methyl (4S,5S)-5-((2S)-2-{[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl}-3-methylbutyl)-4-((2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl}-1,3-oxazolidine-3-carboxylate;
{[(1-aminocyclopropyl)carbonyl]oxy}methyl (4S,5S)-5-((2S)-2-{[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl}-3-methylbutyl)-4-((2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl}-1,3-oxazolidine-3-carboxylate, trifluoroacetate;
{[(1-methyl-1H-imidazol-2-yl)carbonyl]oxy}methyl (4S,5S)-5-((2S)-2-{[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl}-3-methylbutyl)-4-((2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl}-1,3-oxazolidine-3-carboxylate;
1-{[(1-methyl-1H-imidazol-5-yl)carbonyl]oxy}ethyl (4S,5S)-5-((2S)-2-{[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl}-3-methylbutyl)-4-((2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl}-1,3-oxazolidine-3-carboxylate, trifluoroacetate;
1-{[(4S,5S)-5-((2S)-2-{[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl}-3-methylbutyl)-4-{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl}]1,3-oxazolidin-3-yl}carbonyl]oxy}methoxyoxo-(2E)-but-2-enoic acid;
{[(4S,5S)-5-((2S)-2-{[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl}-3-methylbutyl)-4-{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl}]1,3-oxazolidin-3-yl}carbonyl]oxy}methoxycarbonylcyclopropyl]methanaminium

25
trifluoroacetate;
1-{[(1-methyl-1H-imidazol-4-yl)carbonyl]oxy}ethyl (4S,5S)-5-((2S)-2-{[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl}-3-methylbutyl)-4-{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl}-1,3-oxazolidine-3-carboxylate;
1-{[(pyridin-3-yl)carbonyl]oxy}ethyl (4S,5S)-5-((2S)-2-{[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl}-3-methylbutyl)-4-{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl}-1,3-oxazolidine-3-carboxylate;
1. \{(pyridin-2-yl)carbonyl\}oxy ethyl \{(3-amino-2,2-dimethyl-3-oxopropyl)amino\}carbonyl-3-methybutyl]-4-{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methybutyl]-1,3-oxazolidine-3-carboxylate;  
1-{\{(4S,5S)-5-(2S)-2-{\{(3-amino-2,2-dimethyl-3-oxopropyl)amino\}carbonyl]-3-methybutyl]-4-{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methybutyl]-1,3-oxazolidine-3-y}carbonyl\}oxy\}methoxy-4-oxobutanoic acid;  
1-{\{(4S,5S)-5-(2S)-2-{\{(3-amino-2,2-dimethyl-3-oxopropyl)amino\}carbonyl]-3-methybutyl]-4-{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methybutyl]-1,3-oxazolidine-3-y}carbonyl\}oxy\}ethoxyoxo-(2E)-but-2-enoic acid;  
10. \{(1-methylpiperidin-4-yl)methyl \{(3-amino-2,2-dimethyl-3-oxopropyl)amino\}carbonyl]-3-methybutyl]-4-{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methybutyl]-1,3-oxazolidine-3-carboxylate;  
\{(1-hydroxycyclopropyl)carbonyl\}oxy methyl \{(3-amino-2,2-dimethyl-3-oxopropyl)amino\}carbonyl]-3-methybutyl]-4-{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methybutyl]-1,3-oxazolidine-3-carboxylate;  
15. \{(4S,5S)-5-(2S)-2-{\{(3-amino-2,2-dimethyl-3-oxopropyl)amino\}carbonyl]-3-methybutyl]-4-{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methybutyl]-1,3-oxazolidine-3-y}carbonyl\}oxy\}methyl N-pentanoyl-N-\{2'-(1H-tetrazol-5-yl)biphenyl-4-yl\}methyl\}L-valinate;  
20. \{(4S,5S)-ethyl 5-\{(S)-2-(3-amino-2,2-dimethyl-3-oxopropyl)carbonyl\}]-3-methybutyl]-1,3-oxazolidine-3-carboxylate;  
\{(4S,5S)-1-(isobutyryloxy)ethyl \{(S)-2-(3-amino-2,2-dimethyl-3-oxopropyl)carbonyl\}]-3-methybutyl]-1,3-oxazolidine-3-carboxylate;  
25. \{(4S,5S)-1-(isobutyryloxy)ethyl \{(S)-2-(3-amino-2,2-dimethyl-3-oxopropyl)carbonyl\}]-3-methybutyl]-1,3-oxazolidine-3-carboxylate;  
\{(4S,5S)-(N-CBz-val)\}oxyethyl \{(S)-2-(3-amino-2,2-dimethyl-3-oxopropyl)carbonyl\}]]-3-methybutyl]-1,3-oxazolidine-3-carboxylate;  
30. \{(2-methyl-2-(ethoxymethoxy)propanoyl)oxy\}methyl \{(2S)-2-[3-amino-2,2-
dimethyl-[3-oxopropyl]carbamoyl]-3-methylbutyl]-4-{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate;

{[(3-methoxy-2,2-dimethyl-3-oxopropoxy)carbonyl]oxy}methyl (4S,5S)-5-((2S)-2-{{(3-amino-2,2-dimethyl-3-oxopropyl)amino}[carbonyl]-3-methylbutyl]-4-{{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate; 1-{{(1-[(tert-butoxycarbonyl)amino]cyclopropyl}carbonyl]oxy}methyl (4S,5S)-5-((2S)-2-{{(3-amino-2,2-dimethyl-3-oxopropyl)amino}[carbonyl]-3-methylbutyl]-4-{{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate; 1-{{(1-[(tert-butoxycarbonyl)amino]cyclopropyl}carbonyl]oxy}ethyl (4S,5S)-5-((2S)-2-{{(3-amino-2,2-dimethyl-3-oxopropyl)amino}[carbonyl]-3-methylbutyl]-4-{{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate; 1-{{(1-[(tert-butoxycarbonyl)amino]methyl)cyclopropyl}carbonyl]oxy}methyl (4S,5S)-5-((2S)-2-{{(3-amino-2,2-dimethyl-3-oxopropyl)amino}[carbonyl]-3-methylbutyl]-4-{{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate; 1-{{(1-[(tert-butoxycarbonyl)amino]methyl)cyclopropyl}carbonyl]oxy}ethyl tert-butyl butanedioate; 1-{{(4S,5S)-5-((2S)-2-{{(3-amino-2,2-dimethyl-3-oxopropyl)amino}[carbonyl]-3-methylbutyl]-4-{{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate; 1-{{(1-methyl-1H-imidazol-5-yl)carbonyl]oxy}ethyl (4S,5S)-5-((2S)-2-{{(3-amino-2,2-dimethyl-3-oxopropyl)amino}[carbonyl]-3-methylbutyl]-4-{{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate; 1-(Pyridin-3-yl)oxy)ethyl (4S,5S)-5-((2S)-2-{{(3-amino-2,2-dimethyl-3-oxopropyl)amino}[carbonyl]-3-methylbutyl]-4-{{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate; 1-(Pyridin-3-yl)oxy)ethyl (4S,5S)-5-((2S)-2-{{(3-amino-2,2-dimethyl-3-oxopropyl)amino}[carbonyl]-3-methylbutyl]-4-{{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate;
(3-Methylpyridin-2-yl)carbonyloxy)methyl (4S,5S)-5-((2S)-2-][(3-amino-2,2-dimethyl-3-oxopropyl)amino][carbonyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate;
(4-Methyloxazol-5-yl)carbonyloxy)methyl (4S,5S)-5-((2S)-2-][(3-amino-2,2-dimethyl-3-oxopropyl)amino][carbonyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate;
(1-(Hydroxymethyl)cyclopropyl)carbonyloxy)methyl (4S,5S)-5-((2S)-2-][(3-amino-2,2-dimethyl-3-oxopropyl)amino][carbonyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate;
Pyridine-3-ylmethyl (4S,5S)-5-((2S)-2-][(3-amino-2,2-dimethyl-3-oxopropyl)amino][carbonyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate; and
(4S,5S)-ethyl 5-[(S)-2-[(3-amino-2,2-dimethyl-3-oxopropyl)carbamoyl]-3-methylbutyl]-4-[(S)-2-[(3-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-2,2-
dimethyloxazolidine-3-carboxylate;

or a pharmaceutically accepted salt thereof.

In one embodiment of the present invention, there is provided a compound of formula (I) wherein
the radical bonded to the nitrogen atom of the oxazolidine ring of the compound of formula (I) is selected from ethoxycarbonyl; isobutyryloxymethoxy carbonyl;
(chloromethoxy)carbonyl; 1-(isobutyryloxy)ethoxy carbonyl; (1-chloroethyl)oxy)carbonyl; pivaloyloxymethoxy carbonyl; isobutyloxycarbonyl, (N-boc-
valyloxy)methoxy carbonyl; valyloxymethoxy carbonyl; (N-CBz-
valyloxy)methoxy carbonyl; (ethoxycarbonyloxy)methoxy carbonyl; (isopropanoyloxy)carbonyl; (isopropyl)carbonyl; (iodomethoxy)carbonyl; [(2S)-2-
hydroxypropanoyloxy]methyl oxy carbonyl; [(2S)-2-
(ethoxymethoxy)propanoyloxy]methyl oxy carbonyl; [(Morpholine-4-
carboxyloxy)methoxy carbonyl; (nicotinoyloxy)methoxy carbonyl; (picolinoyloxy)methoxy carbonyl; [(2-methylpropoxycarbonyloxyl)methyl oxy carbonyl;
{{2-methyl-2-(ethoxymethoxy)propionyl}oxy}methyl oxycarbonyl; {{(pyridin-3-y1methoxy)carbonyl}oxy}methyl oxycarbonyl; {{(2-methyl-3-morpholin-4-ylpropanoyl)oxy}methyl oxycarbonyl; (1-methylpiperidine-4-carboxyloxy)methyl oxycarbonyl; {{{(1,3-dioxan-5-yl-oxycarbonyl)oxy}methyl oxycarbonyl; {{{(1,3-dioxan-4-ylmethoxy)carbonyl)oxy}methyl oxycabonyl; [{(3-hydroxy-2,2-dimethylpropanoyl)oxy}methyl oxycarbonyl; {{{(4-methoxybenzyl)oxy)carbonyl}oxy}methyl oxycarbonyl

{[(benzoyl)oxy]carbonyl}oxy}methyl oxycarbonyl; (isonicotinoxyloxy)methyl oxycarbonyl

{(1-methyl-1H-imidazol-4-yl)carbonyl}oxy}methyl oxycarbonyl; {{{(1,3-dioxan-5-yl)carbonyl}oxy}methyl oxycarbonyl; {{{(1-methyl-1H-imidazol-2-yl)carbonyl}oxy}methyl oxycarbonyl; {[(1-methyl-1H-imidazol-4-yl)methoxy]carbonyl)oxy}methyl oxycarbonyl; {[(1-methylpiperidin-4-yl)oxy]carbonyl}oxy}methyl oxycarbonyl; {[(1-methylpiperidin-4-yl)methoxy]carbonyl}oxy}methyl oxycarbonyl; {{{1-methylpiperidin-4-yl)methoxy]carbonyl}oxy}methyl oxycarbonyl; {{{(1,3-dioxan-5-yl)methoxy]carbonyl}oxy}methyl oxycarbonyl; {[(pyridin-3-yloxy)methyl oxycarbonyl

{[(3-methoxy-2,2-dimethyl-3-oxopropoxy)carbonyl]oxy}methyl oxycarbonyl;

{[(dimethylamino)carbonyl]oxy}methyl oxycarbonyl; {[(1-[(tert-butoxy)carbonyl]amino)cyclopropyl]carbonyl)oxy}methyl oxycarbonyl; {[(1-aminocyclopropyl)carbonyl]oxy}methyl oxycarbonyl; {[(1-methyl-1H-imidazol-5-yl)carbonyl]oxy}methyl oxycarbonyl; {1-[(1-methyl-1H-imidazol-2-yl)carbonyloxyl]ethyl}oxycarbonyl; 1-[(1-(N-BOC amino)-cyclopropane]carbonyloxyl-ethoxyxycarbonyl; 1-[(1-aminocyclopropane)carbonyloxyl]ethyl]oxycarbonyl; {4-(t-butoxy)-4-oxo-(2E)-but-2-enoyl]oxy}methyl oxycarbonyl; [(E)-(3-carboxy-prop-2-enoyl)oxy]methyl oxycarbonyl; [(1-azabicyclo[2.2.1]heptane-4-carbonyloxyl]methyl oxycarbonyl; {[(1-(N-BOC-amino)methylcyclopropyl]carbonyloxyl]methyl oxycarbonyl; {[(1-(aminomethyl)cyclopropyl]carbonyloxyl]methyl oxycarbonyl; {1-[(1-methyl-1H-imidazol-4-yl)carbonyloxyl]ethyl}oxycarbonyl; 1-[(pyridin-3-yl)carbonyloxyl]ethyl]oxycarbonyl; 1-[(pyridin-2-yl)carbonyloxyl]ethyl]oxycarbonyl; 1-[(t-butoxy)-4-oxo-butanoyl]oxy}methyl oxycarbonyl; [(3-carboxy-propanoyl)oxy]methyl oxycarbonyl; 1-[(4-}
(t-butoxy)-4-oxo-(2E)-but-2-enoyloxyl; 1-[(E)-(3-carboxy-prop-2-enoyloxy)ethyloxyacarbonyl; 1-[(E)-(3-carboxy-prop-2-enoyloxy)ethylcarbonyl; (1-methylpiperidin-4-yl)methyloxyacarbonyl; [(1-hydroxycyclopropyl)carbonyl]oxyethylcarbonyl; 1-[(1-methyl-1H-imidazol-5-yl)carbonyl]oxyethylcarbonyl; 1-(Pyridin-3-yloxy)ethyl]oxycarbonyl; [(2-Methylpyridin-3-yl)carbonyl]oxyethylcarbonyl; [(3-Methylpyridin-2-yl)carbonyl]oxyethylcarbonyl; [(1-(Hydroxymethyl)cyclopropyl)carbonyloxy)methyloxyacarbonyl; (Pyridine-3-yl)methyloxyacarbonyl; (N-pentanoyl-N-[[2-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-L-valyloxy)methyloxyacarbonyl; and [(4-Methyloxazol-5-yl)carbonyloxy]methyloxy]carbonyl.

The scientific and technological terms and nomenclatures used hereinbefore and hereinafter have the same meaning as commonly understood by a person of ordinary skill in the art. In addition, the following definitions shall apply throughout the specification and the appended claims unless specifically stated otherwise:

The term “halogen” denotes fluoro, chloro, bromo and iodo groups.

In this document, the sign “-“ is sometimes added to clarify which bond serves as a connection point. For example, heterocyclyl-C₁₋₃ alkyl represents a C₁₋₃ alkyl radical substituted with a heterocyclyl moiety, wherein C₁₋₃ alkyl and heterocyclyl are as defined below, where the heterocyclyl is bonded through the C₁₋₃ alkyl group. Further, RO- represents a radical wherein R is bonded to an oxygen atom and the said oxygen atom is at the connecting point for the whole radical.

The term “C₁₋₃ alkyl” denotes a straight or branched saturated alkyl group having 1 to n carbon atoms, wherein “n” is an integer from 1 to 18. Examples of “n” include 2, 3, 4, 5, 6, 7, 8 and 18. Examples of said alkyl include, but are not limited to, methyl, ethyl, propyl isopropyl, butyl, isobutyl, tert-butyl, pentyl, isopentyl and hexyl.
The term “C$_2$-C$_n$ alkenyl” denotes a straight or branched alkenyl group having saturated carbon-carbon bonds and at least one carbon-carbon double bond, and having 2 to n carbon atoms, wherein “n” is an integer from 2 to 18. Examples of “n” include 2, 3, 4, 5, 6, 7, 8 and 18. Examples of said alkenyl include, but are not limited to, ethenyl, 1-propenyl, 2-propenyl, isopropenyl and butenyl.

The term “C$_2$-C$_n$ alkynyl” denotes a straight or branched alkynyl group having saturated carbon-carbon bonds and at least one carbon-carbon triple bond, and having 2 to n carbon atoms, wherein “n” is an integer from 2 to 18. Examples of “n” include 2, 3, 4, 5, 6, 7, 8 and 18. Examples of said alkenyl include, but are not limited to ethynyl, propynyl and butynyl.

The term “C$_3$-C$_p$ cycloalkyl” denotes a saturated monocyclic ring having 3 to p carbon atoms, wherein p is an integer from 3 to 18. Examples of “p” include 2, 3, 4, 5, 6, 7, 8 and 18. Examples of said cycloalkyl include, but are not limited to cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term “C$_3$-C$_p$ cycloalkenyl” denotes a monocyclic ring having saturated carbon-carbon bonds and at least one carbon-carbon double bond, and having 3 to p carbon atoms, wherein p is an integer from 3 to 18. Examples of “p” include 2, 3, 4, 5, 6, 7, 8 and 18. Examples of said cycloalkenyl include, but are not limited to, cyclobutenyl, cyclopentenyl and cyclohexenyl.

The term “C$_4$-C$_p$ cycloalkynyl” denotes a monocyclic ring having saturated carbon-carbon bonds and at least one carbon-carbon triple bond, and having 4 to p carbon atoms, wherein p is an integer from 3 to 18. Examples of “p” include 2, 3, 4, 5, 6, 7, 8 and 18. Examples of said cycloalkynyl include, but are not limited to, cyclobutynyl cyclopentynyl and cyclohexynyl.

The term “C$_1$-C$_n$ alkoxy” denotes a C$_1$-C$_n$ alkyl as defined above linked to oxygen, i.e. C$_1$-C$_n$ alkyl-O. Examples of said alkoxy include, but are not limited to, methoxy, ethoxy, n-propoxy, isopropoxy and butyloxy.
The term “oxo” denotes a double-bonded oxygen atom. The oxo group may be attached to a carbon atom forming a carbonyl moiety or to a sulfur atom forming a sulfone moiety.

The term “C_{3-n}cycloalkyl-C_{1-n}alkyl” denotes a C_{1-n}alkyl as defined above substituted with a C_{3-n}cycloalkyl as defined above.

The term “C_{3-n}cycloalkyl-C_{2-n}alkenyl” denotes a C_{2-n}alkenyl as defined above substituted with a C_{3-n}cycloalkyl as defined above.

The term “C_{3-n}cycloalkyl-C_{2-n}alkynyl” denotes a C_{2-n}alkynyl as defined above substituted with a C_{3-n}cycloalkyl as defined above.

The term “aryl” denotes an aromatic ring or an aromatic ring fused with aromatic or non-aromatic carbocyclic or heterocyclic ring or rings forming a mono-, bi- or tricyclic ring system composed of 6-14 carbon atoms, preferably 6-10 carbon atoms. Examples of said aryl include, but are not limited to, phenyl, naphthyl, biphenyl, 2-naphthyl, tetrahydronaphthyl, 2-indenyl, 4-indenyl and indanyl.

The term “aryl-C_{1-n}alkyl” denotes a C_{1-n}alkyl as defined above substituted with an aryl as defined above.

The term “aryl-C_{2-n}alkenyl” denotes a C_{2-n}alkenyl as defined above substituted with an aryl as defined above.

The term “aryl-C_{2-n}alkynyl” denotes a C_{2-n}alkynyl as defined above substituted with an aryl as defined above.

The term “heterocyclyl” denotes a saturated, partially unsaturated or aromatic mono-, bi- or tricyclic ring system composed of 4-18 atoms in which 1, 2, 3 or 4 of the atoms in the ring(s) is an element other than carbon independently selected from one or more of
nitrogen, oxygen or sulphur. The term “nitrogen” shall be understood to include nitrogen oxide (NO). The term “sulphur” shall be understood to include “sulphoxide” (S(O)) and sulphone (SO₂). Examples of said heterocyclyl include, but are not limited to pyrrolidino, piperidino, oxetanyl, pyridinyl, piperazino, morpholino, dioxanyl, thiomorpholino, furanyl, tetrahydrofuranyl, pyranyl, tetrahydropyranyl, thiazolyl, oxazolyl, thiazinolyl, imidazolyl, triazolyl, tetrazolyl, isoxazolyl, oxadiazolyl, indoliny1, isoindoliny1, 2,3-dihydrobenzimidazolyl, 1,2,3,4-tetrahydroquinolyl, 1,2,3,4-tetrahydroisoquinolyl, 1,2,3,4-tetrahydro-1,3-benzodiazinyl, 1,2,3,4-tetrahydro-1,4-benzodiazinyl, 3,4-dihydro-2H-1,4-benzoxazinyl, 3,4-dihydro-2H-1,4-benzothiazinyl, 3,4,5,6,7,8-hexahydro-2H-1,4-benzoxazinyl, 3,4,5,6,7,8-hexahydro-2H-1,4-benzothiazinyl, 9-azabicyclo[3.3.1]non-9-yl, 1-azepan-1-yl, 2,8-diazaspiro[4.5]deca-8-yl, octahydroisoindol-2-yl, 3,7-diazabicyclo[3.3.1]non-3-yl, 3-azabicyclo[3.3.1]non-3-yl, 8-azabicyclo[3.2.1]octa-8-yl, 3-azabicyclo[3.2.2]non-3-yl, 5,6-dihydrophenanthridinyl, isoquinoliny1, tetrahydroisoquinolinyl, quinazoliny1, tetrahydroquinazoliny1, quinoxaliny1, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazinolyl, benzothiazolyl, benzoxazolyl, benzo-1,2,3-triazolyl, benzo-1,2,4-triazolyl, benzotetrazolyl, benzofurany1, benzothienyl, benzopyridyl, benzopyrimidinyl, benzopyrazinyl, benzopyrazolyl, indoliny1, isoindoliny1 indoliny1 and isoindoliny1.

The term “heterocyclyl-C₃-C₈-alkyl” denotes a C₃-C₈-alkyl as defined above substituted with a heterocyclyl as defined above.

The term “heterocyclyl-C₃-C₈-alkenyl” denotes a C₃-C₈-alkenyl as defined above substituted with a heterocyclyl as defined above.

The term “heterocyclyl-C₃-C₈-alkynyl” denotes a C₃-C₈-alkynyl as defined above substituted with a heterocyclyl as defined above.

The radical tetrazolyl-biphenyl-methyl-heterocyclyl denotes heterocyclyl substituted with methyl, said methyl being substituted with biphenyl, said biphenyl being substituted with tetrazolyl. The same reasoning applies to tetrazolyl-biphenyl-methyl-heterocyclymethyl,
tetrazoly1-biphenyl-methyl-amino-C1-C6alkyl, oxadiazolyl-biphenyl-methyl-heterocyclyl and so on.

Unless otherwise indicated, the alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, aryl and heterocyclyl (including those in composite expressions such as aryl-alkyl or heterocyclyl-alkyl) are independently optionally substituted with one or more substituents independently selected from halogen, hydroxyl, amino, oxo, mercapto, amido, cyano, azido, nitro, optionally substituted C1-C3alkyl, C2- C4alkenyl, C2-C4alkynyl, C3-
C6cycloalkyl, C1-C4alkoxy, haloC1-C4alkyl, polyhaloC1-C4alkyl, hydroxyl-C1-C4alkyl, C1-
C8alkylcarbonyl. It should be noted that the radical positions on any molecular moiety used in the definitions may be anywhere on such a moiety as long as it is chemically permitted and stable.

The term “optionally substituted” as used herein, means that substitution is optional, i.e. there may or may not be substitution. For instance, the expression “alkyl group optionally substituted with one or more substituents” means that the alkyl group is substituted by zero, one or more substituents.

The term “substituted” refers to a molecule wherein at least one hydrogen atom is replaced with a substituent.

Radicals used in the definitions of the variables include all possible isomers unless otherwise indicated. For instance pyridyl includes 2-pyridyl, 3-pyridyl and 4-pyridyl; penty1 includes 1-pentyl, 2-pentyl, 3-pentyl and the like. When any variable occurs more than one time in any constituent, each definition is independent.

Commonly used leaving groups, in the present invention also denoted L1 and/or L2, include, but are not limited to Cl, Br, I, sulfonates such as mesylate, brosylate, tosylate, triflate, nosylate, tresylate and the like.

While not wishing to be bound by any specific theory, it is believed that the compounds of the invention may serve as prodrugs. A prodrug may be defined as the temporary derivatization of one or several functional groups of a drug in such a manner as to release

The compounds of formulas (I) or their metabolites have activity as medicaments. In particular, the compounds of formula (I) or their metabolites may be renin inhibitors or prodrugs of renin inhibitors.

The compounds according to the present invention exhibit improved or enhanced properties compared to aliskiren or other renin inhibitors with respect to at least one of the following parameters: bioavailability, absorption, permeability through intestinal tract, permeability through skin, absorption by various drug administration routes, interaction with intestinal efflux system, drug-drug interaction, physico-chemical properties, pharmacokinetic properties, pharmacodynamic properties, such as $t_{1/2}$, $t_{\text{max}}$, clearance, distribution, excretion, metabolic properties, during of action, interaction with Cytochrom p450 isozymes, properties for formulation, properties for production, inhibition of renin, inhibition of plasma renin activity, in vivo efficacy of renin activity inhibition, in vivo efficacy of treating or preventing hypertension, in vivo end-organ protection and properties in combination therapy with other medicines with cardiovascular effect.

Suitable tests for measurement of the above parameters include, but are not limited to, physico-chemical properties, stability in biological fluids, caco-2 permeability, PAMPA permeability (i.e. parallel artificial membrane permeability assay), interaction with efflux system, interaction with intestinal transporters, drug-drug interaction, interaction with CYP isozymes, permeation through skin, formulation properties for transdermal administration, formulation properties for various administration routes, in vivo pharmacokinetics in experimental animals via various administration routes, in vivo pharmacodynamics in experimental animals, in silico simulation of pharmacokinetic or pharmacodynamic properties, in silico simulation of physico-chemical properties, properties for drug delivery formulations, metabolism in liver extracts, metabolism in hepatocytes, safety properties, renin enzymatic assay, plasma renin activity, efficacy of treating or preventing hypertension in experimental animals, efficacy of end-organ protection in experimental
animal, effect in combination therapy for hypertension or hypertension-related disorders and so on.

5 Certain compounds of the present invention may exist as tautomers or stereoisomers (e.g. racemate, enantiomer, diastereomer or E- or Z-isomer). It is to be understood that the present invention encompasses all such tautomers or stereoisomers.

Certain compounds of the present invention may exist as solvates or hydrates. It is to be understood that the present invention encompasses all such solvates or hydrates.

The compounds of the present invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium \(^{(3}H\), iodine-125 \((^{125}I)\) or carbon-14 \((^{14}C)\). All isotopic variations of the compounds of the present invention, whether radioactive or not, are intended to be encompassed within the scope of the present invention.

A suitable pharmaceutically acceptable salt of a compound of the invention is, for example, an acid-addition salt of a compound of the invention which is sufficiently basic, for example, an acid-addition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, nitric, methansulphonic, sulphuric, phosphoric, trifluoroacetic, para-toluene sulphonylic, 2-metylen sulphonylic, citric, acetic, tartaric, fumaric, lactic, succinic, malic, malonic, maleic, 1,2-ethanedisulphonic, adipic, aspartic, benzenesulphonic, benzoic, ethanesulphonic or nicotinic acid. In addition a suitable pharmaceutically acceptable salt of a compound of the invention, is, for example, a base-addition salt of a compound of the invention which is sufficiently acidic, for example, a metal salt, for example, sodium, potassium, calcium, magnesium, zinc or aluminum, an ammonium salt, a salt with an organic base which affords a physiologically acceptable cation, which includes quaterly ammonium hydroxides, for example methylamine, ethylamine, diethylamine, trimethylamine, tert- butylamine, triethylamine, dibenzylamine, N,N-dibenzylethylamine, cyclohexylethylamine, tris-(2-hydroxyethyl)amine, hydroxyethyl
diethylamine, (IR, 2S)-2-hydroxyinden-l-amine, morpholine, N-methylpiperidine, N-ethylpiperidine, piperazine, methylpiperazine, adamantylamine, choline hydroxide, tetrabutylammonium hydroxide, tris-(hydroxymethyl)methylamine hydroxide, L-arginine, N-methyl D-glucamine, lysine or arginine.

The present invention also relates to a process for preparing a compound of formula (I), wherein \( R^1, R^2, R^3 \) and \( R^4 \) are H, said process comprising the steps of

a) reacting a compound of formula (II)

\[
\text{H}_2\text{N}^{\text{III}}\text{Y}\text{M}^{\text{IV}}\text{U}^{\text{V}}\text{V}^{\text{VI}}\text{A}^{\text{VII}}\text{Q}^{\text{VIII}}
\]

wherein \( M, Y, U, V, A, R^5 \) and \( Q \) are as defined above, with a compound of formula (VIII),

\[
\text{L}^2\text{X}^2\text{X}^1\text{L}^1
\]

wherein \( X^1 \) and \( X^2 \) are as defined above and \( L^1 \) and \( L^2 \) are leaving groups independently selected from Cl, Br, I, sulfonates such as mesylate, brosylate, tosylate, triflate, nosylate and tresylate, under basic conditions in an inert solvent or mixture of inert solvents to obtain a compound of formula (IX)
b) subsequently reacting the compound of formula (IX) with a compound of formula (X) or a salt thereof,

$$R^6 \text{OH}$$  

(X)

wherein $R^6$ is as defined in any previous claim, under basic conditions in an inert solvent or mixture of inert solvents.

The present invention also relates to a compound of general formula (IX)

$$L^2$$  

(IX)

wherein $X^1$, $X^2$, $M$, $Y$, $U$, $V$, $A$, $R^5$ and $Q$ are as defined above and $L^2$ is as defined above.

**Pharmaceutical preparations**

The compounds of the present invention will normally be administrated via the oral, parenteral, intravenous, intramuscular, subcutaneous or other injectable ways, buccal, rectal, vaginal, transdermal and/or nasal route and/or via inhalation, in the form of
pharmaceutical preparations comprising the active ingredient or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, in a pharmaceutically acceptable dosage form. Depending upon the disorder and patient to be treated and the route of administration, the compositions may be administered at varying doses.

According to a further aspect of the invention there is provided a pharmaceutical composition including any of the compounds of the invention, or pharmaceutically acceptable derivatives thereof, in admixture with pharmaceutically acceptable excipients, oils which may be glycerides, diluents and/or carriers.

**Pharmacological properties**

The compounds of the formula (I) and their pharmaceutically usable salts, or metalated derivatives thereof (i.e. metal coordinated compounds or metal complexes), are renin inhibitors or prodrugs of renin inhibitors and may be used for the medication related to the inhibition of renin.

The compounds of the present invention may be used for the treatment of hypertension, congestive heart failure, cardiac hypertrophy, cardiac fibrosis, atherosclerosis; cardiac failure, cardiomyopathy, postinfarction, complications owing to diabetes such as nephropathy, vasculopathy and neuropathy, diseases of the cardiac vessels, restenosis after angioplasty, increased intraocular pressure, glaucoma, abnormal vascular growth, hyperaldosteronism, states of anxiety and cognitive disorders. The present invention further provides the use of a compound of formula (I) and pharmaceutically acceptable salts thereof in the treatment or prevention of hypertension and heart failure, and also glaucoma, cardiac infarction and kidney failure.

The present invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof for the preparation of a medicament for the treatment and/or prophylaxis of hypertension, congestive heart failure, cardiac hypertrophy, cardiac fibrosis, atherosclerosis; cardiac failure, cardiomyopathy, postinfarction, complications owing to diabetes such as nephropathy, vasculopathy and neuropathy, diseases of the cardiac vessels, restenosis after angioplasty, increased intraocular pressure, glaucoma, abnormal
vascular growth, hyperaldosteronism, states of anxiety and cognitive disorders, preferably hypertension.

In a further aspect, the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for the treatment and/or prevention of hypertension, congestive heart failure, cardiac hypertrophy, cardiac fibrosis, atherosclerosis; cardiac failure, cardiomyopathy, postinfarction, complications owing to diabetes such as nephropathy, vasculopathy and neuropathy, diseases of the cardiac vessels, restenosis after angioplasty, increased intraocular pressure, glaucoma, abnormal vascular growth, hyperaldosteronism, states of anxiety and cognitive disorders, preferably hypertension.

Further, the present invention provides a method of treating and/or preventing hypertension, congestive heart failure, cardiac hypertrophy, cardiac fibrosis, atherosclerosis; cardiac failure, cardiomyopathy, postinfarction, complications owing to diabetes such as nephropathy, vasculopathy and neuropathy, diseases of the cardiac vessels, restenosis after angioplasty, increased intraocular pressure, glaucoma, abnormal vascular growth, hyperaldosteronism, states of anxiety and cognitive disorders comprising the administration of a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof, to a mammal in need thereof.

The present invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof for the preparation of a medicament for the treatment and/or prophylaxis of severe hypertension, pulmonary hypertension (PH), malignant hypertension, isolated systolic hypertension, familial dyslipidemic hypertension, high blood pressure, unstable coronary syndrome, ischaemic heart disease and ischaemic heart damage, myocardial infarction, unstable coronary syndrome, cardiac fibrosis, atherosclerosis, cardiomyopathy, vasculopathy, diastolic dysfunction, elevated total cholesterol, low LDL cholesterol, peripheral vascular disease (PVD), peripheral artery disease (PAD), peripheral venous disorders, coronary arterial disease (CAD), cerebrovascular diseases, metabolic disorder (Syndrome X), atrial fibrillation (AF), vascular inflammation, vasculitides or closure, aneurysm, angina, restenosis of dialysis
access grafts, renal failure, renoprotection, complications owing to diabetes such as nephropathy, glomerulonephritis, nephrotic syndrome, renal fibrosis, acute interstitial nephritis (AIN), acute tubular nephritis (ATN), acute tubulo-interstitial nephritis, polycystic kidney disease (PKD), endothelial dysfunction and or microalbuminuria,

In a further aspect, the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for the treatment and/or prevention of severe hypertension, pulmonary hypertension (PH), malignant hypertension, isolated systolic hypertension, familial dyslipidemic hypertension, high blood pressure, unstable coronary syndrome, ischaemic heart disease and ischaemic heart damage, myocardial infarction, unstable coronary syndrome, cardiac fibrosis, atherosclerosis, cardiomyopathy, vasculopathy, diastolic dysfunction, elevated total cholesterol, low LDL cholesterol, peripheral vascular disease (PVD), peripheral artery disease (PAD), peripheral venous disorders, coronary arterial disease (CAD), cerebrovascular diseases, metabolic disorder (Syndrome X), atrial fibrillation (AF), vascular inflammation, vasculitides or closure, aneurysm, angina, restenosis of dialysis access grafts, renal failure, renoprotection, complications owing to diabetes such as nephropathy, glomerulonephritis, nephrotic syndrome, renal fibrosis, acute interstitial nephritis (AIN), acute tubular nephritis (ATN), acute tubulo-interstitial nephritis, polycystic kidney disease (PKD), endothelial dysfunction and or microalbuminuria,

Further, the present invention provides a method of treating and/or preventing severe hypertension, pulmonary hypertension (PH), malignant hypertension, isolated systolic hypertension, familial dyslipidemic hypertension, high blood pressure, unstable coronary syndrome, ischaemic heart disease and ischaemic heart damage, myocardial infarction, unstable coronary syndrome, cardiac fibrosis, atherosclerosis, cardiomyopathy, vasculopathy, diastolic dysfunction, elevated total cholesterol, low LDL cholesterol, peripheral vascular disease (PVD), peripheral artery disease (PAD), peripheral venous disorders, coronary arterial disease (CAD), cerebrovascular diseases, metabolic disorder (Syndrome X), atrial fibrillation (AF), vascular inflammation, vasculitides or closure, aneurysm, angina, restenosis of dialysis access grafts, renal failure, renoprotection,
complications owing to diabetes such as nephropathy, glomerulonephritis, nephrotic syndrome, renal fibrosis, acute interstitial nephritis (AIN), acute tubular necrosis (ATN), acute tubulo-interstitial nephritis, polycystic kidney disease (PKD), endothelial dysfunction and or microalbuminuria comprising the administration of a therapeutically effective amount a compound of formula (I) or a pharmaceutically acceptable salt thereof, to a mammal in need thereof.

The present invention relates to the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof or a pharmaceutically acceptable salt thereof for the preparation of a medicament for the treatment and/or prophylaxis of hypertension, severe hypertension, pulmonary hypertension (PH), malignant hypertension, isolated systolic hypertension or familial dyslipidemic hypertension, heart failure, glaucoma, cardiac infarction, kidney failure, or restenosis.

The present invention relates to a method of treating and/or preventing hypertension, severe hypertension, pulmonary hypertension (PH), malignant hypertension, isolated systolic hypertension, familial dyslipidemic hypertension, comprising the administration of a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof or claim hereinbefore or hereinafter or a pharmaceutically acceptable salt thereof to a mammal in need thereof.

The dose may vary within wide limits and has of course to be adapted to the individual circumstances in each individual case. In general, for oral administration, a daily dose of about 1 mg to about 2 g, preferably about 5 mg to about 1 g, per adult (assuming a weight of approximately 70 kg for the adult), divided into preferably 1-3 individual doses which may, for example, be of equal size, may be appropriate, although the upper limit specified may also be exceeded if this should be found to be appropriate; typically, children receive a lower dose according to their age and body weight.
Combinations

The compounds of the present invention and the pharmaceutically usable salts thereof may also be administered in combination with one or more additional agents having cardiovascular action, for example α- and β-blockers, calcium channel blockers, diuretics, 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, acetotolol, 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. 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 flunarzine, prenylamine, diltiazem, fendiline, gallopamil, mibebradil, anipamil, tiapamil, and verapamil and their pharmaceutically acceptable salts.

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

ACE inhibitors include alacepril, benazepril, benazapriat, captoprilm, ceronaprilm, cilazapril, delapril, enalapril, enalaprilat, fosinopril, lisinopril, moexipril, moveltorpl, perindopril, quinapril, quinaprilat, ramipril, ramiprilat, spirapril, temocapril, trandolapril, and zofenopril. Preferred ACE inhibitors are benazepril, enalpril, lisinopril, and ramipril.

Dual ACE/NEP inhibitors are, for example, omapatrilat, fasidotril, and fasidotrilat.
Preferred ARBs include candesartan, eprosartan, irbesartan, losartan, olmesartan, tasosartan, telmisartan, azilsartan and valsartan.

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

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.

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

The present invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof together with one or more of the compounds described in this combination section for the preparation of a medicament for the treatment and/or prophylaxis of hypertension, congestive heart failure, cardiac hypertrophy, cardiac fibrosis, atherosclerosis; cardiac failure, cardiomyopathy, postinfarction, complications owing to diabetes such as nephropathy, vasculopathy and neuropathy, diseases of the cardiac vessels, restenosis after angioplasty, increased intraocular pressure, glaucoma, abnormal vascular growth, hyperaldosteronism, states of anxiety and cognitive disorders, preferably hypertension.

In a further aspect, the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof together with one or more of the compounds described in this combination section for the treatment and/or prevention of hypertension, congestive heart failure, cardiac hypertrophy, cardiac fibrosis, atherosclerosis; cardiac failure, cardiomyopathy, postinfarction, complications owing to diabetes such as nephropathy, vasculopathy and neuropathy, diseases of the cardiac vessels, restenosis after
angioplasty, increased intraocular pressure, glaucoma, abnormal vascular growth, hyperaldosteronism, states of anxiety and cognitive disorders, preferably hypertension.

Further, the present invention provides a method of treating and/or preventing hypertension, congestive heart failure, cardiac hypertrophy, cardiac fibrosis, atherosclerosis; cardiac failure, cardiomyopathy, postinfarction, complications owing to diabetes such as nephropathy, vasculopathy and neuropathy, diseases of the cardiac vessels, restenosis after angioplasty, increased intraocular pressure, glaucoma, abnormal vascular growth, hyperaldosteronism, states of anxiety and cognitive disorders comprising the administration of a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof together with one or more of the compounds described in this combination section, to a mammal in need thereof.

The present invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof together with one or more of the compounds described in this combination section for the preparation of a medicament for the treatment and/or prophylaxis of severe hypertension, pulmonary hypertension (PH), malignant hypertension, isolated systolic hypertension, familial dyslipidemic hypertension, high blood pressure, unstable coronary syndrome, ischaemic heart disease and ischaemic heart damage, myocardial infarction, unstable coronary syndrome, cardiac fibrosis, atherosclerosis, cardiomyopathy, vasculopathy, diastolic dysfunction, elevated total cholesterol, low LDL cholesterol, peripheral vascular disease (PVD), peripheral artery disease (PAD), peripheral venous disorders, coronary arterial disease (CAD), cerebrovascular diseases, metabolic disorder (Syndrome X), atrial fibrillation (AF), vascular inflammation, vasculitides or closure, aneurysm, angina, restenosis of dialysis access grafts, renal failure, renoprotection, complications owing to diabetes such as nephropathy, glomerulonephritis, nephrotic syndrome, renal fibrosis, acute interstitial nephritis (AIN), acute tubular nephritis (ATN), acute tubulo-interstitial nephritis, polycystic kidney disease (PKD), endothelial dysfunction and or microalbuminuria.

In a further aspect, the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof together with one or more of the compounds
described in this combination section for the treatment and/or prevention of severe hypertension, pulmonary hypertension (PH), malignant hypertension, isolated systolic hypertension, familial dyslipidemic hypertension, high blood pressure, unstable coronary syndrome, ischaemic heart disease and ischaemic heart damage, myocardial infarction, unstable coronary syndrome, cardiac fibrosis, atherosclerosis, cardiomyopathy, vasculopathy, diastolic dysfunction, elevated total cholesterol, low LDL cholesterol, peripheral vascular disease (PVD), peripheral artery disease (PAD), peripheral venous disorders, coronary arterial disease (CAD), cerebrovascular diseases, metabolic disorder (Syndrome X), atrial fibrillation (AF), vascular inflammation, vasculitides or closure, aneurysm, angina, restenosis of dialysis access grafts, renal failure, renoprotection, complications owing to diabetes such as nephropathy, glomerulonephritis, nephrotic syndrome, renal fibrosis, acute interstitial nephritis (AIN), acute tubular nephritis (ATN), acute tubulo-interstitial nephritis, polycystic kidney disease (PKD), endothelial dysfunction and or microalbuminuria.

Further, the present invention provides a method of treating and/or preventing severe hypertension, pulmonary hypertension (PH), malignant hypertension, isolated systolic hypertension, familial dyslipidemic hypertension, high blood pressure, unstable coronary syndrome, ischaemic heart disease and ischaemic heart damage, myocardial infarction, unstable coronary syndrome, cardiac fibrosis, atherosclerosis, cardiomyopathy, vasculopathy, diastolic dysfunction, elevated total cholesterol, low LDL cholesterol, peripheral vascular disease (PVD), peripheral artery disease (PAD), peripheral venous disorders, coronary arterial disease (CAD), cerebrovascular diseases, metabolic disorder (Syndrome X), atrial fibrillation (AF), vascular inflammation, vasculitides or closure, aneurysm, angina, restenosis of dialysis access grafts, renal failure, renoprotection, complications owing to diabetes such as nephropathy, glomerulonephritis, nephrotic syndrome, renal fibrosis, acute interstitial nephritis (AIN), acute tubular nephritis (ATN), acute tubulo-interstitial nephritis, polycystic kidney disease (PKD), endothelial dysfunction and or microalbuminuria comprising the administration of a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof together with one or more of the compounds described in this combination section, to a mammal in need thereof.
The present invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof together with one or more of the compounds described in this combination section for the preparation of a medicament for the treatment and/or prophylaxis of hypertension, severe hypertension, pulmonary hypertension (PH), malignant hypertension, isolated systolic hypertension or familial dyslipidemic hypertension.

The present invention provides a method of treating and/or preventing hypertension, severe hypertension, pulmonary hypertension (PH), malignant hypertension, isolated systolic hypertension, familial dyslipidemic hypertension, comprising the administration of a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof together with one or more of the compounds described in this combination section, to a mammal in need thereof.

Methods of preparation

The compounds of the present invention may be prepared as outlined in the Schemes below. However, the invention is not limited to these methods. The compounds may also be prepared as described for structurally related compounds in the prior art. The reactions can be carried out according to standard procedures or as described in the experimental section. Hence, the compounds of the present invention may be prepared by any of the applicable methods and techniques of organic synthesis known to the skilled person.

In the course of the process described below for the preparation of compounds of formula (I), functional groups in starting materials which are prone to participate in undesired side reactions, especially amino, carboxy, hydroxy, and mercapto groups, may be protected by suitable conventional protecting groups which are customarily used in the organic synthesis. 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, or by photolysis. 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 in standard works.

Schemes 1-5 illustrate different processes for synthesizing compounds of formula (I) or a compound which may be converted to a compound of formula (I).

Scheme 1 describes a method of preparation of compounds according to formula (I), wherein $R^1$, $R^2$, $R^3$, $R^4$, $X^1$, $X^2$, $W$, $M$, $Y$, $U$, $V$, $A$, $R^5$ and $Q$ are as defined above hereinbefore or hereinafter. The vicinal aminoalcohol of formula (II), which may be a renin inhibitor, is reacted with a reagent containing $R^1$ and $R^2$ groups such as common
aldehydes, ketones or dialkylacetals which include, for example, formaldehyde, dimethoxymethane, acetone, acetaldehyde, 1,1-dimethoxyethane and 2,2-dimethoxypropane, cyclopropanone, cyclobutanone, cyclopentanone, cyclohexanone, 2-methoxypropene-1 and the like. Solvents, if used, for the reaction may either be a single inert solvent or a mixture of inert solvents, such as dichloromethane, chloroform, acetonitrile, THF, 1,4-dioxane, DMF, benzene, toluene, 2,6-lutidine or acetone. The reaction may require dehydrating agents, such as molecular sieves and/or other water binding materials, or conditions. The reaction may be performed at room temperature or at elevated temperatures. An acid catalyst may be needed for the reaction. Commonly used catalysts for the reaction include organic or inorganic acids such as sulfonic acids, trifluoroacetic acid, Lewis acids, hydrochloric acids and the like. In some cases, the compound of formula (IV) may be prepared by reacting the amino and hydroxyl group of formula (II) with polymerized aldehydes, for example paraformaldehyde. In the reaction with formaldehyde, the product obtained may be a mixture of a monomer and a dimers with methylene bridge connecting the two oxazolidine rings as reported in the literature (Salos-Coronado R. et al, Heterocycles, 60, 2003, 1118). The compound of formula (IV) may be subsequently acylated with the desired acylating agents. The N-acylation reaction may be performed by using activated acylating reagents or by the addition of coupling agents using the typical procedures in chemical literature. Wherever needed, the desired acylating reagent should be properly protected by the appropriate protecting group. The commonly used activated forms of the acylating agents include, but are not limited to, alkoxy carbonyl chloride, alkoxy carbonyl bromide, alkoxy thiocarbonyl chloride, and their appropriate derivatives. The reaction may be performed in the presence of a base, such as triethylamine, DIPEA, DMAP, potassium carbonate, sodium carbonate, cesium carbonate, DBU, pyridines, or other organic or inorganic bases suitable for such reactions. Commonly used solvents for the reaction include dichloromethane, dichloroethane, chloroform, THF, DMF, 1,4-dioxane, acetonitrile and other common solvents suitable for acylation reaction. The reaction may be performed at room temperature or elevated temperature. The reaction process may be monitored by LCMS, TLC and/or other methods. The products are isolated using common purification methods, such as column chromatography, crystallization or distillation.
Scheme 2 describes a method of preparation of compounds according to formula (I), wherein $R^1$, $R^2$, $R^3$, $R^4$, $X^1$, $X^2$, $W$, $M$, $Y$, $U$, $V$, $A$, $R^5$ and $Q$ are as defined above. The amino group of the compound of formula (II), which may be a renin inhibitor, is reacted with an appropriate reagent, for example alkoxy carbonyl chloride, to form an N-acylated intermediate of formula (III) which may subsequently react with various cyclization agent such as aldehyde/ketone like formaldehyde, acetaldehyde, acetone or acetal/ketal like 2,2-dimethoxy propane, 1,1-dimethoxyethane in the presence of acidic catalysts like p-toluenesulfonic acid or Lewis acids, in particular boron trifluoride etherate, to afford a compound of formula (I). (See, for instance, Vidyasagar Reddy G et al, Tetrahedron Lett., 2000, 41, 949-51 and Jian-kang J. et al, J. Med. Chem., 51, 2008, 8012-8.)

It is understood that some compounds of formula (I) may be further modified to obtain desired compounds which can also be represented by formula (I). The methods for such modifications depend on the structures of the desired products and the structure of the compound of formula (I). Such modification reaction may involve deprotection,
substitution, addition, oxidation, reduction and other chemical transformations which are common in organic syntheses.

Scheme 3 describes a method of preparation for a compound of formula (I) wherein W is ZTC(O)O, R₁, R², R³, M, Y, U, V, Z, T, A, R⁵ and Q are as defined above, herein named compound (VI). The amino and hydroxyl group of formula (II) may be converted to a compound of formula (IV) as shown in Scheme 1. The compound of formula (IV) may be subsequently converted to a compound of formula (V) by reaction with a 1-haloalkyloxycarbonyl halide, for example chloromethyl chloroformate, 1-chloroethyl
chloroformate. The chlorine of the compound of formula (V) may be substituted by an appropriate carboxylic acid, its salt or a salt of carbonate monoester. Alternatively, the chloromethyl group of the compound of formula (V) may be converted to bromo- or iodomethyl group, which is then followed by the substitution reaction. The conversion to bromomethyl group or iodomethyl can be performed in situ by standard procedures known to chemists skilled in the art. The compound of formula (V) may be reacted with a carboxylic acid, its salt or a salt of carbonate monoester to afford a compound of formula (I) wherein W is ZTC(O)O-. The reaction may be performed at room temperature or elevated temperature in inert solvents, such as dichloromethane, 1,2-dichloroethane, acetonitrile, THF, DMF, NMP or other suitable solvents. The reaction can be performed with the addition of appropriate bases, for example triethylamine, DIPEA, DMAP, potassium carbonate, sodium carbonate, cesium carbonate, silver carbonate, tetra-n-butylammonium hydroxide or other suitable organic or inorganic bases. The carboxylic acids include for example aliphatic carboxylic acids, aromatic carboxylic acids, heterocyclic containing aliphatic carboxylic acids and so on. The salts of carbonate monoesters include for example cesium salts of carbonate alkyl monoester, carbonate aryl monoester, carbonate heterocycl-containing-alkyl monoester. When carboxylic acids, carboxylic acid salts or salts of carbonate monoester are used, they are containing functional groups which are prone to participate in undesired side reactions, especially amino, carboxy, hydroxy, and mercapto groups, these functional groups may be protected by suitable conventional protecting groups, which are customarily used in organic synthesis.
Scheme 4 describes an alternative method of preparation for a compound of formula (I) wherein W is ZOC(O)O, both R² and R⁴ are H, R¹, R², X¹, M, Y, U, V, A, R⁵ and Q are as defined above, herein named compound of formula (VII). Z is preferably a C₁-C₆ alkyl group as described hereinbefore or hereinafter. The oxazolidine of formula (IV) may be prepared as described above, and subsequently reacted with carbon dioxide in the presence of cesium carbonate followed by reaction with an appropriate reagent such as (alkyloxy)carbonyloxy-chloromethane. This may be a one-pot reaction. Suitable solvents for the reaction include DMF and THF. The product of formula (VII) may be isolated by purification methods known to persons skilled in the art.
Scheme 5 describes a method of preparation of compounds of formula (IX), which may be further converted to compounds of formula (I). The amino group and hydroxyl group of a compound of formula (II) may be reacted with a compound of formula (VIII) to form a compound of formula (IX). In scheme 5, M, Y, U, V, A, R^6, Q, X^1 and X^2 are as defined above. L^1 and L^2 are leaving groups, such as Cl, Br, I, sulfonates such as mesylate, brosylate, tosylate, triflate, nosylate and tresylate. The reaction may be performed in the presence of a base such as sodium carbonate, potassium carbonate or cesium carbonate. The compound of formula (VIII) may be chloromethyl chloroformate.

It is to be understood that the method of preparation described in Scheme 5 is not limited to amino alcohols of formula (II), but may be performed with other vicinal amino alcohols.

**Examples**

The present invention is illustrated, but not limited, by the following Examples.
Abbreviations

DIPEA  \(N,N\)-diisopropylethylamine;

DMAP  4-dimethylaminopyridine;

DBU  2,3,4,6,7,8,9,10-octahydropyrimidol[1,2-a]azepine;

EtOAc  ethyl acetate;

Et\(_3\)N  triethylamine;

THF  tetrahydrofuran;

DMF  \(N,N\)-dimethylformamide;

DCM  dichloromethane;

iPrOH  isopropanol;

LCMS  liquid chromatography mass spectroscopy;

TLC  thin layer chromatography;

TFA  trifluoroacetic acid;

NMP  N-methylpyrrolidone;

NMR  nuclear magnetic resonance;

IR  infrared spectroscopy;

MS  mass spectrometry;

h  hour(s);

min. or min  minute(s);

ng  nanogram;

ml  milliliter;

p.o or p.o  per oral;

AUC  area under the curve;

Rpm.  Rotation per minute;

i.v. or i.v  intravenous.

General Experimental Procedures

All evaporations are performed under reduced pressure, preferably between 2 and 100mmHg. All temperatures are reported in Celsius degree. Unless stated otherwise, the reaction takes place at room temperature. In general, abbreviations used are those conventional in the art. The structure of final products and intermediates is confirmed by
standard analytical methods, e.g. melting points, LC/MS (Agilent 1200/6120 system), NMR (Jeol 500MHz NMR Spectrometer)).

The naming of the compounds in this document was made using the program “ChemOffice Pro Version 11” provided by Cambridge Scientific Computing Inc. If there is any inconsistency between the chemical name of the exemplified chemical compound and corresponding structure of said example, then the chemical structure should be used for determining the chemical compound of said example.

Example 1

\[(4S,5S)-5-\{(2S)-2-\{(3-amino-2,2-dimethyl-3-oxopropyl)amino\}carbonyl\}-3-methylbutyl\}-4-\{(2S)-2-\{4-methoxy-3-(3-methoxypropoxy)benzyl\}-3-methylbutyl\}-1,3-oxazolidine\]

To a solution of Aliskiren (free base, 100 mg) in THF (3 ml), which is cooled in ice bath, formaline (equimolar amount of 37% water solution of paraformaldehyde, 15\(\mu\)l) was added and the reaction was kept under stirring for 5h at cooling in an ice bath. To the reaction was then added water and dichloromethane. After extraction, the dichloromethane layer was collected and washed with brine and dried over magnesium sulfate. The solution was filtered and concentrated by rotary evaporation to give (102 mg) of white foam. MS: 564 [M+1]+, 587[M+Na]+

Example 2

\[(4S,5S)-ethyl\ 5-\{(S)-2-\{(3-amino-2,2-dimethyl-3-oxopropylcarbamoyl)\}carbonyl\}-3-methylbutyl\}-4-\{\{(S)-2-\{4-methoxy-3-(3-methoxypropoxy)benzyl\}-3-methylbutyl\}-1,3-oxazolidine-3-carboxylate\]
To a solution of (4S,5S)-5-((2S)-2-[[3-amino-2,2-dimethyl-3-oxopropyl]amino]carbonyl]-3-methylbutyl)-4-((2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine (90 mg, crude) and DMAP (29 mg, 0.2 mM) in 10 ml dry DCM under nitrogen atmosphere, ethylchloroformate (0.05 ml, 0.4 mM) was added by syringe and the solution was stirred for 48h at room temperature. Reaction mixture was concentrated by rotary evaporation and purified by column chromatography on silica (THF/hexane 4:6, 5% of iPrOH) to give the product as colorless oil 24 mg. MS: 636 [M+1]^+

**Example 3**

(4S,5S)-ethyl 5-((S)-2-(3-amino-2,2-dimethyl-3-oxopropylcarbamoyl)-3-methylbutyl]-4-((S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-2,2-dimethyloxazolidine-3-carboxylate

**Step a**

Ethyl (1S,2S,4S)-4-[[3-amino-2,2-dimethyl-3-oxopropyl]amino]carbonyl]-2-hydroxy-1-[(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-5-methylhexyl]carbamate
To a suspension of Aliskiren (hemifumarate, 200 mg) and sodium carbonate in 10 ml water, ethyl chloroformate (0.2ml) was added dropwise at room temperature. The reaction mixture was stirred overnight and extracted with DCM. The organic layer was dried over MgSO₄, filtered and concentrated by rotary evaporation. The product was isolated by column chromatography on silica (EtOAc, 2% MeOH) to give 190 mg. MS: 624 [M+1]^+ 646 [M+Na]^+.

**Step b**

Ethyl (1S,2S,4S)-4-[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl]-2-hydroxy-1-[(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-5-methylhexylcarbamate (140 mg, 0.2 mM) was dissolved in dimethoxypropane (7 ml) and acetone (3 ml) and boron trifluoride etherate (2 drops) was added until a dark red colour persisted. The solution was stirred for 1.5h at room temperature and then quenched with Et₃N. The solvent was removed by rotary evaporation and the product was isolated by column chromatography on silica gel (THF/hexane 4:6, 5% of iPrOH) to give the product 116 mg. MS: 665 [M+1]^+

**Example 4**

(4S,5S)-1-(isobutyryloxy)methyl 5-[(S)-2-(3-amino-2,2-dimethyl-3-oxopropyl)carbamoyl]-3-methylbutyl]-4-[(S)-2-[4-methoxy-3-(methoxypropoxy)benzyl]-3-methylbutyl]oxazolidine-3-carboxylate
Method A:

Step a

Chloromethyl (4S,5S)-5-((2S)-2-{{[3-amino-2,2-dimethyl-3-oxopropyl]amino} carbonyl}-3-methylbutyl)-4-((2S)-2-[4-methoxy-3-(3-methoxypropoxy) benzyl]-3-methylbutyl}-1,3-oxazolidine-3-carboxylate.

To a suspension of Aliskiren (hemifumarate, 100 mg) and sodium carbonate (100 mg) in water (15 ml), chloromethylchloroformate (0.15 ml) was added dropwise at room temperature. After 40 min of stirring, a sticky mass was formed and dichloromethane (10 ml) was added and reaction was carried out in the bi-phasic system. The reaction mixture was stirred overnight and extracted with more dichloromethane. The organic layer was dried over MgSO₄, filtered and concentrated by rotary evaporation to get product as an oil which was purified by column chromatography on silica to give desired compound as an oil (37 mg). MS: 656 [M+1]⁺

Step b

Chloromethyl (4S,5S)-5-((2S)-2-{{[3-amino-2,2-dimethyl-3-oxopropyl]amino} carbonyl}-3-methylbutyl)-4-((2S)-2-[4-methoxy-3-(3-methoxypropoxy) benzyl]-3-methylbutyl}-1,3-
oxazolidine-3-carboxylate (37 mg) and isobutyric acid (25 mg) were dissolved in dry
dichloromethane and diisopropylethylamine (30 µl) was added to the reaction mixture.
Reaction mixture was under reflux (reflux) for 2 days. The reaction was monitored by LC-
MS. To the reaction mixture was then added 3 ml 10% aqueous solution of citric acid and
extracted into DCM. The organic layer washed with brine and dried over magnesium
sulfate. After concentration under reduced pressure, the oily residue was purified by
column chromatography on silica gel (THF/petroleum ether 4:6 with 5% iPrOH) to give

Method B:
To a solution of (4S,5S)-5-((2S)-2-{{[(3-amino-2,2-dimethyl-3-
oxopropyl)amino]carbonyl}-3-methylbutyl}-4-{{(2S)-2-[4-methoxy-3-(3-
methoxypropoxy)benzyl]-3-methylbutyl}-1,3-oxazolidine (100 mg, prepared using the
method described in Example 1) and DMAP (32 mg, 0.2 mM) in 15 ml dry
dichloromethane under nitrogen atmosphere, (chlorocarbonyloxy)methyl isobutyrate (0.05
ml) prepared using a literature method was added by syringe and the solution was stirred
for 24h at room temperature. Reaction mixture was washed with water, and aqueous phase
was washed with DCM (3x20 ml). Combined organic phases were washed with brine and
dried over MgSO₄, filtered and concentrated by rotary evaporation. Crude product was
purified by column chromatography on silica to give 26 mg product. MS: 708 [M+1]^+, 730
[M+Na]^+.

Example 5
(4S,5S)-1-(isobutyryloxy)ethyl (4S,5S)-5-{{(S)-2-[(3-amino-2,2-dimethyl-3-
oxopropyl)carbamoyl]-3-methylbutyl]-4-{{(S)-2-[4-methoxy-3-
(methoxypropoxy)benzyl]-3-methylbutyl}oxazolidine-3-carboxylate
Step a
1-Chloroethyl (4S,5S)-5-((2S)-2-{{(3-amino-2,2-dimethyl-3-oxopropyl)amino}carbonyl}-3-methylbutyl)-4-((2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl)-oxazolidine-3-carboxylate.

To a solution of (4S,5S)-5-((2S)-2-{{(3-amino-2,2-dimethyl-3-oxopropyl)amino}carbonyl}-3-methylbutyl)-4-((2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl)-1,3-oxazolidine (117 mg, prepared using the method described in Example 1) and DMAP (47 mg) in dry dichloromethane (15 ml) under nitrogen atmosphere, 1-chloroethylchloroformate (35 μl) was added by syringe. The reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with dichloromethane, and then washed with 10% aqueous solution of citric acid, and brine. The organic phase was dried over magnesium sulfate, concentrated in vacuo. The residue was purified by column chromatography on silica gel (THF/petroleum ether 4:6 + 5% of iPrOH) to give 100 mg of colourless oil as main fraction. The intermediate was used directly for next step.
Step b

The above intermediate (100 mg) and isobutyric acid (40 mg) and DIPEA (80 μl) were dissolved in 10 ml THF. The reaction mixture was stirred at 60 °C for 16 h. The reaction was monitored using LC-MS. An additional portion of butyric acid (40 mg) and DIPEA (80 μl) was added and the reaction was under stirring at kept at 60 °C for 40h. After starting material peak disappearing from LC-MS analysis, 10 ml 10% aqueous solution of citric acid reaction mixture was added and the reaction mixture was extracted with dichloromethane. The collected organic phase was washed with brine and dried over magnesium sulfate. After evaporation in vacuo, the oily residue oil was purified by column chromatography on silica gel (THF/petroleum ether 4:6 with 5% iPrOH) to give 70 mg product. MS: 722 [M+H]^+, 744 [M+Na]^+

Example 6

(4S,5S)-pivaloyloxymethyl 5-[(S)-2-(3-amino-2,2-dimethyl-3-oxopropylcarbamoyl)-3-methylbutyl]-4-[(S)-2-[4-methoxy-3-(methoxyprooxy)benzyl]-3-methylbutyl]oxazolidine-3-carboxylate

Chloromethyl (4S,5S)-5-((2S)-2-([(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl)-3-methylbutyl)-4-((2S)-2-[4-methoxy-3-(3-methoxyprooxy)benzyl]-3-methylbutyl)-1,3-oxazolidine-3-carboxylate (97 mg, prepared using the method described in Example 4, Method A), pivalic acid (160 mg) and diisopropylethylamine (0.27 ml) were dissolved in 10 ml dry THF and reaction mixture was stirred at 75 °C for 48h. The reaction was monitored using LC-MS. After starting material peak had disappeared for the LC-MS analysis, the 15 ml 10% aqueous solution of citric acid was added to the reaction mixture, and the reaction mixture was then extracted with dichloromethane. The organic layer was
collected and washed with brine and dried over magnesium sulfate. After evaporation in vacuo, the oily residue was purified by column chromatography on silica gel (EtOAc) to give 15 mg product. MS: 722 [M+H]⁺, 744 [M+Na]⁺

5 Example 7

(4S,5S)-isobutyl 5-[(S)-2-(3-amino-2,2-dimethyl-3-oxopropylcarbamoyl)-3-methylbutyl]-4-[(S)-2-[4-methoxy-3-(methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate

To a solution of (4S,5S)-5-[(2S)-2-[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl]-3-methylbutyl]-4-[(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine (200 mg, 0.4 mM) and DMAP (70 mg, 0.6 mM) in dry dichloromethane under nitrogen atmosphere, isobutylchloroformate (55 mg, 0.4 mM) was added using a syringe. The reaction mixture was stirred for 48h at room temperature. The reaction mixture was washed with brine and 10% aqueous solution of citric acid. The organic phase was collected and dried over magnesium sulfate. It was concentrated by rotary evaporation to give 230 mg crude product which was then purified by column chromatography on silica gel (50g of silica, THF/hexane 4:6 with 5% iPrOH) to give 174 mg product. LCMS: 664 [M+H]⁺, 686 [M+Na]⁺.

10 Example 8

(4S,5S)-(N-Boc-valyloxy)methyl 5-[(S)-2-(3-amino-2,2-dimethyl-3-oxopropylcarbamoyl)-3-methylbutyl]-4-[(S)-2-[4-methoxy-3-(methoxypropoxy)benzyl]-3-methylbutyl]oxazolidine-3-carboxylate

(4S,5S)-
The product was prepared using a method analogous to the method described in Example 4, Method A. LC-MS: 838 [M+1]^+.

Example 9

(4S,5S)-valyloxymethyl 5-[(S)-2-(3-amino-2,2-dimethyl-3-oxopropylcarbamoyl)-3-methylbutyl]-4-[(S)-2-[4-methoxy-3-(methoxypropoxy)benzy]-3-methylbutyl] oxazolidine-3-carboxylate, trifluoroacetic acid salt

(4S,5S)-(N-Boc-Valyloxy)methyl 5-[(S)-2-(3-amino-2,2-dimethyl-3-oxopropylcarbamoyl)-3-methylbutyl]-4-[(S)-2-[4-methoxy-3-(methoxypropoxy)benzy]-3-methylbutyl] oxazolidine-3-carboxylate (60 mg) was dissolved in dry DCM (1 ml) and 150-200 µl of TFA was added to the reaction mixture and stirred for 20 min. LC-MS shows full conversion of starting material peak to peak with mass M+737. Reaction
mixture was concentrated by rotary evaporation and dried under vacuum to give 58 mg product as TFA salt. LC-MS: 737[M+1]+.

Example 10

$\text{(4S,5S)-(N-CBz-valyloxy)methyl 5-[(S)-2-(3-amino-2,2-dimethyl-3-oxopropylcarbamoyl)-3-methylbutyl]-4-[(S)-2-[4-methoxy-3-(methoxypropoxy)benzyl]-3-methylbutyl]oxazolidine-3-carboxylate}$

The product was prepared using a method analogous to the method described in Example 4, LC-MS: mass peaks M+872[M+1]+.

Example 11

$\text{(4S,5S)-(ethoxycarbonyloxy)methyl 5-[(S)-2-(3-amino-2,2-dimethyl-3-oxopropylcarbamoyl)-3-methylbutyl]-4-[(S)-2-[4-methoxy-3-(methoxypropoxy)benzyl]-3-methylbutyl]oxazolidine-3-carboxylate}$
(4S,5S)-5-{[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl}-3-methylbutyl)-4-\{(2S)-2-{4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl\}-1,3-oxazolidine (100 mg, prepared using the method described in Example 1) and cesium carbonate (116 mg) were dissolved in 7 ml dry DMF. To the reaction mixture was added solid carbon dioxide and the reaction was kept under CO₂ atmosphere under an elevated pressure. The reaction mixture was stirred at room temperature for 50 min. Ethyl iodomethyl carbonate (61 mg) was added through a syringe to the stirred reaction mixture and reaction was kept under stirring overnight at room temperature. 40 ml water was then added and the reaction mixture was extracted with dichloromethane (3×20 ml). Combined organic phases were washed with brine and dried over MgSO₄. After evaporation \textit{in vacuo}, the residue was purified by column chromatography on silica gel (EtOAc) to give 13 mg product. LC-MS: 710[M+1]⁺.

\textbf{Example 12}

(4S,5S)-(isopropoxycarbonyloxy)methyl 5-{[(S)-2-{3-amino-2,2-dimethyl-3-oxopropylcarbamoyl}-3-methylbutyl]-4-\{(S)-2-{4-methoxy-3-(methoxypropoxy)benzyl]-3-methylbutyl\}oxazolidine-3-carboxylate

\textbf{Method A}

The compounds was prepared using a method analogous to the method described in Example 11. LC-MS: 724[M+1]⁺.
Method B.

Sodium metal (15 mg) was dissolved in isopropanol and carbon dioxide was bubbled through the solution of sodium propylate obtained during 3h. White precipitate formed. Reaction mixture was concentrated by rotary evaporation and dried under high vacuum.

Sodium salt of isopropyl carbonate was dissolved in DMF (2 ml) and cesium iodide (400 mg) was added, which was followed by the addition of a DMF solution of chloromethyl (4S,5S)-5-((2S)-2-({(3-amino-2,2-dimethyl-3-oxopropyl)amino}carbonyl)-3-methylbutyl)-4-((2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl)-1,3-oxazolidine-3-carboxylate (80 mg, preparation see Example 7). The reaction mixture was stirred overnight at room temperature. To the reaction mixture was added 10% citric acid aqueous solution (40 ml) and the mixture was extracted with dichloromethane (3x20 ml). The combined organic phases were washed with brine and dried over MgSO₄. After evaporation in vacuo, the residue was purified by column chromatography on silica (EtOAc) to give 23 mg product. LC-MS: 724[M+1]+.

Example 13

Chloromethyl (4S,5S)-5-((2S)-2-({(3-amino-2,2-dimethyl-3-oxopropyl)amino}carbonyl)-3-methylbutyl)-4-((2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl)-1,3-oxazolidine-3-carboxylate

Aliskiren (1.1 g) was dissolved in 100 ml of THF and formaldehyde (37% solution in water, 150 ml) was added to the reaction mixture and stirred in ice bath overnight. LC-MC shows about 16% of starting material by TIC, then additional amount of formaline (10 ml) was added and stirred for additional 2h, then a spoon of anhydrous magnesium sulfate was added and stirred for about 60 min. Reaction mixture was then filtered (LC-MS shows 100% conversion) and chloromethyl chloroformate (195 ml) and triethylamine (320 ml) were added to the stirred filtrate at cooling in an ice bath. LC-MS shows full conversion after 30 minutes stirring. Reaction mixture was concentrated by rotary evaporation, then
mixed with 10% citric acid and brine and extracted into DCM. Organic extracts were washed with brine and dried over magnesium sulfate, concentrated and purified by column chromatography on silica gel (EtOAc) to give 961 mg of desired product as white foam. LCMS: 656.5 [M+1]^+; 678.4 [M+Na]^+; 654.4 [M-1]^-.

Example 14

Iodomethyl (4S,5S)-5-((2S)-2-[(3-amino-2,2-dimethyl-3-oxopropyl)amino][carbonyl]-3-methylbutyl)-4-([2S]-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate

Chloromethyl (4S,5S)-5-((2S)-2-[(3-amino-2,2-dimethyl-3-oxopropyl)amino][carbonyl]-3-methylbutyl)-4-((2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate (191 mg) and sodium iodide (135 mg) were mixed with dry acetonitrile and heated under stirring at 75 °C for 1 h 20 min. Full conversion according to LC-MS. Reaction mixture was mixed with water and extracted into DCM, washed with brine, dried over MgSO₄. 186 mg of crude product was obtained, which was purified by column chromatography on silica gel (EtOAc) to give 72 mg of pure material as brown oil. Compound is not stable and decomposes rather rapidly. LCMS: 748.3 [M+1]^+, 770.3 [M+Na]^+. Compound is not stable and decomposes rather rapidly.

Example 15

{(2S)-2-hydroxypropanoyl}oxy)methyl (4S,5S)-5-[(2S)-2-(3-amino-2,2-dimethyl-3-oxopropylaminocarbonyl)-3-methylbutyl]-4-((2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate
L-lactic acid lithium salt (18 mg) and cesium iodide (14 mg) was suspended in DMF (1 ml) and solution of chloromethyl (4S,5S)-5-((2S)-2-{{(3-amino-2,2-dimethyl-3-oxopropyl)amino}carbonyl}-3-methylbutyl)-4-((2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl}-1,3-oxazolidine-3-carboxylate (30 mg) in DMF (1 ml) was added and stirred at r.t. overnight. Reaction mixture was mixed with 10% citric acid (30 ml) and extracted into EtOAc (4x20 ml). Organic extracts were washed with brine and dried over MgSO₄. Concentrated by rotary evaporation and purified by column chromatography on silica gel (EtOAc/THF 9:1) to give 19 mg of colorless oil.

Example 16

{(2S)-2-(ethoxymethoxy)propanoyl]oxy}methyl (4S,5S)-5-((2S)-2-{(3-amino-2,2-dimethyl-3-oxopropyl)carbamoyl}-3-methylbutyl]-4-((2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl}-1,3-oxazolidine-3-carboxylate

Cesium (2S)-2-(Ethoxymethoxy)propanoate (30 mg), cesium iodide (5 mg) and chloromethyl (4S,5S)-5-((2S)-2-{{(3-amino-2,2-dimethyl-3-oxopropyl)amino}carbonyl}-3-methylbutyl)-4-((2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl}-1,3-oxazolidine-3-carboxylate (30 mg) was mixed with 1,5 ml of DMF and stirred at r.t. for
3h. Reaction mixture was mixed with 40 ml of 10% citric acid and extracted into DCM (4x20 ml), washed with brine (3x20 ml) and dried over magnesium sulfate. Concentrated and purified by column chromatography on silica gel (EtOAc) and 18 mg of colorless oil was obtained. LCMS: 768.5 [M+1]^+, 790.5 [M+Na]^+.

Example 17

{(4S,5S)-5-[(2S)-2-(3-amino-2,2-dimethyl-3-oxopropylaminocarbonyl)-3-methylbutyl]-4-[(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidin-3-yl-carbonyloxy} methyl morpholine-4-carboxylate

Morpholine (50 mg), cesium carbonate (80 mg), Csl (40 mg) were mixed with 2-3 ml of DMF in 2 neck 100 ml flask with balloon to keep CO₂ pressure and small amount of dry ice was added to the reaction mixture. Reaction mixture was stirred for about 2h at r.t. Then chloromethyl (4S,5S)-5-[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl]-3-methylbutyl]-4-[(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate (60 mg) in 2 ml of DMF was added to the reaction mixture and carbon dioxide tube was attached. Pressure of carbon dioxide was regulated from the cylinder. Reaction mixture was stirred at room temperature under CO₂ gas pressure for approximately 30h. Progress was monitored by LC-MS. Reaction mixture was then mixed with 10% citric acid solution (30 ml) and some brine and extracted into DCM. Combined organic extract was washed with brine (20 ml) and dried over MgSO₄ and kept under high vacuum to remove residual DMF. Purified by column chromatography on YMC silica gel (EtOAc/THF 9:1) and 32 mg of pure (LC-MS) product was obtained as colorless oil. LCMS: 751.5 [M+1]^+, 773.5 [M+Na]^+; 749.5 [M-1]^−

Example 18
(4S,5S) nicotinoyloxymethyl 5-[(S)-2-(3-amino-2,2-dimethyl-3-oxopropylcarbamoyl)-3-methylbutyl]-4-[(S)-2-[4-methoxy-3-(methoxypropoxy)benzyl]-3-methylbutyl]oxazolidine-3-carboxylate

5 Nicotinic acid (25 mg), cesium carbonate (as a base, 67 mg), cesium iodide (17 mg) and chloromethyl (4S,5S)-5-((2S)-2-[[3-amino-2,2-dimethyl-3-oxopropyl]amino]carbonyl]-3-methylbutyl)-4-((2S)-2-[4-methoxy-3-(methoxypropoxy)benzyl]-3-methylbutyl)-1,3-oxazolidine-3-carboxylate (27 mg) were mixed with dry DMF and stirred for about 27h. Reaction progress was monitored by LC-MS. Reaction mixture was mixed with water (acidified to neutral pH with 10% citric acid) and extracted into DCM (4x20 ml).

Combined organic phases were washed with brine, dried over anhydrous MgSO4 and concentrated by rotary evaporation and kept under high vacuum to remove traces of DMF left. Purified by column chromatography on YMC silica gel (EtOAc/absTHF 9:1) and 25 mg of desired product was obtained. LCMS: 743.5 [M+1]⁺, 765.4 [M+Na]⁺; 741.4 [M-1]⁻

Example 19

(4S,5S) [(pyridine-2-yl)carbonyloxy]methyl 5-[(S)-2-(3-amino-2,2-dimethyl-3-oxopropylcarbamoyl)-3-methylbutyl]-4-[(S)-2-[4-methoxy-3-(methoxypropoxy)benzyl]-3-methylbutyl]oxazolidine-3-carboxylate

The compound was prepared using a method analogous to the method described in Example 18 from 2-picolinic acid (20 mg), cesium iodide (20 mg), cesium carbonate (as a
base, 62 mg), and chloromethyl (4S,5S)-5-((2S)-2-\{[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl\}-3-methylbutyl)-4-\{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl\}-1,3-oxazolidine-3-carboxylate (27 mg) to give 19 mg of desired product. LCMS: 743,5 [M+1]^+, 765,4 [M+Na]^+; 741,5 [M-1]^-  

**Example 20**

\[(2\text{-methylpropoxycarbonyloxy})methyl\ (4S,5S)-5-\{(2S)-2-\{[(3-amino-2,2-dimethyl-3-oxopropyl)carbamoyl]-3-methylbutyl\}-4-\{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl\}-1,3-oxazolidine-3-carboxylate\]

The compound was prepared using a method analogous to the method described in literature (Kim S-I, Chu F, Dueño E, Jung K W, J. Org. Chem., 64(1999), 4578) from cesium carbonate (126 mg), terabutylammonium iodide(13 mg) and isobutanol (0.1 ml) and chloromethyl (4S,5S)-5-\{(2S)-2-\{[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl\}-3-methylbutyl\}-4-\{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl\}-1,3-oxazolidine-3-carboxylate (20 mg) to give 21 mg of desired product. LCMS: 738.5 [M+1]^+, 760.4 [M+Na]^+; 736.5 [M-1]^-  

**Example 21**

\[\{2\text{-methyl-2-(ethoxymethoxy)propanoyloxy}methyl\ (4S,5S)-5-\{(2S)-2-\{[(3-amino-2,2-dimethyl-3-oxopropyl)carbamoyl]-3-methylbutyl\}-4-\{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl\}-1,3-oxazolidine-3-carboxylate\]
The compound was prepared using a method analogous to the method described in Example 16 from cesium 2-(ethoxymethoxy)-2-methylpropanoate (15 mg), cesium iodide (10 mg) and chloromethyl (4S,5S)-5-((2S)-2-[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl)-3-methylbutyl)-4-((2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate (24 mg) to give 17 mg of desired product as an oil. LCMS: 782.5 [M+H]^+, 804.5 [M+Na]^+; 780.6 [M-1]^-

Example 22

\[{\text{{[(pyridin-3-ylmethoxy)carbonyl]oxy}methyl}} (4S,5S)-5-((2S)-2-[(3-amino-2,2-dimethyl-3-oxopropyl)carbamoyl]-3-methylbutyl)-4-((2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate\]

The compound was prepared using a method analogous to the method described in Example 20 from 3-pyridinemethanol (100 mg), cesium carbonate (180 mg), TBAI (19 mg) and chloromethyl (4S,5S)-5-((2S)-2-[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl]-3-methylbutyl)-4-((2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate (30 mg). Purification by column chromatography on YMC silica gel (EtOAc, 7% of MeOH) gave 15 mg of desired product as an oil. LCMS: 773.4 [M+H]^+, 795.5 [M+Na]^+; 771.5 [M-1]^−
Example 23

\[((2\text{-methyl-3-morpholin-4-ylpropanoyl)}\text{oxy})\text{methyl} (4S,5S)-5-\text{of}((2S)-2-\text{[(3-amino-2,2-dimethyl-3-oxopropyl)amino}\text{carboxyl}]\text{-3-methylbutyl})\text{-4-\text{[(2S)-2-\text{[4-methoxy-3-(3-methoxypropoxy)benzyl]}}\text{-3-methylbutyl}]\text{-1,3-oxazolidine-3-carboxylate}}

The compound was prepared using a method analogous to the method described in Example 16 from cesium 2-methyl-3-(morpholin-4-yl)propanoate (30 mg), cesium iodide (24 mg) and chloromethyl (4S,5S)-5-((2S)-2-\text{[(3-amino-2,2-dimethyl-3-oxopropyl)amino}\text{carboxyl]}\text{-3-methylbutyl})\text{-4-\text{[(2S)-2-\text{[4-methoxy-3-(3-methoxypropoxy)benzyl]}}\text{-3-methylbutyl}]\text{-1,3-oxazolidine-3-carboxylate}} (30 mg) to give 33 mg of desired product as an oil. LCMS: 793.5 \text{[M+H]}^+, 815.5 \text{[M+Na]}^+

Example 24

\text{(1-methylpiperidine-4-carboxyloxy)methyl} (4S,5S)-5-\text{of}((2S)-2-\text{[(3-amino-2,2-dimethyl-3-oxopropyl)amino}\text{carboxyl}]\text{-3-methylbutyl})\text{-4-\text{[(2S)-2-\text{[4-methoxy-3-(3-methoxypropoxy)benzyl]}}\text{-3-methylbutyl}]\text{-1,3-oxazolidine-3-carboxylate}}

The compound was prepared using a method analogous to the method described in Example 18 from 1-methylpiperidine-4-carboxylic acid (19 mg), cesium iodide (23 mg),
cesium carbonate (as a base, 60 mg), and chloromethyl (4S,5S)-5-((2S)-2-\{[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl\}-3-methylbutyl)-4-\{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl\}-1,3-oxazolidine-3-carboxylate (50 mg) to give 40 mg of desired product as foam. LCMS: 763.5 [M+H]⁺, 785.4 [M+Na]⁺; 761.6 [M-1]⁻

Example 25
{[(1,3-dioxan-5-yl-oxy)carbonyl]oxy}methyl (4S,5S)-5-((2S)-2-\{[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl\}-3-methylbutyl)-4-\{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl\}-1,3-oxazolidine-3-carboxylate

![](image)

The compound was prepared using a method analogous to the method described in Example 20 from 5-hydroxy-1,3-dioxane (40 mg), cesium carbonate (100 mg), tetrabutylammonium iodide(28 mg) and chloromethyl (4S,5S)-5-((2S)-2-\{[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl\}-3-methylbutyl)-4-\{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl\}-1,3-oxazolidine-3-carboxylate (50 mg). Purification by column chromatography on YMC silica gel (EtOAc) gave 37 mg of desired product as an oil. LCMS: 768.5 [M+H]⁺, 790.4 [M+Na]⁺; 766.5 [M-1]⁻

Example 26
{[(1,3-dioxolan-4-ylmethoxy)carbonyl]oxy}methyl (4S,5S)-5-((2S)-2-\{[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl\}-3-methylbutyl)-4-\{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl\}-1,3-oxazolidine-3-carboxylate (racemate)
The compound was prepared using a method analogous to the method described in Example 20 from (1,3-dioxolan-4-yl)methanol (50 mg, racemate), cesium carbonate (100 mg), tetrabutylammonium iodide (28 mg) and chloromethyl (4S,5S)-5-((2S)-2-{{(3-amino-2,2-dimethyl-3-oxopropyl)amino}carbonyl}-3-methylbutyl)-4-{{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl}-1,3-oxazolidine-3-carboxylate (50 mg). Purification by column chromatography on YMC silica gel (EtOAc) gave 50 mg of desired product as an oil. LCMS: 768.5 [M+1]^+, 790.5 [M+Na]^+; 766.5 [M-1]

Example 27

[(3-hydroxy-2,2-dimethylpropanoyl)oxy]methyl (4S,5S)-5-((2S)-2-{{(3-amino-2,2-dimethyl-3-oxopropyl)amino}carbonyl}-3-methylbutyl)-4-{{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl}-1,3-oxazolidine-3-carboxylate

The compound was prepared using a method analogous to the method described in Example 16 from cesium 2,2-dimethyl-3-hydroxypropanoate (77 mg), cesium iodide (23 mg) and chloromethyl (4S,5S)-5-((2S)-2-{{(3-amino-2,2-dimethyl-3-oxopropyl)amino}carbonyl}-3-methylbutyl)-4-{{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl}-1,3-oxazolidine-3-carboxylate (50 mg) to give 20 mg of desired product as an oil. LCMS: 738.5 [M+1]^+, 760.5 [M+Na]^+
Example 28

\[((4\text{-}methoxybenzyl)oxy)\text{carbonyl}]\text{methyl } (4S,5S)-5-\{(2S)-2-\{[3\text{-}amino-2,2\text{-}dimethyl-3\text{-}oxopropy]}\text{amino[carbonyl]-3-methylbutyl}]-4-\{(2S)-2-[4\text{-}methoxy-3\text{-}(3\text{-}methoxypropoxy)benzyl]-3\text{-}methylbutyl}\}-1,3\text{-}oxazolidine\text{-}3\text{-}carboxylate

The compound was prepared using a method analogous to the method described in Example 20 from 4-methoxybenzyl alcohol (30 mg), cesium carbonate (60 mg), TBAI (17 mg) and chloromethyl (4S,5S)-5-\{(2S)-2-\{[3\text{-}amino-2,2\text{-}dimethyl-3\text{-}oxopropy]}\text{amino[carbonyl]-3-methylbutyl}]-4-\{(2S)-2-[4\text{-}methoxy-3\text{-}(3\text{-}methoxypropoxy)benzyl]-3\text{-}methylbutyl}\}-1,3\text{-}oxazolidine\text{-}3\text{-}carboxylate (30 mg) to give 19 mg of desired product as white foam. LCMS: 802.5 [M+1]^+, 824.5 [M+Na]^+, 800.5 [M-1]^-.

Example 29

\{([benzyl]oxy)\text{carbonyl}]\text{methyl } (4S,5S)-5-\{(2S)-2-\{[3\text{-}amino-2,2\text{-}dimethyl-3\text{-}oxopropy]}\text{amino[carbonyl]-3-methylbutyl}]-4-\{(2S)-2-[4\text{-}methoxy-3\text{-}(3\text{-}methoxypropoxy)benzyl]-3\text{-}methylbutyl}\}-1,3\text{-}oxazolidine\text{-}3\text{-}carboxylate
The compound was prepared using a method analogous to the method described in Example 20 from benzyl alcohol (15 mg), cesium carbonate (67 mg), tetrabutylammonium iodide (17 mg) and chloromethyl (4S,5S)-5-((2S)-2-[[3-amino-2,2-dimethyl-3-oxopropyl]amino]carbonyl]-3-methylbutyl)-4-((2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate (33 mg) to give 19 mg of desired product as white foam. LCMS: 772.5 [M+1]^+, 794.5 [M+Na]^+; 770.6 [M-1]^-

Example 30

[(pyridine-4-yl)carbonyl]oxy)methyl (4S,5S)-5-((2S)-2-[[3-amino-2,2-dimethyl-3-oxopropyl]carbamoyl]-3-methylbutyl]-4-((2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate

The compound was prepared using a method analogous to the method described in Example 18 from isonicotinic acid (6 mg), cesium iodide (14 mg), cesium carbonate (as a base, 23 mg), and chloromethyl (4S,5S)-5-((2S)-2-[[3-amino-2,2-dimethyl-3-oxopropyl]amino]carbonyl]-3-methylbutyl)-4-((2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate (31 mg) to give 16 mg of desired product. LCMS: 743.5 [M+1]^+, 765.4 [M+Na]^+; 741.4 [M-1]

Example 31

[(1-methyl-1H-imidazol-4-yl)carbonyl]oxy)methyl (4S,5S)-5-((2S)-2-[[3-amino-2,2-dimethyl-3-oxopropyl]amino]carbonyl]-3-methylbutyl)-4-((2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate
The compound was prepared using a method analogous to the method described in Example 18 from 1-methylimidazole-4-carboxylic acid (8 mg), cesium iodide (19 mg), cesium carbonate (as a base, 21 mg), and chloromethyl (4S,5S)-5-((2S)-2-{{[3-amino-2,2-dimethyl-3-oxopropyl]amino}[carbonyl]}-3-methylbutyl)-4-{{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]}-1,3-oxazolidine-3-carboxylate (33 mg).

Purification by column chromatography on YMC silica gel (EtOAc with 10% MeOH) gave 19 mg of desired product as an oil to give 16 mg of desired product. LCMS: 746.5 [M+1]^+, 768.5 [M+Na]^+; 744.5 [M-1]^-

Example 32

{(1,3-dioxan-5-ylcarbonyloxy)methyl (4S,5S)-5-((2S)-2-{{[(3-amino-2,2-dimethyl-3-oxopropyl)amino][carbonyl]}-3-methylbutyl})-4-{{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]}-1,3-oxazolidine-3-carboxylate

The compound was prepared using a method analogous to the method described in Example 18 from 1,3-dioxane-5-carboxylic acid (11 mg, obtained using procedures described in Finlay MacCorquodale et al, J.Chem. Soc., Perkin Trans 2, 1991, 1893-9), cesium iodide (19 mg), cesium carbonate (as a base, 29 mg), and chloromethyl (4S,5S)-5-((2S)-2-{{[(3-amino-2,2-dimethyl-3-oxopropyl)amino][carbonyl]}-3-methylbutyl})-4-{{(2S)-2-
[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate (50 mg) to give 30 mg of desired product as white foam. LCMS: 752.5 [M+1]^+, 774.5 [M+Na]^+.

Example 33

\[
\{(1\text{-}methyl\text{-}1\text{H}\text{-}imidazol\text{-}2\text{-}yl)\text{carbonyl}oxy\}\text{methyl (4S,5S)-5\text{-}((2S)-2\text{-}[[3\text{-}amino\text{-}2,2\text{-}dimethyl\text{-}3\text{-}oxopropyl]amino[carbonyl]-3\text{-}methylbutyl]-4\text{-}((2S)-2\text{-}[4\text{-}methoxy\text{-}3\text{-}(3\text{-}methoxypropoxy)benzyl]-3\text{-}methylbutyl]-1,3\text{-}oxazolidine-3\text{-}carboxylate}
\]

The compound was prepared using a method analogous to the method described in Example 31 from 1-methyl-1H-imidazole-2-carboxylic acid (12 mg), cesium iodide (27 mg), cesium carbonate (as a base, 45 mg), and chloromethyl (4S,5S)-5-((2S)-2-[[3-amino-2,2-dimethyl-3-oxopropyl]amino[carbonyl]-3-methylbutyl]-4-((2S)-2-[[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate (50 mg) to give 16 mg of desired product as colorless oil. LCMS: 746.5 [M+1]^+, 768.5 [M+Na]^+; 744.5 [M-1]^+.

Example 34

\[
\{(1\text{-}methyl\text{-}1\text{H}\text{-}imidazol\text{-}4\text{-}yl)methoxy[carbonyl]oxy\}\text{methyl (4S,5S)-5\text{-}((2S)-2\text{-}[[3\text{-}amino\text{-}2,2\text{-}dimethyl\text{-}3\text{-}oxopropyl]amino[carbonyl]-3\text{-}methylbutyl]-4\text{-}((2S)-2\text{-}[4\text{-}methoxy\text{-}3\text{-}(3\text{-}methoxypropoxy)benzyl]-3\text{-}methylbutyl]-1,3\text{-}oxazolidine-3\text{-}carboxylate}
\]

The compound was prepared using a method analogous to the method described in Example 20 from 1-methylimidazole-4-methanol (18 mg), cesium carbonate (108 mg), tetrabutylammonium iodide (25 mg) and chloromethyl (4S,5S)-5-((2S)-2-[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl)-3-methylbutyl)-4-{{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl}-1,3-oxazolidine-3-carboxylate (50 mg).

Purification by column chromatography on YMC silica gel (EtOAc with 10% MeOH) gave 26 mg of desired product as white foam. LCMS: 776.5 [M+1]⁺, 798.5 [M+Na]⁺; 774.5 [M-1]⁻.

Example 35

(((1-methylpiperidin-4-yl)oxy)carbonyl)oxy)methyl (4S,5S)-5-((2S)-2-[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl)-3-methylbutyl)-4-{{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl}-1,3-oxazolidine-3-carboxylate

1-Methyl-4-piperidinol (46 mg), cesium carbonate (53 mg), cesium iodide (25 mg) and chloromethyl (4S,5S)-5-((2S)-2-[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl)-3-methylbutyl)-4-{{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl}-1,3-
oxazolidine-3-carboxylate (100 mg) were mixed with dry DMF and bubbled with carbon dioxide at stirring. Reaction progress was monitored by LC-MS. Full conversion was achieved after 40 h. Reaction mixture was acidified to pH 6 with 10% citric acid solution (20 ml) and some water and brine was added and extracted into DCM. Combined organic extract was washed with brine (20 ml), dried over MgSO₄, filtered and the crude oil was kept in high vacuum to remove residual DMF to obtain 126 mg of crude product as slightly yellow oil. Purification by preparative HPLC (C18 column; acetonitrile/water with 0.1% TFA) gave 32 mg of desired product as an oil (in form of TFA salt). LCMS: 779.5 [M+1]+, 801.5 [M+Na]+; 777.5 [M-1]-

Example 36

[(1-methylpiperidin-4-yl)oxy]methyl (4S,5S)-5-((2S)-2-[(3-amino-2,2-dimethyl-3-oxopropyl)amino][carbonyl]-3-methylbutyl)-4-((2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate

![Chemical Structure](image)

Compound was obtained in the reaction described in Example 35. Product was isolated by preparative HPLC from crude mixture (Example 35) as 39 mg of white foam (TFA salt). LCMS: 735.5 [M+1]+; 733.5 [M-1]-

Example 37

([(1-methylpiperidin-4-yl)methoxy][carbonyl]oxy)methyl (4S,5S)-5-((2S)-2-[(3-amino-2,2-dimethyl-3-oxopropyl)amino][carbonyl]-3-methylbutyl)-4-((2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate
The compound was prepared using a method analogous to the method described in Example 20 from 1-methyl-4-piperidinemethanol (20 mg), cesium carbonate (112 mg), TBAI (22 mg) and chloromethyl (4S,5S)-5-((2S)-2-{{(3-amino-2,2-dimethyl-3-oxopropyl)amino} carbonyl}-3-methylbutyl)-4-{{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl}-1,3-oxazolidine-3-carboxylate (50 mg). Purification by column chromatography on YMC silica gel (EtOAc with 10% MeOH) gave 10.4 mg of desired product as colorless oil. LCMS: 793.5 [M+1]⁺, 815.5 [M+Na]⁺; 791.6 [M-1]⁻

Example 38

{(1,3-dioxan-5-ylmethoxy)carbonyl}oxy methyl (4S,5S)-5-((2S)-2-{{(3-amino-2,2-dimethyl-3-oxopropyl)amino} carbonyl}-3-methylbutyl)-4-{{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl}-1,3-oxazolidine-3-carboxylate

Cesium carbonate (230 mg), cesium iodide (18 mg) and 1,3-dioxane-5-methanol (20 mg, obtained using procedures described in Finlay MacCorquodale et al, J. Chem. Soc., Perkin Trans 2, (1991) 1893-9) were mixed with 1-2 ml of DMF and bubbled at stirring with carbon dioxide for about 1h at r.t.. Then chloromethyl (4S,5S)-5-((2S)-2-{{(3-amino-2,2-
79
dimethyl-3-oxopropyl]amino[carbonyl]-3-methylbutyl)-4-{(2S)-2-[4-methoxy-3-(3-
methoxypropoxy)benzyl]-3-methylbutyl}-1,3-oxazolidine-3-carboxylate (50 mg) in 2 ml
of DMF was added to the reaction mixture and carbon dioxide was bubbled at stirring
overnight. Reaction progress was monitored by LC-MS. After about 42h reaction mixture
was mixed with 10% citric acid solution (20 ml) and some brine and extracted into DCM.
Combined organic extract was washed with brine (20 ml) and dried over MgSO₄, crude oil
was dried in high vacuum to remove residual DMF. Purified by column chromatography
on YMC silica gel (EtOAc) gave 19 mg of white foam. LCMS: 782.5 [M+1]⁺, 804.5
[M+Na]⁺; 780.5 [M-1]⁻

Example 39
(pyridin-3-yloxy)methyl (4S,5S)-5-((2S)-2-{{(3-amino-2,2-dimethyl-3-
oxopropyl)amino[carbonyl]-3-methylbutyl}-4-{(2S)-2-[4-methoxy-3-(3-
methoxypropoxy)benzyl]-3-methylbutyl}-1,3-oxazolidine-3-carboxylate

Chloromethyl (4S,5S)-5-((2S)-2-{{(3-amino-2,2-dimethyl-3-oxopropyl)amino[carbonyl]-
3-methylbutyl})-4-{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl}-1,3-
oxazolidine-3-carboxylate (50 mg) was mixed with cesium carbonate (110 mg), cesium
iodide (21 mg), and 3-hydroxypyridine (32 mg). Then 2 ml DMF was added and the
reaction mixture was stirred for about 2-3h. Reaction mixture was then mixed with 10%
icric acid solution (20 ml) and some brine and extracted into DCM. Combined organic
extract was washed with brine (20 ml) and dried over MgSO₄. Crude oil was kept under
high vacuum to remove residual DMF. Purified by column chromatography on YMC silica
gel (EtOAc:MeOH 9:1) gave 50 mg of slightly yellow oil. LCMS: 715.5 [M+1]⁺, 737.5
[M+Na]⁺; 713.5 [M-1]⁻
Example 40

\[[(3\text{-methoxy}-2,2\text{-dimethyl}-3\text{-oxopropoxy})\text{carbonyl}oxy]methyl\ (4S,5S)-5-\{(2S)-2-\{[(3-amino-2,2\text{-dimethyl}-3\text{-oxopropyl})\text{amino}][\text{carbonyl}]\text{-3-methylbutyl}\}-4-\{(2S)-2-\{4\text{-methoxy}-3\text{-}(3\text{-methoxypropoxy})\text{benzyl}\}-3\text{-methylbutyl}\}-1,3\text{-oxazolidine-3-carboxylate}

The compound was prepared using a method analogous to the method described in Example 38 from methyl 2,2-dimethyl-3-hydroxypropionate (20 mg), cesium carbonate (80 mg), cesium iodide (30 mg) and chloromethyl (4S,5S)-5-\{(2S)-2-\{[(3-amino-2,2\text{-dimethyl}-3\text{-oxopropyl})\text{amino}][\text{carbonyl}]\text{-3-methylbutyl}\}-4-\{(2S)-2-\{4\text{-methoxy}-3\text{-}(3\text{-methoxypropoxy})\text{benzyl}\}-3\text{-methylbutyl}\}-1,3\text{-oxazolidine-3-carboxylate (53 mg) to give 47 mg of desired product as colorless oil. LCMS: 796.5 [M+1]^+, 818.5 [M+Na]^+; 794.6 [M-1]^-

Example 41

\[\{[(\text{dimethylamino})\text{carbonyl}oxy]methyl\ (4S,5S)-5-\{(2S)-2-\{[(3\text{-amino-2,2\text{-dimethyl-3-oxopropyl})\text{amino}][\text{carbonyl}]\text{-3-methylbutyl}\}-4-\{(2S)-2-\{4\text{-methoxy-3\text{-}(3\text{-methoxypropoxy})\text{benzyl}\}-3\text{-methylbutyl}\}-1,3\text{-oxazolidine-3-carboxylate}

The compound was prepared using a method analogous to the method described in Example 17 (bubbling with carbon dioxide was used instead of addition of dry ice to the
reaction mixture) from dimethyl hydrochloride (36 mg), cesium carbonate (277 mg),
cesium iodide (36 mg) and chloromethyl (4S,5S)-5-((2S)-2-\{[(3-amino-2,2-dimethyl-3-
oxopropyl)amino]carbonyl\}-3-methylbutyl)-4-\{(2S)-2-[4-methoxy-3-(3-
methoxypropoxy)benzyl]-3-methylbutyl\}-1,3-oxazolidine-3-carboxylate (60 mg) to give
30 mg of desired product as colorless oil. LCMS: 709.5 [M+1]^+; 731.5 [M+Na]^+; 707.5
[M-1]^-

**Example 42**

\[\text{[(1-[(tert-butoxycarbonyl)amino]cyclopropyl)carbonyloxy]methyl (4S,5S)-5-((2S)-2-\{[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl\}-3-methylbutyl)-4-\{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl\}-1,3-oxazolidine-3-carboxylate} \]

The compound was prepared using a method analogous to the method described in
Example 18 from 1-tert-butoxycarbonylaminocyclopropylcarboxylic acid (20 mg), cesium
iodide (19 mg), cesium carbonate (30 mg), and chloromethyl (4S,5S)-5-((2S)-2-\{[(3-
amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl\}-3-methylbutyl)-4-\{(2S)-2-[4-methoxy-
3-(3-methoxypropoxy)benzyl]-3-methylbutyl\}-1,3-oxazolidine-3-carboxylate (50 mg) to
give 50 mg of desired product as an oil. LCMS: 821.5 [M+1]^+; 843.5 [M+Na]^+; 819.7 [M-
1]^-

**Example 43**

\[\text{[(1-aminocyclopropyl)carbonyloxy]methyl (4S,5S)-5-((2S)-2-\{[(3-amino-2,2-
dimethyl-3-oxopropyl)amino]carbonyl\}-3-methylbutyl)-4-\{(2S)-2-[4-methoxy-3-(3-
methoxypropoxy)benzyl]-3-methylbutyl\}-1,3-oxazolidine-3-carboxylate,} \]

trifluoroacetate
The compound was prepared using a method analogous to the method described in Example 9 from [\{1-[(tert-butoxycarbonyl)amino]cyclopropyl}carbonyl]oxy]methyl (4S,5S)-5-((2S)-2-\{[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl\}-3-methylbutyl)-4-\{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl\}-1,3-oxazolidine-3-carboxylate (52 mg) to give 52 mg of desired product (as TFA salt) as an oil. LCMS: 721.5 [M+1]^+, 743.5 [M+Na]^+; 719.5 [M-1]^-

Example 44

\{(1-methyl-1H-imidazol-5-yl)carbonyl\}oxy]methyl (4S,5S)-5-((2S)-2-\{[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl\}-3-methylbutyl)-4-\{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl\}-1,3-oxazolidine-3-carboxylate

The compound was prepared using a method analogous to the method described in Example 31 from 3-methyl-3H-imidazole-4-carboxylic acid (23 mg), cesium iodide (57 mg), cesium carbonate (90 mg), and chloromethyl (4S,5S)-5-((2S)-2-\{[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl\}-3-methylbutyl)-4-\{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl\}-1,3-oxazolidine-3-carboxylate (109 mg) to give
65 mg of desired product as colorless oil. LCMS: 746.5 [M+1]⁺, 768.5 [M+Na]⁺; 744.5 [M-1]⁻

**Example 45**

1-Chloroethyl (4S,5S)-5-(((2S)-2-((((3-amino-2,2-dimethyl-3-oxopropyl)amino)carbonyl)-3-methylbutyl)-4-((2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-oxazolidine-3-carboxylate

The compound was prepared using a method analogous to the method described in Example 13 from Aliskiren (550 mg) and 1-chloroethyl chloroformate (131 ml) to give 335 mg of desired product as white foam. LCMS: 670.5 [M+1]⁺, 792.5 [M+Na]⁺

**Example 46**

1-{((1-methyl-1H-imidazol-2-yl)carbonyl)oxy}ethyl (4S,5S)-5-(((2S)-2-((((3-amino-2,2-dimethyl-3-oxopropyl)amino)carbonyl)-3-methylbutyl)-4-((2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate

The compound was prepared using a method analogous to the method described in Example 31 from 1-methyl-1H-imidazole-2-carboxylic acid (8 mg), cesium carbonate (30 mg), cesium iodide (16 mg) and 1-chloroethyl (4S,5S)-5-(((2S)-2-((((3-amino-2,2-dimethyl-3-oxopropyl)amino)carbonyl)-3-methylbutyl)-4-((2S)-2-[4-methoxy-3-(3-
methoxypropoxy)benzyl]-3-methylbutyl]-oxazolidine-3-carboxylate (40 mg) to give 8 mg of desired product as colorless oil. LCMS: 760.5 [M+H]^+; 782.5 [M+Na]^+; 758.5 [M-1]^-

Example 47

1-[(tert-butoxycarbonyl)amino]cyclopropanecarbonyloxy]-ethyl (4S,5S)-5-((2S)-2-[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl]-3-methylbutyl)-4-((2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate

The compound was prepared using a method analogous to the method described in Example 42 from 1-tert-butoxycarbonylaminocyclopropylcarboxylic acid (21 mg), cesium iodide (23 mg), cesium carbonate (27 mg), and 1-chloroethyl (4S,5S)-5-((2S)-2-[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl]-3-methylbutyl)-4-((2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-oxazolidine-3-carboxylate (50 mg) to give 50 mg of desired product as an oil. LCMS: 835.5 [M+H]^+; 857.5 [M+Na]^+; 833.5 [M-1]^-

Example 48

1-(1-aminocyclopropanecarbonyloxy)ethyl (4S,5S)-5-((2S)-2-[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl]-3-methylbutyl)-4-((2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate, trifluoroacetate
The compound was prepared using a method analogous to the method described in Example 43 from 1-{[[1-{[(tert-butoxycarbonyl)amino]cyclopropanecarbonyloxy}]-ethyl (4S,5S)-5-{(2S)-2-[[3-amino-2,2-dimethyl-3-oxopropyl]amino]carbonyl}-3-methylbutyl}-4-{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl}-1,3-oxazolidine-3-carboxylate (46 mg) to give 55 mg of desired product (as TFA salt) as an oil. LCMS: 735.5 [M+H]^+, 757.5 [M+Na]^+, 733.5 [M-1]^-

Example 49

{{4S,5S}-5-{(2S)-2-[[3-amino-2,2-dimethyl-3-oxopropyl]amino]carbonyl}-3-methylbutyl}-4-{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl}-1,3-oxazolidin-3-yl)carbonyloxy]methyl tert-butyl (2E)-but-2-enedioate

The compound was prepared using a method analogous to the method described in Example 18 from fumaric acid mono tert-butylate (20 mg), cesium iodide (20 mg), cesium carbonate (as a base, 38 mg), and chloromethyl (4S,5S)-5-{(2S)-2-[[3-amino-2,2-dimethyl-3-oxopropyl]amino]carbonyl}-3-methylbutyl}-4-{(2S)-2-[4-methoxy-3-(3-
methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate (50 mg) to give 44 mg of desired product as colorless oil. LCMS: 792.5 [M+1]$^+$, 814.5 [M+Na]$^+$

Example 50

1-(((4S,5S)-5-((2S)-2-(((3-amino-2,2-dimethyl-3-oxopropyl)amino)carbonyl)-3-methylbutyl)-4-((2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidin-3-yl)carbonyl)oxy) methoxyoxo-(2E)-but-2-enoic acid

{{((4S,5S)-5-((2S)-2-(((3-amino-2,2-dimethyl-3-oxopropyl)amino)carbonyl)-3-methylbutyl)-4-((2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidin-3-yl)carbonyl)oxy} methyl tert-butyl (2E)-but-2-enedioate (44 mg) was dissolved in dry DCM (1 ml) and trifluoroactic acid (0.5 ml) was added to the stirred solution at r.t. Reaction course was monitored by LC-MS. After 1 h stirring reaction mixture was concentrated by rotary evaporation and coevaporated with water (2x1 ml), methanol (2 ml) and 3 times with toluene to remove excess of trifluoromethyl acid and water. Product obtained was dried under high vacuum for 18-20 h to give desired material as slightly rose oil 29 mg. LCMS: 736.4 [M+1]$^+$, 758.4 [M+Na]$^+$; 734.4 [M-1]$^-$

Example 51

{{((4S,5S)-5-((2S)-2-(((3-amino-2,2-dimethyl-3-oxopropyl)amino)carbonyl)-3-methylbutyl)-4-((2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidin-3-yl)carbonyl)oxy} methyl 1-azabicyclo[2.2.1]heptane-4-carboxylate
The compound was prepared using a method analogous to the method described in Example 16 from 1-azabicyclo[2.2.1]heptane-4-carboxylic acid cesium salt (76 mg, obtained by hydrolysis of corresponding ethyl ester hydrobromide in the presence of excess of cesium carbonate; ethyl 1-azabicyclo[2.2.1]heptane-4-carboxylate was prepared by literature procedure described in Eckhardt W et al, Helv. Chim. Acta, 55(7), 1972, 2432), cesium iodide (34 mg) and chloromethyl (4S,5S)-5-((2S)-2-(((3-amino-2,2-dimethyl-3-oxopropyl)amino)carbonyl)-3-methylbutyl)-4-(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate (50 mg) to give 40 mg of desired product as yellow oil without chromatographic purification. Purity of the product obtained was 80% (by UV at 230 nm). LCMS: 761.5 [M+1]^+, 783.5 [M+Na]^+; 759.5 [M-1]^−.

**Example 52**

\[(1-(((tert-butoxycarbonyl)amino)methyl)cyclopropyl)carbonyl]oxy\]methyl (4S,5S)-5-((2S)-2-(((3-amino-2,2-dimethyl-3-oxopropyl)amino)carbonyl)-3-methylbutyl)-4-((2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate
The compound was prepared using a method analogous to the method described in Example 42 from 1-tert-butoxycarbonylaminomethylocyclopropylcarboxylic acid (20 mg), cesium iodide (20 mg), cesium carbonate (as a base, 37 mg), and chloromethyl (4S,5S)-5-
(2S)-2-[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl]-3-methylbutyl)-4-[(2S)-2-
[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate
(50 mg) to give 45 mg of desired product as colorless oil. LCMS: 835.5 [M+1]+, 857.5
[M+Na]+

10 Example 53
{1-[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl]-3-
methylbutyl}-4-[(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-
oxazolidin-3-yl]carbonyl[oxy]methoxy)carbonyl[cyclopropyl]methanaminium
trifluoroacetate

The compound was prepared using a method analogous to the method described in Example 43 from {[(1-[(tert-
\text{amino}-2,2\text{-dimethyl-3-oxopropyl)amino[carbonyl]}-3\text{-methylbutyl})-4-\text{[(2S)-2-}[4\text{-methoxy-}
3\text{-}(3\text{-methoxypropoxy)benzyl]}\text{-3-methylbutyl}]}-1,3\text{-oxazolidine-3-carboxylate (42 mg) to}
give 39 mg of desired product (as TFA salt) as rose-brown foam.

\[
\text{LCMS: 735.5 [M+1]^+}, \; 757.5 \text{ [M+Na]^+}; \; 733.6 \text{ [M-1]^+}
\]

Example 54

1-\{[(1\text{-methyl-1H-imidazol-4-yl)carbonyl]oxy}ethyl (4S,5S)-5-\(((2S)-2-\text{[(3-}
\text{amino}-2,2\text{-dimethyl-3-oxopropyl)amino[carbonyl]}-3\text{-methylbutyl})-4-\text{[(2S)-2-}[4\text{-methoxy-3-}(3-
\text{methoxypropoxy)benzyl]}\text{-3-methylbutyl}]}-1,3\text{-oxazolidine-3-carboxylate}

\[
\text{The compound was prepared using a method analogous to the method described in}
\text{Example 31 from 1-methylimidazole-4-carboxylic acid (36 mg), cesium iodide (59 mg),}
\text{cesium carbonate (75 mg), and 1-chloroethyl (4S,5S)-5-\(((2S)-2-\text{[(3-}
\text{amino-2,2\text{-dimethyl-3-oxopropyl)amino[carbonyl]}-3\text{-methylbutyl})-4-\text{[(2S)-2-}[4\text{-methoxy-3-}(3-
\text{methoxypropoxy)benzyl]}\text{-3-methylbutyl}]}-1,3\text{-oxazolidine-3-carboxylate (85 mg). Product was}
\text{purified by preparative HPLC to give 18.9 mg of desired product as foam. LCMS: 760.5}
\text{[M+1]^+}, \; 782.4 \text{ [M+Na]^+}; \; 758.5 \text{ [M-1]^+}}
\]

Example 55

1-\{[(pyridin-3-yl)carbonyl]oxy}ethyl (4S,5S)-5-\(((2S)-2-\text{[(3-}
\text{amino}-2,2\text{-dimethyl-3-oxopropyl)amino[carbonyl]}-3\text{-methylbutyl})-4-\text{[(2S)-2-}[4\text{-methoxy-3-}(3-
\text{methoxypropoxy)benzyl]}\text{-3-methylbutyl}]}-1,3\text{-oxazolidine-3-carboxylate}
The compound was prepared using a method analogous to the method described in Example 18 from nicotinic acid (19 mg), cesium iodide (21 mg), cesium carbonate (57 mg), and 1-chloroethyl (4S,5S)-5-((2S)-2-{{(3-amino-2,2-dimethyl-3-oxypropyl)amino}carbonyl}-3-methylbutyl)-4-{{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl}-oxazolidine-3-carboxylate (50 mg) to give 38 mg of desired product as colorless oil. LCMS: 757.5 [M+1]^+, 779.5 [M+Na]^+; 755.5 [M-1]^-

Example 56

1-{{(pyridin-2-yl)carbonyl}oxy}ethyl (4S,5S)-5-((2S)-2-{{(3-amino-2,2-dimethyl-3-oxopropyl)amino}carbonyl}-3-methylbutyl)-4-{{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl}-1,3-oxazolidine-3-carboxylate

The compound was prepared using a method analogous to the method described in Example 18 from picolinic acid (20 mg), cesium iodide (22 mg), cesium carbonate (as a base, 53 mg), and 1-chloroethyl (4S,5S)-5-((2S)-2-{{(3-amino-2,2-dimethyl-3-oxopropyl)amino}carbonyl}-3-methylbutyl)-4-{{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl}-oxazolidine-3-carboxylate (53 mg) to give 26 mg of desired product as colorless oil. LCMS: 757.4 [M+1]^+, 779.4 [M+Na]^+; 755.5 [M-1]^-

20
Example 57

1-{{(4S,5S)-5-((2S)-2-{{(3-amino-2,2-dimethyl-3-oxopropyl)amino}carbonyl}-3-methylbutyl)-4-{{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl}-1,3-oxazolidin-3-yl}carbonyl}oxy}ethyl tert-butyl butanedioate

The compound was prepared using a method analogous to the method described in Example 49 from succinic acid mono tert-butylate (10 mg), cesium iodide (14 mg), cesium carbonate (as a base, 19 mg), and chloromethyl (4S,5S)-5-((2S)-2-{{(3-amino-2,2-dimethyl-3-oxopropyl)amino}carbonyl}-3-methylbutyl)-4-{{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl}-1,3-oxazolidine-3-carboxylate (35 mg) to give 32 mg of desired product as colorless oil. LCMS: 794.5 [M+1]⁺, 816.5 [M+Na]⁺

Example 58

1-{{(4S,5S)-5-((2S)-2-{{(3-amino-2,2-dimethyl-3-oxopropyl)amino}carbonyl}-3-methylbutyl)-4-{{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl}-1,3-oxazolidin-3-yl}carbonyl}oxy}methoxy)-4-oxobutanoic acid

The compound was prepared using a method analogous to the method described in Example 50 from 1-{{(4S,5S)-5-((2S)-2-{{(3-amino-2,2-dimethyl-3-
oxopropyl]amino[carbonyl]-3-methylbutyl)-4-[(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidin-3-yl]carbonyloxy]ethyl tert-butyl butanedioate (32 mg) to give 25 mg of desired product as slightly rose oil. LCMS: 738.5 [M+1]^+, 760.5 [M+Na]^+; 736.4 [M-1]^−.

Example 59

1-{{[(4S,5S)-5-[(2S)-2-{{[3-amino-2,2-dimethyl-3-oxopropyl]amino[carbonyl]-3-methylbutyl}-4-[(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidin-3-yl]carbonyloxy}ethyl tert-butyl (2E)-but-2-enedioate

The compound was prepared using a method analogous to the method described in Example 49 from fumaric acid mono tert-butylate (27 mg), cesium iodide (35 mg), cesium carbonate (as a base, 51 mg), and 1-chloroethyl (4S,5S)-5-[(2S)-2-{{[3-amino-2,2-dimethyl-3-oxopropyl]amino[carbonyl]-3-methylbutyl}-4-[(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl}-3-carboxylate (90 mg) to give 60 mg of desired product as colorless oil. LCMS: 806.5 [M+1]^+, 828.4 [M+Na]^+

Example 60

1-{{[(4S,5S)-5-[(2S)-2-{{[3-amino-2,2-dimethyl-3-oxopropyl]amino[carbonyl]-3-methylbutyl}-4-[(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidin-3-yl]carbonyloxy}ethyl oxo-(2E)-but-2-enoic acid
The compound was prepared using a method analogous to the method described in Example 50 from 1-\([(4S,5S)-5-((2S)-2-\{(3-amino-2,2-dimethyl-3-oxopropyl)amino\}carbonyl\}-3-methylbutyl)-4-\{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl\}-1,3-oxazolidin-3-yl)carbonyl]oxy\}ethyl tert-butyl (2E)-but-2-enedioate (60 mg) to give 35.1 mg of desired product as slightly rose oil.

LCMS: 750.4 [M+1]^+, 772.4 [M+Na]^+, 748.4 [M-1]

Example 61

(1-methylpiperidin-4-yl)methyl (4S,5S)-5-((2S)-2-\{(3-amino-2,2-dimethyl-3-oxopropyl)amino\}carbonyl\}-3-methylbutyl)-4-\{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl\}-1,3-oxazolidine-3-carboxylate

To a solution of 1-methyl-4-piperidinemethanol (23 mg) in DCM, was added bis(trichloromethyl) carbonate (30 mg), followed by DMAP (73 mg); and the resulting milky suspension was stirred at r.t. for 15 min. Then a solution of (4S,5S)-5-((2S)-2-\{(3-amino-2,2-dimethyl-3-oxopropyl)amino\}carbonyl\}-3-methylbutyl)-4-\{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl\}-1,3-oxazolidine (100 mg) in DCM was added and the resulting clear solution was stirred for 3 h at r.t. Reaction mixture was
concentrated by rotary evaporation and purified by preparative HPLC to give 36 mg of desired product as red-brown oil. LCMS: 719.5 [M+1]^+, 741.5 [M+Na]^+; 717.6 [M-1]^-

**Example 62**

\[\text{[(1-hydroxycyclopropyl)carbonyl]oxy\text{-}methyl (4S,5S)-5-((2S)-2-\{[3\text{-}amino\text{-}2,2\text{-}dimethyl\text{-}3\text{-}oxopropyl]amino\text{-}carbonyl\}3\text{-}methylbutyl)-4-\{2\text{-}4\text{-}methoxy\text{-}3\text{-}(3\text{-}methoxypropoxy)benzyl\}3\text{-}methylbutyl\}-1,3\text{-}oxazolidine\text{-}3\text{-carboxylate}}\]

The compound was prepared using a method analogous to the method described in Example 18 from 1-hydroxy-1-cyclopropanecarboxylic acid (6 mg), cesium iodide (14 mg), cesium carbonate (17 mg), and chloromethyl (4S,5S)-5-((2S)-2-\{[3\text{-}amino\text{-}2,2\text{-}dimethyl\text{-}3\text{-}oxopropyl]amino\text{-}carbonyl\}3\text{-}methylbutyl)-4-\{2\text{-}4\text{-}methoxy\text{-}3\text{-}(3\text{-}methoxypropoxy)benzyl\}3\text{-}methylbutyl\}-1,3\text{-}oxazolidine\text{-}3\text{-carboxylate} (30 mg) to give 24 mg of desired product as white foam after purification by column chromatography on YMC silica gel (EtOAc with 5% MeOH). LCMS: 722.5 [M+1]^+, 744.5 [M+Na]^+

**Example 63**

\[\text{1-\{[(1\text{-}methyl-1H-imidazol-5-yl)carbonyl]oxy\text{-}ethy (4S,5S)-5-((2S)-2-\{[3\text{-}amino\text{-}2,2\text{-}dimethyl\text{-}3\text{-}oxopropyl]amino\text{-}carbonyl\}3\text{-}methylbutyl)-4-\{2\text{-}4\text{-}methoxy\text{-}3\text{-}(3\text{-}methoxypropoxy)benzyl\}3\text{-}methylbutyl\}-1,3\text{-}oxazolidine\text{-}3\text{-carboxylate}}\]
The compound was prepared using a method analogous to the method described in Example 33 from 1-methyl-1H-imidazole-2-carboxylic acid (42 mg), cesium iodide (43 mg), cesium carbonate (as a base, 88 mg), and 1-chloroethyl (4S,5S)-5-((2S)-2-[[3-amino-2,2-dimethyl-3-oxopropyl]amino]carbonyl]-3-methylbutyl)-4-((2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate (100 mg) to give 25 mg of desired product as colorless oil. LCMS: 760.5 [M+1]^+, 782.5 [M+Na]^+; 758.5 [M-1]^-

Example 64

2-Chloroethyl (4S,5S)-5-((2S)-2-[[3-amino-2,2-dimethyl-3-oxopropyl]amino]carbonyl]-3-methylbutyl)-4-((2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-oxazolidine-3-carboxylate

The compound was prepared using a method analogous to the method described in Example 13 from Aliskiren (300 mg) and 2-chloroethyl chloroformate (60 μl) to give 121 mg of desired product as white foam. LCMS: 670.5 [M+1]^+, 792.5 [M+Na]^+; 668.4 [M-1]^-

Example 65

2-[(1,3-Dioxan-5-ylcarbonyloxy)ethyl (4S,5S)-5-((2S)-2-[[3-amino-2,2-dimethyl-3-oxopropyl]amino]carbonyl]-3-methylbutyl)-4-((2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate.
1,3-Dioxane-5-carboxylic acid (20 mg), cesium carbonate (49 mg), cesium iodide (21 mg) and 2-chloroethyl (4S,5S)-5-((2S)-2-{{(3-amino-2,2-dimethyl-3-oxopropyl)amino}carbonyl}-3-methylbutyl)-4-{{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl}]-oxazolidine-3-carboxylate (55 mg) were mixed with dry DMF (1ml) heated in a closed vial at 80 °C for 18h at stirring. Reaction mixture was then cooled down and acidified with 10% citric acid, mixed with water and brine and extracted into DCM (4x20 ml). Combined organic extracts were washed with brine, dried over MgSO₄, filtered and concentrated by rotary evaporation to give crude product as oil, which was kept under high vacuum to remove residual DMF. Purified by column chromatography on YMC silica gel (EtOAc then EtOAc/MeOH 9:1) gave about 35 mg of product as colorless oil/white foam. LCMS: 766,5 [M+1]⁺, 788,5 [M+Na]⁺

Example 66

2-{{(1-Methyl-1H-imidazol-5-yl)carbonyl}oxy}ethyl (4S,5S)-5-((2S)-2-{{(3-amino-2,2-dimethyl-3-oxopropyl)amino}carbonyl}-3-methylbutyl)-4-{{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl}]-1,3-oxazolidine-3-carboxylate
The compound was prepared using a method analogous to the method described in Example 65 from 2-chloroethyl (4S,5S)-5-((2S)-2-{{(3-amino-2,2-dimethyl-3-oxopropyl)amino}carbonyl}-3-methylbutyl)-4-{{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl}-oxazolidine-3-carboxylate (55 mg), cesium carbonate (57 mg), cesium iodide (41 mg) and 3-methyl-3H-imidazole-4-carboxylic acid (21 mg) to give 35 mg of desired product as colorless oil. LCMS: 760.5 [M+1]+, 782.5 [M+Na]+; 758.6 [M-1] 

**Example 67**

1-(Pyridin-3-yl)oxyethyl (4S,5S)-5-((2S)-2-{{(3-amino-2,2-dimethyl-3-oxopropyl)amino}carbonyl}-3-methylbutyl)-4-{{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl}-1,3-oxazolidine-3-carboxylate

1-Chloroethyl (4S,5S)-5-((2S)-2-{{(3-amino-2,2-dimethyl-3-oxopropyl)amino}carbonyl}-3-methylbutyl)-4-{{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl}-oxazolidine-3-carboxylate (51 mg), cesium carbonate (58 mg) and 3-hydroxypyridine (11 mg) were mixed with dry DMF (1 ml) and stirred overnight at room temperature. Reaction mixture was then mixed with 10% citric acid and brine and extracted into DCM.
Combined organic extracts were washed with brine and dried over magnesium sulfate. Crude material after concentration of organic extract was purified by column chromatography on silica gel (EtOAc) to afford 32 mg of product as colorless oil. LCMS: 729.5 [M+1]⁺, 751.5 [M+Na]⁺; 727.5 [M-1]

**Example 68**

\[
\{[(2-Methylypyridin-3-yl)carbonyl]oxy\}methyl (4S,5S)-5-((2S)-2-\{[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl\}-3-methylbutyl)-4-\{2S-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl\}-1,3-oxazolidine-3-carboxylate
\]

The compound was prepared using a method analogous to the method described in Example 18 from 2-methylpyridine-3-carboxylic acid (20 mg), cesium iodide (24 mg), cesium carbonate (53 mg), and chloromethyl (4S,5S)-5-((2S)-2-\{[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl\}-3-methylbutyl)-4-\{2S-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl\}-1,3-oxazolidine-3-carboxylate (51 mg) to give 41 mg of desired product as colorless oil. LCMS: 757.5 [M+1]⁺, 779.5 [M+Na]⁺; 755.6 [M-1]

**Example 69**

\[
\{[(3-Methylypyridin-2-yl)carbonyl]oxy\}methyl (4S,5S)-5-((2S)-2-\{[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl\}-3-methylbutyl)-4-\{2S-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl\}-1,3-oxazolidine-3-carboxylate
\]
The compound was prepared using a method analogous to the method described in Example 18 from 3-methylpicolinic acid (18 mg), cesium iodide (30 mg), cesium carbonate (54 mg), and chloromethyl (4S,5S)-5-((2S)-2-{{[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl}-3-methylbutyl}-4-{{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl}}-1,3-oxazolidine-3-carboxylate (50 mg) to give 32 mg of desired product as colorless oil. LCMS: 757.5 [M+1]^+, 779.5 [M+Na]^+; 755.6 [M-1]^-

Example 70

\[
\text{([1-(Hydroxymethyl)cyclopropyl]carbonyl} \text{oxy} \text{methyl (4S,5S)-5-((2S)-2-{{[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl}-3-methylbutyl}}-4-{{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl}}-1,3-oxazolidine-3-carboxylate}
\]

The compound was prepared using a method analogous to the method described in Example 18 from 1-hydroxymethyl-1-cyclopropanecarboxylic acid (12 mg), cesium iodide (28 mg), cesium carbonate (35 mg), and chloromethyl (4S,5S)-5-((2S)-2-{{[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl}-3-methylbutyl}-4-{{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl}}-1,3-oxazolidine-3-carboxylate (62 mg) to give 51 mg of desired product as colorless oil after purification by column chromatography on
YMC silica gel (EtOAc with 5% MeOH). LCMS: 736.5 [M+H]+, 758.5 [M+Na]+; 734.6 [M-1]-

**Example 71**

Pyridine-3-ylmethyl (4S,5S)-5-((2S)-2-{{(3-amino-2,2-dimethyl-3-oxopropyl)amino}[carbonyl]-3-methylbutyl}-4-((2S)-2-{4-methoxy-3-(3-methoxypropoxy)benzyl}-3-methylbutyl}-1,3-oxazolidin-3-carboxylate

Sodium hydride (5 mg, 60% in mineral oil) was mixed with absolute DMF (1.5 ml) and stirred for 10 min, then 3-pyridinemethanol (18 μl) was added to the reaction mixture and stirred for additional 20 min. Then chloromethyl (4S,5S)-5-((2S)-2-{{(3-amino-2,2-dimethyl-3-oxopropyl)amino}[carbonyl]-3-methylbutyl}-4-((2S)-2-{4-methoxy-3-(3-methoxypropoxy)benzyl}-3-methylbutyl}-1,3-oxazolidin-3-carboxylate (50 mg) was added as DMF solution (1.5 ml) to the reaction mixture and stirred overnight at r.t. Reaction mixture was acidified with 10% citric acid and extracted into DCM. Combined organic extract was washed with brine, dried over magnesium sulfate and concentrated by rotary evaporation. Crude material was purified by column chromatography on silica gel (EtOAc) to give 25 mg of desired compound as colorless oil. LCMS: 699.5 [M+H]+, 721.4 [M+Na]+; 697.5 [M-1]-

**Example 72**

{((4S,5S)-5-((2S)-2-{{(3-amino-2,2-dimethyl-3-oxopropyl)amino}[carbonyl]-3-methylbutyl}-4-((2S)-2-{4-methoxy-3-(3-methoxypropoxy)benzyl}-3-methylbutyl}-1,3-oxazolidin-3-yl)[carbonyloxy]methyl N-pentanoyl-N-{[2'-1H-tetrazol-5-yl]biphenyl-4-yl}methyl]-L-valinate
The compound was prepared using a method analogous to the method described in Example 8 from (S)-2-\{N-[(2'-\{(1H-tetrazol-5-yl)biphenyl-4-yl)methyl\}pentanamido\}-3-methylbutanoic acid (22 mg), cesium carbonate (15 mg), cesium iodide (12 mg) and chloromethyl (4S,5S)-5-\{(2S)-2-\{[3-amino-2,2-dimethyl-3-oxopropyl]amino\}carbonyl\}-3-methylbutyl)-4-\{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl\}-1,3-oxazolidine-3-carboxylate (30 mg) to give 10 mg of desired product as white foam after purification by column chromatography on YMC silica gel (EtOAc with 5% MeOH).

LCMS: 1055,7 [M+H]^+, 1077,6 [M+Na]^+; 1053,8 [M-1]^-

**Example 73**

\{(4-Methyloxazol-5-yl)carbonyl\}oxy\}methyl (4S,5S)-5-\{(2S)-2-\{[3-amino-2,2-dimethyl-3-oxopropyl]amino\}carbonyl\}-3-methylbutyl)-4-\{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl\}-1,3-oxazolidine-3-carboxylate
The compound was prepared using a method analogous to the method described in Example 31 from 4-methyloxazole-5-carboxylic acid (17 mg), cesium carbonate (66 mg), cesium iodide (30 mg) and chloromethyl (4S,5S)-5-[(2S)-2-[[3-amino-2,2-dimethyl-3-oxopropyl]amino][carbonyl]-3-methylbutyl]-4-[(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate (71 mg) to give 40 mg of desired product as white foam after purification by column chromatography on YMC silica gel (EtOAc with 5% MeOH). LCMS: 747,5 [M+1]^+, 769,5 [M+Na]^+; 745,4 [M-1]^-

10 Chemical Stability Studies

The compounds of the invention were studied for their chemical stability:

Stability at pH 2.0:
10 mM DMSO solution of the compound of the formula (I) was prepared. 10 μl of the solution was added to 1 ml of pH 2 aqueous buffer at 37 °C. The solution was kept at 37 °C. At each time point, a small aliquote was taken and the sample was analyzed by LCMS.

Stability at pH 7.4:
10 mM DMSO solution of the compound of the formula (I) was prepared. 10 μl of the solution was added to 1 ml of pH 7.4 aqueous phosphate buffer at 37 °C. The solution was kept at 37 °C. At each time points, a small aliquote was taken and the sample was analyzed by LCMS.

Stability study in human plasma

10 mM solution of the compound of formula (I) in DMSO was added to human plasma (pooled), making the final compound concentration of 20μM. The sample was incubated at 37 °C. At each time point, an aliquot of 100 μl was taken. The aliquot was kept on ice and to it was added 200 μl acetonitrile immediately. After mixing for a few seconds, the sample was centrifuged at 30000rpm at 10°C for 7 min. The supernatant was taken and analyzed by LCMS.
**In vivo bioavailability experiment**

The following study was employed to investigate the oral bioavailability of representative compounds of the invention by measuring the plasma concentration of aliskiren following a single dose of the compounds of the invention. For comparison, aliskiren hemifumarate was dosed both i.v. (intravenous) and orally. For all experiment, the compounds were administrated to three individually weighted male Sprague-Dawley rats. For all po dosing, the dose was 25 μmole/kg in a dose volume of 8ml/kg and the dose vehicle was 50% propylene glycol/50% pH 4.75 buffer (0.1M aqueous buffer of NaOAc/HOAc) by volume ratio. For i.v. dosing, aliskiren hemi-fumarate was dosed at 5μmole/kg (calculated based on free base) in a volume of 1.5ml/kg and the vehicle was saline. For the i.v. dosing of the compounds of invention, a vehicle of 45% PEG400 / 55% pH 4.75 buffer (0.1M aqueous buffer of NaOAc/HOAc) by volume ratio was used and the dose were 5 μmole/kg in a dose volume of 1.5 ml/kg. Male Sprague-Dawley rats were fasted for about 16 - 17 h before po dosing and fasting lasted about 2-3 h post-dose. Water was given *ad libitum*. The blood samples were taken at different time points up to 24 h. For i.v. dosing group, at 5 min, 15 min, 30 min, 1 h, 2 h, 4 h, 6 h, 8 h, 24 h. For oral doing group, at 15 min, 30 min, 1 h, 2 h, 4 h, 6 h, 24 h. The blood samples were collected in heparinized tube and centrifuged at 3500 rpm for 5 min. The plasma samples were stored at about −20 °C for analysis.

After the work-up of the plasma samples, LC-MS/MS was used for the quantitation of the aliskiren and the compounds of the invention. Standard curves were made for aliskiren and the substances for study. The lowest LOQ (limit of quantitation) for aliskiren in plasma was 0.5 ng/ml.
Results of some compounds of the invention

Table 1. Chemical stability of the compounds

<table>
<thead>
<tr>
<th>Compound</th>
<th>pH 2</th>
<th>pH 7.4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aliskiren</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Example 6</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Example 12</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Example 27</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Example 32</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Example 35</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Example 43</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Example 44</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Example 46</td>
<td>C</td>
<td>A</td>
</tr>
<tr>
<td>Example 53</td>
<td>A</td>
<td>C</td>
</tr>
</tbody>
</table>

A: Less than 5 % decomposition after 3 h incubation at 37°C.
B: Less than 25% decomposition after 3 h incubation at 37°C.
C: Less than 50% decomposition after 3 h incubation at 37°C.
Table 2. *In vivo* bioavailability study after iv and oral dosing of the compounds in rats

<table>
<thead>
<tr>
<th>Dosed Compounds</th>
<th>AUC(_{0-4}) (h* ng/ml) of aliskiren</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aliskiren hemifumarate i.v. (5μmole/kg)</td>
<td>994±162</td>
</tr>
<tr>
<td>Aliskiren hemifumarate p.o. (25μmole/kg)</td>
<td>28.0±20.5</td>
</tr>
<tr>
<td>Example 6 p.o. (25μmole/kg)</td>
<td>A</td>
</tr>
<tr>
<td>Example 12 p.o. (25μmole/kg)</td>
<td>A</td>
</tr>
<tr>
<td>Example 27 p.o. (25μmole/kg)</td>
<td>B</td>
</tr>
<tr>
<td>Example 32 p.o. (25μmole/kg)</td>
<td>B</td>
</tr>
<tr>
<td>Example 35 p.o. (25μmole/kg)</td>
<td>B</td>
</tr>
<tr>
<td>Example 43 p.o. (25μmole/kg)</td>
<td>B</td>
</tr>
<tr>
<td>Example 44 p.o. (25μmole/kg)</td>
<td>C</td>
</tr>
<tr>
<td>Example 46 p.o. (25μmole/kg)</td>
<td>A</td>
</tr>
<tr>
<td>Example 53 p.o. (25μmole/kg)</td>
<td>A</td>
</tr>
<tr>
<td>Example 63 p.o. (25μmole/kg)</td>
<td>C</td>
</tr>
</tbody>
</table>

A: AUC\(_{0-4}\) (h* ng/ml) of aliskiren is between 40 and 100

B: AUC\(_{0-4}\) (h* ng/ml) of aliskiren is between 100 and 300

C: AUC\(_{0-4}\) (h* ng/ml) of aliskiren is > 300
CLAIMS

1. A compound of formula (I)

\[
\begin{array}{c}
\text{W} \\
\text{X}^1 \\
\text{X}^2 \\
\text{Y} \\
\text{Z} \\
\text{R}^1 \\
\text{R}^2 \\
\text{R}^3 \\
\text{R}^4 \\
\text{R}^5 \\
\end{array}
\]

(II)

wherein

R\(^1\) and R\(^2\) independently represent

H, C\(_1\)-C\(_6\)alkyl, C\(_3\)-C\(_6\)cycoloalkyl or C\(_3\)-C\(_6\)cycoloalkyl-C\(_1\)-C\(_3\)alkyl, wherein said C\(_1\)-C\(_6\)alkyl, C\(_3\)-C\(_6\)cycoloalkyl or C\(_3\)-C\(_6\)cycoloalkyl-C\(_1\)-C\(_3\)alkyl is optionally substituted by one or more substituents independently selected from halogen, CN, NH(C\(_1\)-C\(_6\)alkyl), N(C\(_1\)-C\(_6\)alkyl)\(_2\), C\(_1\)-C\(_6\)alkyl and C\(_1\)-C\(_6\)alkoxy;

or R\(^1\) and R\(^2\) together with the carbon to which they are bonded form

a C\(_3\)-C\(_6\)cycoloalkyl or a 4-6 membered heterocyclyl, wherein said C\(_3\)-C\(_6\)cycoloalkyl or 4-6 membered heterocyclyl is optionally substituted by one or more substituents independently selected from halogen, CN, NH(C\(_1\)-C\(_6\)alkyl), N(C\(_1\)-C\(_6\)alkyl)\(_2\), C\(_1\)-C\(_6\)alkyl and C\(_1\)-C\(_6\)alkoxy;

R\(^3\) and R\(^4\) independently represent

H, C\(_1\)-C\(_8\)alkyl, C\(_2\)-C\(_8\)alkenyl, C\(_2\)-C\(_8\)alkynyl, C\(_3\)-C\(_6\)cycoloalkyl, C\(_3\)-C\(_6\)cycoloalkyl-C\(_1\)-C\(_8\)alkyl, C\(_1\)-C\(_8\)alkoxy, C\(_1\)-C\(_8\)alkoxy-C\(_1\)-C\(_8\)alkyl, aryl-C\(_1\)-C\(_8\)alkyl, heterocyclyl-C\(_1\)-C\(_8\)alkyl, aryl, aryloxy, heterocyclyl or heterocyclyloxy, wherein said C\(_1\)-C\(_8\)alkyl, C\(_2\)-C\(_8\)alkenyl, C\(_2\)-C\(_8\)alkynyl, C\(_3\)-C\(_6\)cycoloalkyl, C\(_3\)-C\(_6\)cycoloalkyl-C\(_1\)-C\(_8\)alkyl, C\(_1\)-
C₈alkoxy, C₁₋C₈alkoxy-C₁₋C₈alkyl, heterocyclyl-C₁₋C₈alkyl, aryl, aryloxy, heterocyclyl or heterocyclyloxy is optionally substituted by one or more substituents independently selected from halogen, OH, CN, NO₂, NH₂, NH(C₁₋C₆alkyl), N(C₁₋C₆alkyl)₂, C₁₋C₆alkyl, C₁₋C₆alkoxy and C₃₋C₆cycloalkyl;

or R³ and R⁴ together with the carbon to which they are bonded form a C₂₋C₈cycloalkyl or a 4-8 membered heterocyclyl, wherein said C₂₋C₈cycloalkyl or 4-8 membered heterocyclyl is optionally substituted by one or more substituents independently selected from halogen, OH, CN, NO₂, NH₂, NH(C₁₋C₃alkyl), N(C₁₋C₃alkyl)₂, C₁₋C₃alkyl, C₃₋C₆cycloalkyl and C₁₋C₃alkoxy;

X¹ represents

O or S;

X² represents

O or S;

W represents

H, R⁶X¹₋, C₂₋C₆alkyl, halogen, (OH)₂P(O)O, [R⁴C(O)OCH₂O]₂P(O)O, or [R⁴C(O)OCH(C₁₋C₃alkyl)O]₂P(O)O, [R⁶C(O)SCH₂CH₂O]₂P(O)O;

R⁶ represents

C₁₋C₆alkyl, C₃₋C₆cycloalkyl, C₂₋C₆-alkenyl, heterocyclyl or aryl, wherein said C₁₋C₆alkyl, C₃₋C₆cycloalkyl, C₂₋C₆-alkenyl, heterocyclyl or aryl is optionally substituted by one or more substituents independently selected from halogen, OH, NH₂, NH(C₁₋C₃-alkyl), N(C₁₋C₃-alkyl)₂, C₁₋C₃alkyl, C₁₋C₃alkoxy, aryl and heterocyclyl;

R⁶ represents

–C(=X¹)TZ ;
T represents
O, S, NH, N(C₁-C₃alkyl) or a single bond;

Z represents

C₁-C₁₈alkyl, C₂-C₁₈alkenyl, C₂-C₁₈alkynyl, C₃-C₈cycloalkenyl, C₄-C₈cycloalkynyl,
aryl, heterocyclyl, C₃-C₈cycloalkyl, C₁-C₁₈alkyl-heterocyclyl, tetrazolyl-biphenyl-
methyl-heterocyclyl, tetrazolyl-biphenyl-methyl-heterocyclylmethyl, tetrazolyl-
biphenyl-methyl-amino-C₁-C₆alkyl, oxadiazolyl-biphenyl-methyl-heterocyclyl,
heterocyclylmethyl-aryl, C₁-C₆alkyl-aryl or C₁-C₆alkyl-C₁-C₈cycloalkyl, wherein
said C₁-C₁₈alkyl, C₂-C₁₈alkenyl, C₂-C₁₈alkynyl, C₃-C₈cycloalkenyl, C₄-
C₈cycloalkynyl, aryl, heterocyclyl, C₃-C₈cycloalkyl, C₁-C₁₈alkyl-heterocyclyl,
tetrazolyl-biphenyl-methyl-heterocyclyl, tetrazolyl-biphenyl-methyl-
heterocyclylmethyl, tetrazolyl-biphenyl-methyl-amino-C₁-C₆alkyl, oxadiazolyl-
biphenyl-methyl-heterocyclyl, heterocyclylmethyl-aryl, C₁-C₆alkyl-aryl or C₁-
C₆alkyl-C₁-C₈cycloalkyl is optionally substituted by one or more substituents
independently selected from halogen, OH, CN, oxo, N₃, NO₂, NH₂, NH(C₁-C₆alkyl),
N(C₁-C₆alkyl)₂, C₁-C₆alkanoylNH, C₂-C₆alkoxy carbonylNH, C₁-C₆alkanoyl, C₁-
C₆alkanoyloxy, COOH, (OH)₂P(Ο)Ο, [R₈C(O)OCH₂Ο]₂P(Ο)Ο, [R₄C(O)OCH(C₁-
C₅alkyl)Ο]₂P(Ο)Ο, [R₈C(O)SCH₂CH₂Ο]₂P(Ο)Ο, NH₂C(Ο), C₁-C₆alkyl, C₂-
C₆alkenyl, C₂-C₆alkynyl, C₁-C₆alkoxy, C₁-C₆alkoxy carbonyl, C₁-
C₆alkoxy carbonylNH, NH₂C₁-C₆alkyl, C₁-C₆alkoxy carbonylNH, C₁-C₆alkyl, C₃-C₆alkyl, C₃-C₆cycloalkenyl, C₃-C₆cycloalkoxy, C₃-
C₆cycloalkenylOxy, C₁-C₆alkoxy-C₁-C₆alkoxy, aryl, arylOxy, heterocyclOxy and
heterocyclyl;

M represents

\[
\begin{array}{c}
\text{R}\text{7}^\text{2} & \text{R}\text{8} \\
\end{array}
\]

O, S, SO₂, N(R⁻) or

R⁷ represents

H, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₆cycloalkyl, aryl, heterocyclyl or
aryl(C₁-C₆)alkyl, wherein said C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-
C₆cycloalkyl, aryl, heterocyclyl or aryl(C₁-C₆)alkyl is optionally substituted by one or more substituents independently selected from halogen, C₃-C₆cycloalkyl or C₁-C₆alkyl, wherein said C₃-C₆cycloalkyl or C₁-C₆alkyl is optionally substituted by one or more substituents selected from halogen, aryl and heterocyclyl;

R⁸ represents

H, OH, halogen, C₁-C₆alkyl or C₁-C₆alkoxy;

or R⁷ and R⁸ together with the carbon atom to which they are bonded form a C₃-

C₅cycloalkyl;

Y represents

a single bond, CH₂, C₂-C₆alkanoyloxyethylenene, O, S, SO, SO₂, NH, N(C₁-C₄alkyl), C(O), or CH(OH);

U represents

a single bond, CH₂, C(O), C(O)NH, NHC(O), NH or N(C₁-C₄alkyl);

V represents

a 3-18-membered saturated, partially unsaturated or aromatic mono-, bi- or tricyclic system, said system is a carbocyclic ring system or a heterocyclic ring system selected from C₃-C₁₂cycloalkyl, C₃-C₁₂cycloalkenyl, C₄-C₁₂cycloalkynyl, heterocyclyl and aryl, wherein said system is optionally substituted with one, two, three or four substituents independently selected from halogen, OH, CN, oxo,

COOH, CF₃, NO₂, NH₂, NH(C₁-C₆alkyl), N(C₁-C₆alkyl)₂, C₁-C₆alkoxy, C₁-C₆alkoxy-C₁-C₆alkoxy, NH₂C(O), C₃-C₆cycloalkyl, C₂-C₆alkenyl, C₃-C₆cycloalkoxy-C₁-C₆alkoxy, C₃-C₆cycloalkyl-C₁-C₆alkoxy, dioxalanyl, hydroxyl-C₂-C₇alkoxy, haloC₂-C₇alkoxy, carbamoylexy-C₂-C₇alkoxy, [(C₅H₅N)NHC(O)]C₁-C₇alkoxy, C₃-C₆cycloalkoxy, C₂-C₇alkenylxylox, C₁-C₆alkanoxyloxy, C₁-C₆alkoxy carbonyl, C₁-C₆alkoxycarbonyl, C₁-C₆alkylenedioxy, aryl, phenoxy, phenylthio, pyridyl and C₁-C₆alkyl, wherein said C₁-C₆alkyl is optionally substituted by C₃-C₆cycloalkoxy, C₁-C₆alkoxy, (C₅H₅N)C(O)NH, NH₂C(O), NH(C₁-C₆alkyl)
C₃alkyl)C(O), N(C₁₋C₃)₂C(O), NH₂C(O)C₁₋C₃alkoxy, NH(C₁₋C₃alkyl)C(O)C₁₋C₃alkoxy, N(C₁₋C₃alkyl)₂C(O)C₁₋C₃alkoxy or phenyl;

A represents

CH or N;

R⁵ represents

H, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₆cycloalkyl or C₁-C₆alkoxy,

wherein said C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₆cycloalkyl or C₁-C₆alkoxy is optionally substituted by one or more of substituents independently selected from halogen, OH, C₃-C₆cycloalkyl, C₁-C₆alkoxy and aryl;

Q represents

C₁-C₆alkyl, C₁-C₆cycloalkyl, NH(C₁-C₆alkyl)C(O)C₁-C₆alkyl, N(C₁-C₆alkyl)₂C(O)C₁-C₆alkyl, aryl, heterocyclyl or heterocyclic-C₁-C₆alkyl;

or Q is selected from the group of partial structures consisting of E₁ and E₂

\[
\begin{align*}
&\text{E₁} \\ &\text{E₂}
\end{align*}
\]

G represents

R⁹ or N(R⁹);

R¹⁰ represents

H or C₁-C₆alkyl;

or R⁵, Q and A, wherein A is N, form a 3-18-membered saturated, partially unsaturated or aromatic mono-, bi- or tricyclic ring system, wherein said system is optionally substituted
by one, two, three or four substituents independently selected from halogen, OH, oxo, CN, C₁-C₆alkyl, C₃-C₈cycloalkyl, C₃-C₈cycloalkanoyl, C₁-C₈alkanoyl, aryl-C₁-C₆alkanoyl, C₁-C₆alkoxy carbonyl, C₁-C₆alkyl-SO₂, heterocyclylSO₂, aryl and heterocyclyl;

5 R⁹ represents

H, C₁-C₆alkyl, C₃-C₈cycloalkyl, C₂-C₆alkenyl or C₁-C₆alkoxy, wherein said C₁-C₆alkyl, C₃-C₈cycloalkyl, C₂-C₆alkenyl or C₁-C₆alkoxy is optionally substituted by one or more halogen;

10 R¹⁰ represents

H, C₁-C₁₂alkyl, C₂-C₁₂alkenyl, C₃-C₁₂cycloalkyl, C₃-C₁₂cycloalkenyl, heterocyclyl or aryl, wherein said C₁-C₁₂alkyl, C₂-C₁₂alkenyl, C₃-C₁₂cycloalkyl, C₃-C₁₂cycloalkenyl, heterocyclyl or aryl is optionally substituted by one or more substituents independently selected from halogen, OH, CN, NO₂, C₁-C₈alkoxy, C₃-C₆cycloalkyl, aryloxy, heterocycloxy, NH₂C(O), NH(C₁-C₈alkyl), NH(aryl), NH(heterocyclyl), NH(aryl)C(O), NH(heterocyclyl)C(O), C₁-C₈alkyl-C(O)NH, arylC(O)NH, C₁-C₈alkanoyl, C₁-C₆alkoxyC(O), C₁-C₈alkylSO₂, aryl-SO₂, aryl and heterocyclyl;

or R¹⁰ is

C₁-C₈alkyl or C₁-C₈alkenyl, wherein said C₁-C₈alkyl or C₁-C₈alkenyl is optionally substituted by NH₂C(O), NH(C₁-C₈alkyl)C(O), NH(C₁-C₈cycloalkyl)C(O), NH(C₃-C₆-alkenyl)C(O), N(C₁-C₈alkyl)₂C(O), C₁-C₆alkoxy carbonylNHC(O), N(C₃-C₈cycloalkyl)₂C(O), N(C₃-C₆cycloalkyl)(C₁-C₃alkyl)C(O), N(heterocyclyl)(C₁-C₆alkyl)C(O), NH₂C(S) or NH(C₁-C₈alkyl)C(S);

or R¹⁰ is

C₁-C₆alkyl or C₂-C₆alkenyl, wherein said C₁-C₆alkyl or C₂-C₆alkenyl is optionally substituted with NH₂C(O)C₃-C₆cycloalkyl;

30 or R⁹ and R¹⁰ together with the atom of G to which R⁹ and R¹⁰ are bonded form a 3-18-membered saturated, partially unsaturated or aromatic mono-, bi- or tricyclic system, said system is a carbocyclic ring system or a heterocyclic ring system,
wherein said system is optionally substituted by one, two, three or four substituents independently selected from halogen, OH, oxo, C₁-C₆alkyl, C₃-C₈cycloalkyl, C₁-C₈alkoxy, C₃-C₈cycloalkoxy, C₁-C₈alkanoyl, C₁-C₈alkanoyloxy, aryl-C₁-C₈alkanoyl, C₁-C₈alkoxycarbonyl, C₁-C₈alkyl-SO₂, heterocyclyl-SO₂, aryl and heterocyclyl;

with the proviso that R² is not aryl when R³ and W are H;
and with the proviso that R³ is not aryl when R¹ and W are H;
or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein

Z represents

C₁-C₁₈alkyl, C₂-C₁₈alkenyl, C₂-C₁₈alkynyl, C₃-C₈cycloalkenyl, C₄-C₈cycloalkynyl, aryl, heterocyclyl or C₃-C₈cycloalkyl, wherein said C₁-C₁₈alkyl, C₂-C₁₈alkenyl, C₂-C₁₈alkynyl, C₃-C₈cycloalkenyl, C₄-C₈cycloalkynyl, aryl, heterocyclyl or C₃-C₈cycloalkyl is optionally substituted by one or more of the substituents independently selected from: halogen, OH, CN, oxo, N₃, NO₂, NH₂, NH(C₁-C₆alkyl), N(C₁-C₆alkyl)₂, C₁-C₆alkanoylNH, C₂-C₆alkoxycarbonylNH, C₁-C₆alkanoyl, C₁-C₆alkanoyloxy, COOH, (OH)₂P(O)O, [R²C(O)OCH₂O]₂P(O)O, [R²C(O)OCH(C₁-C₈alkyl)O]₂P(O)O, [R²C(O)SCH₂CH₂O]₂P(O)O, NH₂C(O), C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆alkoxy, C₁-C₆alkoxycarbonyl, C₃-C₈cycloalkyl, C₃-C₈cycloalkenyl, C₃-C₈cycloalkynyl, C₁-C₆alkoxycarbonyloxyster, C₁-C₆alkoxy-C₁-C₆alkoxycarbonyl, aryl, aryloxy, heterocyclyl, and heterocyclyl oxyxo and heterocyclyl.

3. A compound according to claim 1 or claim 2, wherein

X¹ is O;
X² is O or S; and
W is R³O⁻.

4. A compound according to claim 3, wherein

X² is O.
5. A compound according to any one of claims 1 to 4, wherein
   \( X^1 \) is O;
   \( X^2 \) is O;
   \( R^1 \)
   \( R^6 \)
   \( M \) is ; and
   U is a single bond.

6. A compound according to any one of claims 1 to 5, wherein
   \( X^1 \) is O;
   \( X^2 \) is O;
   W is \( R^6 O^- \);
   \( R^7 \)
   \( R^8 \)
   \( M \) is ;
   U is a single bond;
   A is CH and
   Q is E1.

7. A compound according to any one of claims 1 to 6, wherein
   \( R^5 \) is
   \( C_1 - C_6 \) alkyl or \( C_3 - C_6 \) cycloalkyl.

8. A compound according to any one of claims 1 to 7, wherein
   V-Y-U-M is:

   R^5 is isopropyl;
   Q is E1, wherein G is N(R^6); and
9. A compound according to any one of claims 1 to 8, wherein,
V-U-Y-M is

\[
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{O} \\
\text{O}
\end{array}
\]

\[A(R^5)Q\text{ is}
\]

\[
\begin{array}{c}
\text{N} \\
\text{R}^{10}
\end{array}
\]

and

\[R^{10}\text{ is}
\]

\[
\begin{array}{c}
\text{C}_1\text{-C}_6\text{alkyl, NH}_2\text{C(O)C}_2\text{-C}_6\text{alkyl, NH(C}_1\text{-C}_6\text{alkyl)C(O)C}_2\text{-C}_5\text{alkyl, N(C}_7\text{-}
\text{C}_6\text{alkyl)C(O)C}_2\text{-C}_5\text{alkyl, C}_1\text{-C}_6\text{alkoxycarbonylNHC(O)-C}_2\text{-C}_6\text{alkyl, aryl-C}_1\text{-}
\text{C}_3\text{alkyl, C}_3\text{-C}_6\text{cycloalkyl-C}_1\text{-C}_2\text{alkyl, NH}_2\text{C(O)cyclopropyl, C}_3\text{-C}_6\text{cycloalkyl or aryl.}
\end{array}
\]

10. A compound according to any one of claims 1 to 9, wherein
V-U-Y-M is

\[
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{O} \\
\text{O}
\end{array}
\]

\[A(R^5)Q\text{ is}
\]
11. A compound according to any one of claims 1 to 10, wherein $X^1$ is O;
5 $X^2$ is O;
$W$ is $R^6O$-
$V-U-Y-M$ is 

; and

$A(R^5)Q$ is 

12. A compound according to any one of claims 1 to 11, wherein 
$V-U-Y-M$ is
5  \( R^1 \) and \( R^2 \) independently represent
   H, methyl or ethyl;

or \( R^1 \) and \( R^2 \) together with the carbon to which they are bonded form
   a \( C_3-C_6 \) cycloalkyl or a 4-6 membered heterocyclyl, wherein said \( C_3-C_6 \) cycloalkyl
10  or 4-6 membered heterocyclyl is optionally substituted by one or more substituents
    independently selected from halogen, CN, NH(C\(_1\)-C\(_3\)alkyl), N(C\(_1\)-C\(_3\)alkyl)\(_2\), C\(_1\)-C\(_3\)alkyl and C\(_1\)-C\(_3\)alkoxy;

\( R^3 \) and \( R^4 \) independently represent
15  H or methyl;

or \( R^3 \) and \( R^4 \) together with the carbon to which they are bonded form
   a \( C_3-C_8 \) cycloalkyl or a 4-8 membered heterocyclyl, wherein said \( C_3-C_8 \) cycloalkyl
20  or 4-8 membered heterocyclyl is optionally substituted by one or more substituents
    independently selected from halogen, OH, NH\(_2\), NH(C\(_1\)-C\(_3\)alkyl), N(C\(_1\)-C\(_3\)alkyl)\(_2\),
    C\(_1\)-C\(_3\)alkyl or C\(_1\)-C\(_3\)alkoxy;

\( X^1 \) is O;
X² is O

W is R⁶O⁻.

5

R⁶ is \(-\frac{C}{(=C)}T\)Z

T is a single bond or O;

10 Z represents

\[ \text{C}_1-\text{C}_{18}\text{alkyl, C}_2-\text{C}_{18}\text{alkenyl, C}_2-\text{C}_{18}\text{alkynyl, C}_3-\text{C}_8\text{cycloalkenyln, C}_4-\text{C}_8\text{cycloalkynyl, aryl, heterocyclyl or C}_3-\text{C}_8\text{cycloalkyl, wherein said } \text{C}_1-\text{C}_{18}\text{alkyl, C}_2-\text{C}_{18}\text{alkenyl, C}_2-\text{C}_{18}\text{alkynyl, C}_3-\text{C}_8\text{cycloalkenyln, C}_4-\text{C}_8\text{cycloalkynyl, aryl, heterocyclyl or C}_3-\text{C}_8\text{cycloalkyl is optionally substituted by one or more of the substituents independently selected from: halogen, OH, CN, oxo, N}_3, \text{NO}_2, \text{NH}_2, \text{NH(C}_1-\text{C}_6\text{alkyl), N(C}_1-\text{C}_6\text{alkyl})_2, C}_1-\text{C}_6\text{alkanoylNH, C}_2-\text{C}_6\text{alkoxycarbonylNH, C}_1-\text{C}_6\text{alkanoyl, C}_1-\text{C}_6\text{alkanoyloxy, COOH, (OH)}_2\text{P(O)O, [R}^8\text{C(O)OCH}_2\text{O]}_2\text{P(O)O, [R}^8\text{C(O)OCH}(-\text{C}_1-\text{C}_3\text{alkyl})\text{O]}_2\text{P(O)O, [R}^8\text{C(O)SCH}_2\text{CH}_2\text{O]}_2\text{P(O)O, NH}_2\text{C(O)}_2-, C}_1-\text{C}_6\text{alkyl, C}_2-\text{C}_6\text{alkenyl, C}_2-\text{C}_6\text{alkynyl, C}_1-\text{C}_6\text{alkoxy, C}_1-\text{C}_6\text{alkoxycarbonyl, C}_3-\text{C}_6\text{cycloalkyl, C}_3-\text{C}_6\text{cycloalkenyln, C}_3-\text{C}_6\text{cycloalkoxy, C}_1-\text{C}_3\text{alkoxy-C}_1-\text{C}_6\text{alkoxy-}, aryl, arloxy, heterocyclyloxy and heterocyclyl.} \]

13. A compound according to claim 1, wherein

R¹ and R² independently represent

25 H or C₁-C₂alkyl;

R³ and R⁴ independently represent

H or C₁-C₃alkyl;

30 X¹ represents O;

X² represents O;
W represents
\[ \text{R}^6 \ X^1 \ - \ \text{or H}_2 \]

5 \ R^6 \ represents
\[ \text{C}(=X^1)TZ \ ; \]

T represents
\[ \text{O or a single bond} ; \]

10
Z represents
\[ \text{C}_1-\text{C}_8 \text{alkyl, C}_2-\text{C}_18 \text{alkenyl, C}_3-\text{C}_8 \text{cycloalkyl, aryl, heterocyclyl, or C}_1-\text{C}_6 \text{alkyl-} \text{C}_3-\text{C}_8 \text{cycloalkyl, wherein said C}_1-\text{C}_8 \text{alkyl, C}_2-\text{C}_18 \text{alkenyl, C}_3-\text{C}_8 \text{cycloalkyl, aryl, heterocyclyl, C}_1-\text{C}_6 \text{alkyl-aryl or C}_1-\text{C}_6 \text{alkyl-C}_3-\text{C}_8 \text{cycloalkyl is optionally substituted by one or two substituents independently selected from halogen, OH, oxo, NH}_2, N(C}_1-\text{C}_6 \text{alkyl}, C}_2-\text{C}_4 \text{alkoxycarbonylNH, C}_1-\text{C}_6 \text{alkyl, C}_1-\text{C}_6 \text{alkoxy, C}_1-\text{C}_6 \text{alkoxycarbonylNH, C}_1-\text{C}_6 \text{alkoxycarbonylNH, C}_3-\text{C}_6 \text{cycloalkyl, C}_1-\text{C}_3 \text{alkoxy-C}_1-\text{C}_6 \text{alkoxy}, heterocyclyloxy, heterocyclyl, NH}_2 C}_1-\text{C}_6 \text{alkyl, C}_1-\text{C}_6 \text{alkoxycarbonylNH}_{\text{C}_1-}\text{C}_3 \text{alkyl and arylC}_1-\text{C}_4 \text{alkylcarbonylNH}} ; \]

20

V-U-Y-M is

\[ \text{A} \ (R^5) \ Q \ is \]
R^{10} represents C_{1-4}alkyl, said C_{1-4}alkyl is optionally substituted by one NH_2C(O).

14. A compound according to claim 1, wherein

R^{1} and R^{2} independently represent

H or C_{1-2}alkyl;

R^{3} and R^{4} independently represent

H or C_{1-3}alkyl;

X^{1} represents O;

X^{2} represents O;

W represents R^{6} X^{1};

R^{6} represents \(-C(=X^{1})TZ\);

T represents

O or a single bond;

Z represents

C_{1-18}alkyl-heterocyclyl, [2'-((1H-tetrazol-5-yl)biphenyl-4-yl)methyl-heterocyclyl, [2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl-heterocyclyl-methyl, [2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methylamino-C_{1-6}alkyl, oxadiazolyl-biphenyl-methyl-heterocyclyl or heterocyclylmethyl-biphenyl, wherein said C_{1-18}alkyl-heterocyclyl, [2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl-heterocyclyl, [2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl-heterocyclyl-methyl, [2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methylamino-C_{1-6}alkyl, oxadiazolyl-biphenyl-methyl-heterocyclyl or heterocyclylmethyl-biphenyl is optionally substituted by one or more substituents

independently selected from halogen, OH, C_{2-6}alkanoyl, C_{1-6}alkyl, C_{1-6}alkoxy, heterocyclyloxy, hydroxyC_{1-4}alkyl and heterocyclyl;

V-U-Y-M is
15. A compound selected from;

(4S,5S)-1-(isobutyryloxy)ethyl 5-[(S)-2-(3-amino-2,2-dimethyl-3-oxopropylcarbamoyl)-3-methylbutyl]-4-[(S)-2-[4-methoxy-3-(methoxypropoxy)benzyl]-3-methylbutyl] oxazolidine-3-carboxylate;

(4S,5S)-pivaloyloxymethyl 5-[(S)-2-(3-amino-2,2-dimethyl-3-oxopropylcarbamoyl)-3-methylbutyl]-4-[(S)-2-[4-methoxy-3-(methoxypropoxy)benzyl]-3-methylbutyl] oxazolidine-3-carboxylate;

(4S,5S)-isobutyl 5-[(S)-2-(3-amino-2,2-dimethyl-3-oxopropylcarbamoyl)-3-methylbutyl]-4-[(S)-2-[4-methoxy-3-(methoxypropoxy)benzyl]-3-methylbutyl] oxazolidine-3-carboxylate, trifluoroacetic acid salt;

(4S,5S)-(ethoxycarbonyloxy)methyl 5-[(S)-2-(3-amino-2,2-dimethyl-3-oxopropylcarbamoyl)-3-methylbutyl]-4-[(S)-2-[4-methoxy-3-(methoxypropoxy)benzyl]-3-methylbutyl] oxazolidine-3-carboxylate;

(4S,5S)-(isopropoxycarbonyloxy)methyl 5-[(S)-2-(3-amino-2,2-dimethyl-3-oxopropylcarbamoyl)-3-methylbutyl]-4-[(S)-2-[4-methoxy-3-(methoxypropoxy)benzyl]-3-methylbutyl] oxazolidine-3-carboxylate;
{(2S)-2-hydroxypropanoyl}oxy)methyl (4S,5S)-5-{(2S)-2-(3-amino-2,2-dimethyl-3-oxopropylaminocarbonyl)-3-methylbutyl}-4-{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl}-1,3-oxazolidine-3-carboxylate;

{(2S)-2-(ethoxymethoxy)propanoyl}oxy)methyl (4S,5S)-5-{(2S)-2-[3-amino-2,2-dimethyl-3-oxopropylcarbamoyl]-3-methylbutyl}-4-{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl}-1,3-oxazolidine-3-carboxylate;

{(4S,5S)-5-[(2S)-2-(3-amino-2,2-dimethyl-3-oxopropylaminocarbonyl)-3-methylbutyl]-4-{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl}-1,3-oxazolidin-3-yl-carbonyloxy}methyl morpholine-4-carboxylate;

(4S,5S) [(pyridine-3-yl)carbonyloxy]methyl 5-[(S)-2-(3-amino-2,2-dimethyl-3-oxopropylcarbamoyl)-3-methylbutyl]-4-{(S)-2-[4-methoxy-3-(methoxypropoxy)benzyl]-3-methylbutyl}oxazolidine-3-carboxylate;

(4S,5S) [(pyridine-2-yl)carbonyloxy]methyl 5-[(S)-2-(3-amino-2,2-dimethyl-3-oxopropylcarbamoyl)-3-methylbutyl]-4-{(S)-2-[4-methoxy-3-(methoxypropoxy)benzyl]-3-methylbutyl}oxazolidine-3-carboxylate;

[(2-methylpropoxycarbonyl)oxy)methyl (4S,5S)-5-{(2S)-2-[3-amino-2,2-dimethyl-3-oxopropylcarbamoyl]-3-methylbutyl}-4-{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl}-1,3-oxazolidine-3-carboxylate;

{{(pyridin-3-ylmethoxy)carbonyloxy}methyl (4S,5S)-5-{(2S)-2-[3-amino-2,2-dimethyl-3-oxopropylcarbamoyl]-3-methylbutyl}-4-{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl}-1,3-oxazolidine-3-carboxylate;

[(2-methyl-3-morpholin-4-ylpropanoyl)oxy)methyl (4S,5S)-5-{(2S)-2-[3-amino-2,2-dimethyl-3-oxopropylamino]carbonyl]-3-methylbutyl}-4-{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl}-1,3-oxazolidine-3-carboxylate;

(1-methylpiperidine-4-carbonyloxy)methyl (4S,5S)-5-{(2S)-2-[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl]-3-methylbutyl}-4-{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl}-1,3-oxazolidine-3-carboxylate;

{{(1,3-dioxan-5-yl-oxy)carbonyl}oxy)methyl (4S,5S)-5-{(2S)-2-[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl]-3-methylbutyl}-4-{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl}-1,3-oxazolidine-3-carboxylate;
{[(1,3-dioxolan-4-ylmethoxy)carbonyl]oxy}methyl (4S,5S)-5-((2S)-2-{[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl}-3-methylbutyl)-4-((2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl}-1,3-oxazolidine-3-carboxylate;

([(3-hydroxy-2,2-dimethylpropanoyl)oxy]methyl (4S,5S)-5-((2S)-2-{[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl}-3-methylbutyl)-4-((2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl}-1,3-oxazolidine-3-carboxylate;

{[(4-methoxybenzyl oxy)carbonyl]oxy}methyl (4S,5S)-5-((2S)-2-{[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl}-3-methylbutyl)-4-((2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl}-1,3-oxazolidine-3-carboxylate;

{[(benzyl oxy)carbonyl]oxy}methyl (4S,5S)-5-((2S)-2-{[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl}-3-methylbutyl)-4-((2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl}-1,3-oxazolidine-3-carboxylate;

[(pyridine-4-yl)carbonyloxy]methyl (4S,5S)-5-((2S)-2-{[(3-amino-2,2-dimethyl-3-oxopropyl)carbamoyl]-3-methylbutyl}-4-((2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl}-1,3-oxazolidine-3-carboxylate;

{[(1-methyl-1H-imidazol-4-yl)carbonyl]oxy}methyl (4S,5S)-5-((2S)-2-{[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl}-3-methylbutyl)-4-((2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl}-1,3-oxazolidine-3-carboxylate;

{(1,3-dioxan-5-ylcarbonyl)oxy}methyl (4S,5S)-5-((2S)-2-{[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl}-3-methylbutyl)-4-((2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl}-1,3-oxazolidine-3-carboxylate;

{(1-methyl-1H-imidazol-5-yl)carbonyl]oxy}methyl (4S,5S)-5-((2S)-2-{[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl}-3-methylbutyl)-4-((2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl}-1,3-oxazolidine-3-carboxylate;

{(1-methyl-1H-imidazol-4-yl)methoxy]carbonyl]oxy}methyl (4S,5S)-5-((2S)-2-{[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl}-3-methylbutyl)-4-((2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl}-1,3-oxazolidine-3-carboxylate;

{(1-methylpiperidin-4-yl)oxy]carbonyl]oxy}methyl (4S,5S)-5-((2S)-2-{[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl}-3-methylbutyl)-4-((2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl}-1,3-oxazolidine-3-carboxylate;
([(1-methylpiperidin-4-yl)oxy)methyl (4S,5S)-5-((2S)-2-((((3-amino-2,2-dimethyl-3-oxopropyl)amino)carbonyl)-3-methylbutyl)-4-((2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl)-1,3-oxazolidine-3-carboxylate; 

(1-(((1-methylpiperidin-4-yl)methoxy)carbonyl)oxy)methyl (4S,5S)-5-((2S)-2-((((3-amino-2,2-dimethyl-3-oxopropyl)amino)carbonyl)-3-methylbutyl)-4-((2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl)-1,3-oxazolidine-3-carboxylate; 

[(1,3-dioxan-5-ylmethoxy)carbonyl]oxy)methyl (4S,5S)-5-((2S)-2-((((3-amino-2,2-dimethyl-3-oxopropyl)amino)carbonyl)-3-methylbutyl)-4-((2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl)-1,3-oxazolidine-3-carboxylate; 

(Pyridin-3-ylmethoxy)methyl (4S,5S)-5-((2S)-2-((((3-amino-2,2-dimethyl-3-oxopropyl)amino)carbonyl)-3-methylbutyl)-4-((2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl)-1,3-oxazolidine-3-carboxylate; 

([(dimethylamino)carbonyl]oxy)methyl (4S,5S)-5-((2S)-2-((((3-amino-2,2-dimethyl-3-oxopropyl)amino)carbonyl)-3-methylbutyl)-4-((2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl)-1,3-oxazolidine-3-carboxylate; 

([(1-aminocyclopropyl)carbonyl]oxy)methyl (4S,5S)-5-((2S)-2-((((3-amino-2,2-dimethyl-3-oxopropyl)amino)carbonyl)-3-methylbutyl)-4-((2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl)-1,3-oxazolidine-3-carboxylate, trifluoroacetate; 

([(1-methyl-1H-imidazol-2-yl)carbonyl]oxy)methyl (4S,5S)-5-((2S)-2-((((3-amino-2,2-dimethyl-3-oxopropyl)amino)carbonyl)-3-methylbutyl)-4-((2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl)-1,3-oxazolidine-3-carboxylate; 

1-([(1-methyl-1H-imidazol-5-yl)carbonyl]oxy)ethyl (4S,5S)-5-((2S)-2-((((3-amino-2,2-dimethyl-3-oxopropyl)amino)carbonyl)-3-methylbutyl)-4-((2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl)-1,3-oxazolidine-3-carboxylate; 

1-([(4S,5S)-5-((2S)-2-((((3-amino-2,2-dimethyl-3-oxopropyl)amino)carbonyl)-3-methylbutyl)-4-((2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl)-1,3-oxazolidine-3-carboxylate, trifluoroacetate; 

1-([(4S,5S)-5-((2S)-2-((((3-amino-2,2-dimethyl-3-oxopropyl)amino)carbonyl)-3-methylbutyl)-4-((2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl)-1,3-oxazolidine-3-yl)carbonyl]oxy)methoxy)oxo-(2E)-but-2-enoic acid;
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1-[(4S,5S)-5-((2S)-2-[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl)-3-methylbutyl]-4-[(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidin-3-yl]carbonyl]oxy] methyl 1-azabicyclo[2.2.1]heptane-4-carboxylate;


1-[(1-methyl-1H-imidazol-4-yl)carbonyl]oxy] ethyl (4S,5S)-5-((2S)-2-[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl]-3-methylbutyl]-4-[(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate;

1-[(pyridin-3-yl)carbonyl]oxy] ethyl (4S,5S)-5-((2S)-2-[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl]-3-methylbutyl]-4-[(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate;

1-[(pyridin-2-yl)carbonyl]oxy] ethyl (4S,5S)-5-((2S)-2-[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl]-3-methylbutyl]-4-[(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate;

1-[(pyridin-3-yl)carbonyl]oxy] ethyl (4S,5S)-5-((2S)-2-[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl]-3-methylbutyl]-4-[(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate;

1-[(pyridin-2-yl)carbonyl]oxy] ethyl (4S,5S)-5-((2S)-2-[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl]-3-methylbutyl]-4-[(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate;

1-[(pyridin-3-yl)carbonyl]oxy] ethyl (4S,5S)-5-((2S)-2-[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl]-3-methylbutyl]-4-[(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate;

1-[(pyridin-2-yl)carbonyl]oxy] ethyl (4S,5S)-5-((2S)-2-[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl]-3-methylbutyl]-4-[(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate;

1-[(pyridin-3-yl)carbonyl]oxy] ethyl (4S,5S)-5-((2S)-2-[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl]-3-methylbutyl]-4-[(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate;

1-[(pyridin-2-yl)carbonyl]oxy] ethyl (4S,5S)-5-((2S)-2-[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl]-3-methylbutyl]-4-[(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate;

1-[(pyridin-3-yl)carbonyl]oxy] ethyl (4S,5S)-5-((2S)-2-[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl]-3-methylbutyl]-4-[(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate;

1-[(pyridin-2-yl)carbonyl]oxy] ethyl (4S,5S)-5-((2S)-2-[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl]-3-methylbutyl]-4-[(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate;
(4S,5S)-ethyl 5-[(S)-2-(3-amino-2,2-dimethyl-3-oxopropylcarbamoyl)-3-methylbutyl]-4-{(S)-2-[4-methoxy-3-(methoxypropoxy)benzyl]-3-methylbutyl}-1,3-oxazolidine-3-carboxylate;

(4S,5S)-1-(isobutyryloxy)ethyl (4S,5S)-5-[(S)-2-(3-amino-2,2-dimethyl-3-oxopropylcarbamoyl)-3-methylbutyl]-4-{(S)-2-[4-methoxy-3-(methoxypropoxy)benzyl]-3-methylbutyl}-1,3-oxazolidine-3-carboxylate;

(4S,5S)-1-(isobutyryloxy)ethyl (4S,5S)-5-[(S)-2-(3-amino-2,2-dimethyl-3-oxopropylcarbamoyl)-3-methylbutyl]-4-{(S)-2-[4-methoxy-3-(methoxypropoxy)benzyl]-3-methylbutyl}-1,3-oxazolidine-3-carboxylate;

(4S,5S)-(N-CBz-valyloxy)methyl 5-[(S)-2-(3-amino-2,2-dimethyl-3-oxopropylcarbamoyl)-3-methylbutyl]-4-{(S)-2-[4-methoxy-3-(methoxypropoxy)benzyl]-3-methylbutyl}-1,3-oxazolidine-3-carboxylate;

{{[2-methyl-2-(ethoxymethoxy)propanoyloxy]methyl (4S,5S)-5-[(2S)-2-[3-amino-2,2-dimethyl-3-oxopropylcarbamoyl]-3-methylbutyl]}}-4-{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl}-1,3-oxazolidine-3-carboxylate;

{{[(3-methoxy-2,2-dimethyl-3-oxopropoxy)carbonyloxy]methyl (4S,5S)-5-[(2S)-2-[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl]-3-methylbutyl]}}-4-{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl}-1,3-oxazolidine-3-carboxylate;

{{[(1-[(tert-butoxycarbonyl)amino]cyclopropyl)carbonyloxy]methyl (4S,5S)-5-[(2S)-2-[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl]-3-methylbutyl]}}-1,3-oxazolidine-3-carboxylate;

{{[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl]-3-methylbutyl]}}-4-{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate;

1-{{[(tert-butoxycarbonyl)amino]cyclopropanecarbonyloxy}ethyl (4S,5S)-5-[(2S)-2-[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl]-3-methylbutyl]}}-4-{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate;

{{[(4S,5S)-5-[(2S)-2-[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl]-3-methylbutyl]}}-4-{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]}}-1,3-oxazolidine-3-carboxylate;

{{[(1-[(tert-butoxycarbonyl)amino]cyclopropyl)carbonyloxy]methyl tert-butyl (2E)-but-2-enedioate;}}

{{[(1-[(tert-butoxycarbonyl)amino]cyclopropyl)carbonyloxy]methyl (4S,5S)-5-[(2S)-2-[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl]-3-methylbutyl]}}-4-{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate;

{{[(4S,5S)-5-[(2S)-2-[(3-amino-2,2-dimethyl-3-oxopropyl)amino]carbonyl]-3-methylbutyl]}}-4-{(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]}}-1,3-oxazolidine-3-carboxylate;
oxazolidin-3-yl)[carbonyloxy]ethyl tert-butyl butanedioate; 1-\{[(4S,5S)-5-((2S)-2-[(3-amino-2,2-dimethyl-3-oxopropyl)amino][carbonyl]-3-methylbutyl]-4-[(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidin-3-yl)[carbonyloxy]ethyl tert-butyl (2E)-but-2-enedioate; 5 1-\{[(1-methyl-1H-imidazol-5-yl)[carbonyloxy]ethyl (4S,5S)-5-((2S)-2-[(3-amino-2,2-dimethyl-3-oxopropyl)amino][carbonyl]-3-methylbutyl]-4-[(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate; 1-(Pyridin-3-yloxy)ethyl (4S,5S)-5-((2S)-2-[(3-amino-2,2-dimethyl-3-oxopropyl)amino][carbonyl]-3-methylbutyl]-4-[(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate; 10 \{[(3-Methylpyridin-2-yl)[carbonyloxy]methyl (4S,5S)-5-((2S)-2-[(3-amino-2,2-dimethyl-3-oxopropyl)amino][carbonyl]-3-methylbutyl]-4-[(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate; 15 \{[(4-Methylthiazol-5-yl)[carbonyloxy]methyl (4S,5S)-5-((2S)-2-[(3-amino-2,2-dimethyl-3-oxopropyl)amino][carbonyl]-3-methylbutyl]-4-[(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate; 20 \{(1-Hydroxymethyl)cyclopropyl)[carbonyloxy]methyl (4S,5S)-5-((2S)-2-[(3-amino-2,2-dimethyl-3-oxopropyl)amino][carbonyl]-3-methylbutyl]-4-[(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate; Pyridine-3-ylmethyl (4S,5S)-5-((2S)-2-[(3-amino-2,2-dimethyl-3-oxopropyl)amino][carbonyl]-3-methylbutyl]-4-[(2S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-1,3-oxazolidine-3-carboxylate; and 25 (4S,5S)-ethyl 5-[(S)-2-[(3-amino-2,2-dimethyl-3-oxopropyl)carbamoyl]-3-methylbutyl]-4-[(S)-2-[4-methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutyl]-2,2-dimethylthiazolidine-3-carboxylate; or a pharmaceutically accepted salt thereof.
16. A process for preparing a compound according to any previous claim, wherein $R^1$, $R^2$, $R^3$ and $R^4$ are H, said process comprising the steps of

a) reacting a compound of formula (II)

$$
\text{H}_2\text{N} \quad \text{OH} \quad \text{R}^5
\text{V} \quad \text{U} \quad \text{Y} \quad \text{M} \quad \text{A} \quad \text{Q}
$$

wherein $M$, $Y$, $U$, $V$, $A$, $R^5$ and $Q$ are as defined in any previous claim, with a compound of formula (VIII),

$$
\text{L}^2 \quad \text{X}^1 \quad \text{X}^2 \quad \text{L}^1
$$

wherein $X^1$ and $X^2$ are as defined in any previous claim and $L^1$ and $L^2$ are leaving groups independently selected from Cl, Br, I, sulfonates such as mesylate, brosylate, tosylate, triflate, nosylate and tresylate, under basic conditions in an inert solvent or mixture of inert solvents to obtain a compound of formula (IX)

$$
\text{L}^2 \quad \text{X}^2 \quad \text{N} \quad \text{O} \quad \text{R}^5
\text{V} \quad \text{U} \quad \text{Y} \quad \text{M} \quad \text{A} \quad \text{Q}
$$

b) subsequently reacting the compound of formula (IX) with a compound of formula (X) or a salt thereof,

$$
\text{R}^8 \quad \text{OH}
$$

(X)
wherein $R^6$ is as defined in any previous claim, under basic conditions in an inert solvent or mixture of inert solvents.

17. A compound of general formula (IX)

![Chemical structure diagram]

wherein $X^1$, $X^2$, $M$, $Y$, $U$, $V$, $A$, $R^5$ and $Q$ are as defined in any previous claim and $L^2$ is as defined in claim 16.

18. A compound according to any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, as a medicament in therapy.

19. Use of a compound according to any one of claims 1 to 15 for the preparation of a medicament for the treatment and/or prophylaxis of renin related disorders.

20. Use of a compound according to any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for the treatment and/or prophylaxis of hypertension, heart failure, glaucoma, cardiac infarction, kidney failure, or restenosis.

21. A method of treating and/or preventing hypertension, heart failure, glaucoma, cardiac infarction, kidney failure or restenosis comprising the administration of a therapeutically effective amount of a compound according to any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, to a mammal in need thereof.
22. A pharmaceutical composition comprising a compound according to any one of claims 1 to 15, or a pharmaceutically acceptable salt or solvate thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent and/or carrier.

23. A pharmaceutical composition comprising a compound according to any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, and one or more additional agents having cardiovascular action, preferably valsartan, amlodipine or hydrochlorothiazide.