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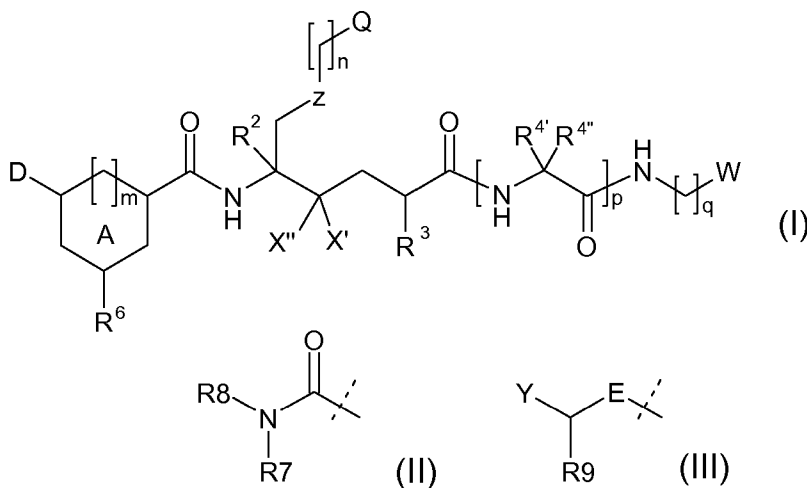
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(54) Title: AMIDE DERIVATIVES AS INHIBITORS OF ASPARTYL PROTEASES



(57) Abstract: The invention provides compounds of the formula (I). N-oxides, addition salts, quaternary amines, metal complexes, stereochemically isomeric forms and metabolites thereof, wherein W is H, C₁-C₆alkyl, C₃-C₆cycloalkyl, aryl or heterocyclyl; Q is aryl or heterocyclyl; A is a five or six membered saturated, partially unsaturated or aromatic ring; D is formula (II) or formula (III); and the other variables are as defined in the specification. The compounds of the invention are inhibitors of aspartyl proteases such as renin and BACE and are among other things useful for the treatment and/or prophylaxis of conditions associated with activities of the RAS, such as hypertension, heart failure and renal

insufficiency and for the treatment and or prophylaxis of conditions associated with BACE activity such as of Alzheimer's disease.

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AMIDE DERIVATIVES AS INHIBITORS OF ASPARTYL PROTEASES

Technical field

This invention relates to novel compounds having inhibitory activity on aspartyl proteases such as rennin and β -secretase (β -site amyloid precursor protein-cleaving enzyme, BACE). It further concerns pharmaceutical compositions comprising these compounds as active ingredients as well as processes for preparing these compounds and compositions and their use in the preparation of a medicament or their use in therapy.

Background to the invention

A number of aspartic proteases are known to date, including pepsin A and C, Renin, BACE, BACE2, Napsin and Cathepsin D, which have been implicated in pathological conditions. For example the aspartyl protease BACE causes the production of the protein β amyloid ($A\beta$) in the brain, which is characteristic of Alzheimer's disease (AD).

AD is a progressive neurodegenerative disease of the brain characterized by gradual loss of cognitive function related to memory, reasoning, orientation and judgement and eventually death. Pathological features of AD is accumulation of abnormal aggregated protein breakdown products, β -amyloid plaque and neurofibrillary tangles, in the brain. Plaque relatively specific for AD is primarily a result from extracellular accumulation of aggregated $A\beta$. Fibrillary tangles consists mainly of hyperphosphorylated tau protein and are also found in other neurodegenerative disorders. It is believed that $A\beta$ is the fundamental causative agent of neuronal cell loss and dysfunction which is associated with cognitive and behavioural decline. $A\beta$ is a peptide comprised of 40-42 amino acid residues, which is formed by proteolytic cleavage of the large transmembrane amyloid precursor protein (APP).

APP is processed along two pathways, the major α - and the minor β -secretase pathway. The α -secretase pathway results in non-pathogenic products known as soluble APP, whereas the β -secretase pathway produces pathogenic $A\beta$ peptides by cleavage by β -secretase at the position corresponding to the N-terminus of $A\beta$, followed by cleavage by γ -secretase at the C-terminus.

The sequential proteolytic cleavage of APP by β - and γ -secretase is a key step in the production of $A\beta$. The amyloid cascade hypothesis, supported by genetic and pathological evidence, claims that the formation of $A\beta$ plays an early and vital role in all cases of AD. $A\beta$ forms aggregates that are thought to initiate a pathogenic cascade that leads to neuronal loss and dementia.

BACE was identified a few years ago as a type 1 glycosylated transmembrane homodimer with two aspartic acids at the active catalytic site. BACE and BACE-2 (64 % amino acid sequence similarity to BACE) constitute a novel class of aspartic proteases closely related to the pepsin family. The function of BACE-2 is relatively unknown and several studies indicate that this enzyme is not involved in the $A\beta$ generation. BACE knockout homozygote mice show complete absence of producing $A\beta$ and the animals appear to develop normally and have no

discernable abnormalities. Tissue cultures and animal studies indicated that β -secretase is expressed in all tissues but at highest levels in the neurons in the brain. Therefore, in vivo inhibition of BACE is likely to reduce the production of A β and is considered to be an attractive therapeutic target for the treatment and prevention of AD.

Presently there are no known effective treatments for preventing, delaying or reversing the progression of AD. Current available therapies for mild to moderate AD are safe but of limited benefit to most of the patients since they treat the symptoms and do not affect the progression of aggregated protein breakdown products underlying the pathology of the disease. In view of the fact that amyloid β peptides are formed as a result of BACE activity, inhibition of BACE is an attractive therapeutic approach to the treatment and prevention of AD and other cognitive and degenerative diseases caused by A β plaque deposition. Desirable characteristics for inhibitors of BACE include low molecular weight and features that would allow them to cross the blood-brain barrier.

The protease Renin is involved in the renin-angiotensin system (RAS) which is critical for the control of blood pressure and salt balance in mammals. Renin has a high substrate specificity, its only known substrate is angiotensinogen. Renin cleaves the N terminus of circulating angiotensinogen to angiotensin I (Ang I) which thereafter is further processed to the active peptide hormone angiotensin II (Ang II) by the less specific angiotensin-converting enzyme (ACE). Ang II increases blood pressure both directly by arterial vasoconstriction and indirectly by liberating the sodium-ion-retaining hormone aldosterone. Ang II is known to work on at least two receptor subtypes called AT1 and AT2. AT1 seems to transmit most of the known functions of Ang II, while the role of AT2 is still unknown.

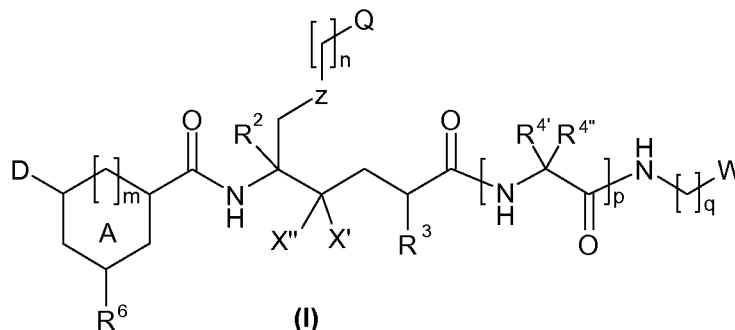
Modulation of the RAS represents a major advance in the treatment of cardiovascular diseases. Inhibition of the enzymatic activity of renin leads to a reduction in the formation of Ang I, and as a consequence, a smaller amount of Ang II is produced. The reduced concentration of that active peptide hormone is a direct cause of the hypotensive effect of renin inhibitors.

ACE inhibitors and AT1 blockers have been accepted to treat hypertension and ACE inhibitors are used for renal protection in the prevention of congestive heart failure and myocardial infarction. The rationale to develop renin inhibitors is the specificity of renin. Renin inhibitors are expected to demonstrate a different pharmaceutical profile than ACE inhibitors and AT1 blockers with regard to efficacy in blocking the RAS and in safety aspects.

Only limited clinical experience has been created with renin inhibitors because of their insufficient oral activity. The clinical development of several compounds has been stopped because of this problem together with the high cost of goods. Only one compound has entered clinical trials (Rahuel J. et al., Chem. Biol., 2000, 7, 493; Mealy N. E., Drugs of the Future, 2001, 26, 1139). Thus, renin inhibitors with good oral bioavailability and long duration of action are required. The present invention concerns inhibitors of renin which exhibit beneficial potency, selectivity and/or pharmacokinetic properties.

Brief description of the Invention

In accordance with the present invention, there is provided aspartyl protease inhibitors which can be represented by the formula (I):



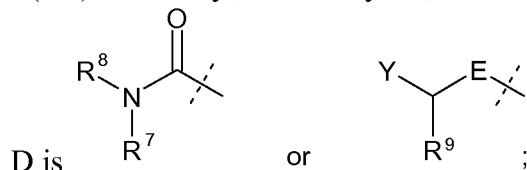
wherein

R^2 is H or C_1 - C_6 alkyl;

R^3 is C_1 - C_6 alkyl, C_1 - C_6 alkoxy C_1 - C_3 alkyl, C_1 - C_3 alkanediylaryl, C_1 - C_3 alkanediylheterocyclyl;

$R^{4'}$ is C_1 - C_6 alkyl and $R^{4''}$ is H; or $R^{4'}$ and $R^{4''}$ together with the carbon atom to which they are attached define C_3 - C_6 cycloalkyl;

R^6 is hydrogen, C_1 - C_6 alkyl, $N(Ra)S(=O)_rC_1$ - C_6 alkyl, $N(Ra)S(=O)_rNRaRb$, $S(=O)_rNRaRb$, $S(=O)_rC_1$ - C_6 alkyl, halo or cyano;



R^7 is C_1 - C_6 alkyl, C_1 - C_6 alkoxy C_1 - C_3 alkyl, hydroxy C_1 - C_3 alkyl, C_1 - C_3 alkanediylNRaRb, aryl, heterocyclyl, C_3 - C_6 cycloalkyl, C_1 - C_3 alkanediyl C_3 - C_6 cycloalkyl, C_1 - C_3 alkanediylaryl, C_1 - C_3 alkanediylheterocyclyl, C_1 - C_3 alkanediyl-O- C_0 - C_3 alkanediyl aryl or C_1 - C_3 alkanediyl-O- C_0 - C_3 alkanediyl heterocyclyl;

wherein the C_1 - C_3 alkanediyl moiety is optionally substituted with C_1 - C_6 alkyl;

R^8 is H, C_1 - C_6 alkyl; or

R^7 and R^8 together with the N atom to which they are attached define a heterocyclyl group;

R^9 is H, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 alkoxy C_1 - C_3 alkyl or C_1 - C_6 alkoxy C_1 - C_6 alkoxy C_0 - C_3 alkyl;

E is -CH(Rc)-CH(Rc)-, -NRd-CH(Rd)-, -CH(Rd)-NRd-, NRd-NRd-, -CH(Rd)-O-, -O-CH(Rd)-, -CH(Rc)-, -NRd-, or -O-;

Q is aryl or heterocyclyl;

W is H, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, aryl or heterocyclyl;

X' is H, F, OH, or NRaRb;

X'' is H or when X' is F, X'' can also be F;

Y is H, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 alkoxy C_1 - C_3 alkyl, C_1 - C_6 alkoxy- C_1 - C_6 alkoxy, C_0 - C_3 alkankedylaryl, C_0 - C_3 alkankedyl C_3 - C_6 cycloalkyl or C_0 - C_3 alkankedylheterocyclyl;

Z is O, S(=O)_r or NR_a;

ring A is a saturated, partially unsaturated or aromatic ring;

m is 0 or 1, whereby ring A defines a cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl or a phenyl ring;

n is 0, 1, 2 or 3;

p is 0 or 1;

q is 0, 1 or 2; thereby defining a bond, methylene or ethylene, or when q is 1, the methylene may alternatively be a 1,1-cyclopropyl group;

r is 0, 1 or 2;

R_a is H or C₁-C₆alkyl;

R_b is H or C₁-C₆alkyl; or R_a and R_b together with the nitrogen to which they are attached define a heterocyclyl group;

R_c is H, C₁-C₇alkyl, C₁-C₆alkoxy, C₁-C₆alkoxyC₁-C₃alkyl, C₁-C₆alkoxyC₁-C₆alkoxy, hydroxyC₀-C₃alkyl or C₀-C₃alkandiylnR_aR_b;

R_d is H, C₁-C₇alkyl, C₁-C₆alkoxyC₁-C₃alkyl, C₁-C₆alkoxyC₁-C₆alkoxyC₁-C₃alkyl, hydroxyC₁-C₃alkyl or C₁-C₃alkandiylnR_aR_b;

where aryl is independently phenyl, naphthyl, or phenyl fused to C₅-C₆cycloalkyl or C₅-C₆cycloalkenyl;

aryl is phenyl, naphthyl or phenyl fused to C₅-C₆cycloalkyl or C₅-C₆cycloalkenyl;

heterocyclyl is independently a 5 or 6 membered, saturated, partially unsaturated or heteroaryl ring containing 1 to 3 heteroatoms independently selected from S, O and N, the ring being optionally fused with a benzene ring;

and wherein each occurrence of C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₆cycloalkyl, aryl and heterocyclyl above (including those in composite expressions such as alkoxy or alkanediylaryl) is optionally substituted with 1 or 2, or where valence permits up to 3,

substituents independently selected from C₁-C₄alkyl (optionally substituted with 1 or 2

substituents independently selected from C₀-C₃alkandiyaryl^{*}, amino, carbamoyl, amido or C₁-C₄alkoxyamido), C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₄cycloalkyl, C₁-C₄alkoxy, C₁-C₄alkoxyC₁-C₃alkyl, C₁-C₄alkoxyC₁-C₆alkoxyC₀-C₃alkyl, halo, haloC₁-C₄alkyl, polyhaloC₁-C₄alkyl,

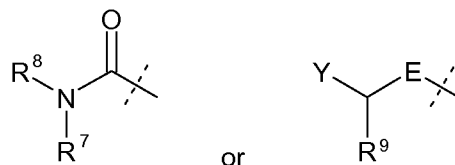
hydroxy, hydroxyC₁-C₄alkyl, amino, aminoC₁-C₄alkyl, carbamoyl, amido, cyano, azido, C₁-C₄alkylcarbonyl, a cyclic amine selected from pyrrolidiny, piperidiny, piperazinyl and morpholinyl, (any of which cyclic amines being optionally substituted with C₁-C₄alkyl or fluoro),

C₀-C₃alkanediylC₃-C₆cycloalkyl, C₀-C₃alkanediylaryl^{*}, C₀-C₃alkanediylheterocyclyl^{*}, C₂-C₃alkenediylC₃-C₆cycloalkyl^{*}, C₂-C₃alkenediylaryl^{*}, C₂-C₃alkenediylheterocyclyl^{*}, C₂-C₃alkynediylC₃-C₆cycloalkyl, C₂-C₃alkynediylaryl^{*}, C₂-C₃alkynediylheterocyclyl^{*};

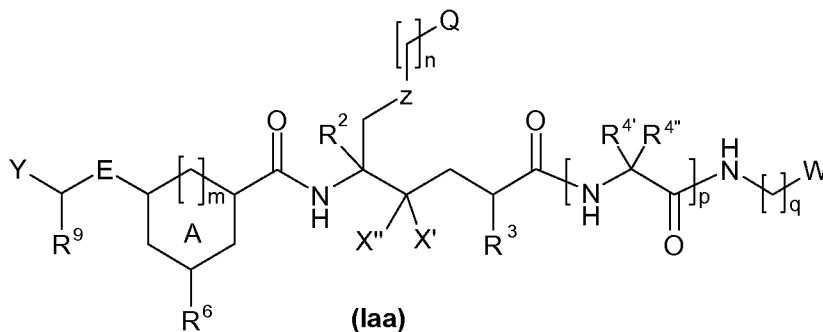
and wherein each occurrence of aryl^{*} and heterocyclyl^{*} above (including those in composite expressions such as alkanediylaryl^{*} and alkanediylheterocyclyl^{*}) is independently optionally substituted with 1 or 2, or where valence permits up to 3, substituents independently selected from C₁-C₄alkyl, halo and haloC₁-C₄alkyl;

or a pharmaceutically acceptable salt hydrate or N-oxide thereof.

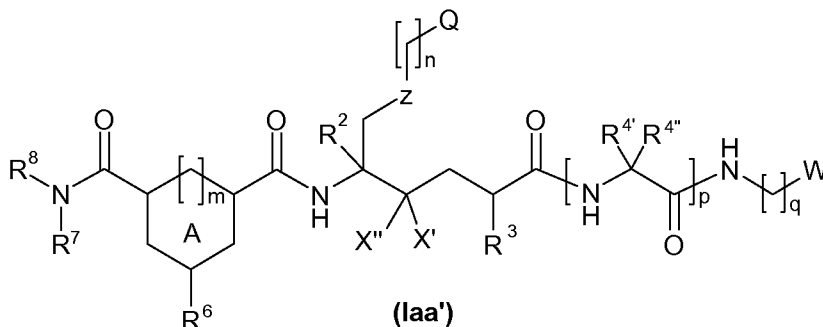
As indicated above, D is



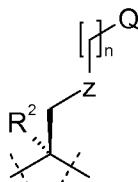
Consequently, according to some embodiments of the invention, compounds are included wherein D is $\text{YCH(R}^9\text{)E}$, thus giving compounds according to formula Iaa.



According to other embodiments of the invention, compounds are included wherein D is $(\text{R}^8)(\text{R}^7)\text{NC(=O)}$, i.e an amide moiety, thus giving compounds according to formula Iaa'.



The compounds of general formula (I) have several centres of chirality, conveniently the compounds display at least 75%, preferably at least 90%, such as in excess of 95%, enantiomeric purity at each of the chiral centres. In typical embodiments of the invention, the chiral centre whereto the group R^2 is attached has the stereochemistry shown in the partial structure:



According to preferred embodiments of the invention, Z is O.

According to other embodiments Z is NRa, wherein Ra is hydrogen or C₁-C₃alkyl, preferably hydrogen or methyl.

The group Q is bonded either directly to Z, i.e. n is 0, or Q is bonded via a methylene, ethylene or propylene moiety, i.e. n is 1, 2 or 3 respectively. In favoured embodiments of the invention Q is bonded to Z via an ethylene moiety, i.e. n is 2. In more favoured embodiments of the invention, Q is bonded via a bond or a methylene moiety, i.e. n is 0 or 1 respectively.

As defined above, Q is aryl or heterocyclyl, optionally substituted with one, two or three substituents independently selected from C₁-C₄alkyl (optionally substituted with C₀-C₃alkandylaryl*, amino, carbamoyl, amido or C₁-C₄alkoxyamido), C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₆cycloalkyl, C₁-C₄alkoxy, halo, haloC₁-C₄alkyl, polyhaloC₁-C₄alkyl, C₁-C₄alkoxyC₁-C₃alkyl, C₁-C₄alkoxyC₁-C₆alkoxyC₀-C₃alkyl, hydroxy, hydroxyC₁-C₄alkyl, cyano, azido, C₁-C₄alkylcarbonyl, carbamoyl, amino, amido, a cyclic amine selected from pyrrolidinyl, piperidinyl, piperazinyl and morpholinyl (any of which cyclic amines being optionally substituted with C₁-C₄alkyl or fluoro) C₀-C₃alkanediylcarbocyclyl*, C₀-C₃alkanediylaryl*, C₀-C₃alkanediylheterocyclyl*, C₂-C₃alkenediylcarbocyclyl*, C₂-C₃alkenediylaryl*, C₂-C₃alkanediylheterocyclyl*, C₂-C₃alkynediylcarbocyclyl*, C₂-C₃alkynediylaryl* and C₂-C₃alkanediylheterocyclyl*; wherein the carbocyclyl*, aryl* and heterocyclyl* moiety of the composite expressions is independently optionally substituted with 1 or 2, or where valence permits up to 3, substituents independently selected from C₁-C₄alkyl, halo and haloC₁-C₄alkyl.

According to some embodiments of the invention Q is an optionally substituted mono or bicyclic aryl moiety such as phenyl or naphthyl.

According to further embodiments of the invention, Q is an optionally substituted mono- or bicyclic ring containing 1, 2 or 3 heteroatoms, preferably 1 or 2 heteroatoms, independently selected from nitrogen, oxygen and sulphur. Representative monocyclic rings according to this embodiment include pyridyl, thiazolyl, pyrimidyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, triazolyl, tetrazolyl, piperidyl, piperazinyl and morpholinyl and the like, representative bicyclic rings include quinolinyl, isoquinolinyl, indolyl, isoindolyl, indolinyl isoindolinyl each of which is optionally substituted wherein each of the mono and bicyclic rings is optionally substituted.

Typical values for Q include 5 or 6 membered aryl or heterocyclyl, preferably phenyl or pyridyl, which is optionally substituted with one two or three substituents.

Currently preferred heterocyclyl groups for Q include pyrid-2-yl, pyrid-3-yl or pyrid-4-yl, any of which may be substituted as defined above, such as with 1 or 2 C₁-C₄ alkyl (preferably methyl),

C₁-C₄alkoxy (preferably methoxy), C₁-C₄alkoxyC₁-C₆alkoxyC₀-C₃alkyl, (preferably methoxypropoxy) groups or with one or two halogen atoms (preferably fluoro).

A further typical value for Q is optionally substituted naphthyl.

Optional substituents to Q are as defined above. Representative values include one or two substituents independently selected from C₁-C₄alkyl, C₃-C₆cycloalkyl, C₁-C₄alkoxy, C₁-C₃alkoxy-C₁-C₆alkoxyC₀-C₃alkyl, halo and haloC₁-C₄alkyl.

Currently favoured values for the optional substituents to Q include cyclopropyl, methoxy-ethoxy, fluoro, optionally substituted phenyl and benzyl, more favoured substituents are chloro, methyl and methoxy-propoxy.

Further optional substituents to Q include C₀-C₃alkanediylaryl which aryl is optionally substituted, C₀-C₃alkanediylheterocyclyl and C₀-C₃alkanediylheteroaryl. Typical heterocyclyl and heteroaryl include, but are not limited to, pyrrolyl, pyrrolinyl, pyrazolyl, imidazolyl, oxazolyl, pyrimidinyl, pyrazinyl, morpholinyl and especially furyl, thienyl, thiazolyl and pyridyl.

According to some embodiments of the invention Q is a monosubstituted 6-membered aryl or heterocyclyl, wherein the substituent is preferably in the meta or para position. In a preferred configuration according to this embodiment, Q is para substituted phenyl. In a further preferred configuration according to this embodiment, Q is meta substituted phenyl. Preferred substituents according to this embodiment include chloro and fluoro.

According to further embodiments, Q is disubstituted phenyl with the substituents in the two meta positions or with one substituent in the meta position and the other in the para position. Preferred substituents to Q according to this embodiment are independently chloro, fluoro, methoxypropoxy and methyl.

A typical embodiment for Q is phenyl, which is optionally substituted with one or two substituents independently selected from C₁-C₄alkyl such as methyl, ethyl or isopropyl, cycloalkyl such as cyclopropyl, halo such as fluoro or chloro, and C₁-C₄alkoxyC₁-C₆alkoxy such as 2-methoxy-ethoxy or 3-methoxy-propoxy.

Further embodiments for Q include phenyl which is substituted with pyridyl, phenyl, substituted phenyl such as fluoro- or chloro-phenyl, cycloalkyl such as cyclopropyl or C₁-C₆alkyl such as methyl, ethyl or isopropyl.

In typical embodiments Q is mono- or di-substituted phenyl, wherein the substituents are in the meta position and/or in the para position.

Suitable configurations for Q include phenyl which is substituted in the meta position with C₁-C₄alkoxyC₁-C₆alkoxy, and in the para position with C₁-C₄alkyl, cyano or halo.

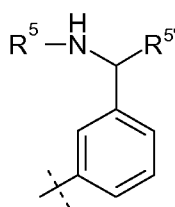
Further suitable configurations for Q include phenyl which is substituted in the meta position with C₁-C₄alkoxyC₁-C₆alkoxy, such as 3-methoxy-propoxy or 2-methoxy-ethoxy and in the para position with methyl, ethyl, cyclopropyl, fluoro, chloro or cyano.

Further suitable configurations for Q include phenyl which is substituted in the meta position with C₁-C₄alkoxyC₁-C₆alkoxy, such as 3-methoxypropoxy or 2-methoxy-ethoxy and/or in the para position with optionally substituted heteroaryl or optionally substituted phenyl.

Further suitable configurations for Q include phenyl which is substituted in the meta position with 3-methoxy-propoxy and/or in the para position with pyridyl, thienyl or furyl or with optionally substituted phenyl, such as p-fluorophenyl.

A further configuration for the optional substituents to Q is benzyl which is substituted at the benzylic position. Suitable substituents for the benzylic position includes for example amino, amido or alkoxyamido such as C₁-C₄alkylamino or tert.butoxycarbonylamino.

According to this embodiment, the compounds of formula (I) or any subgroup of formula (I) wherein Q has the structure shown below are included:



wherein R⁵ is C₁-C₄alkyl, C₁-C₄alkylcarbonyl or C₁-C₄alkyloxycarbonyl and R^{5'} is hydrogen, methyl or especially phenyl.

R² is C₁-C₆alkyl such as methyl or ethyl, or preferably R² is hydrogen.

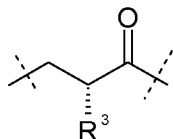
The chiral centre to which X' and X'' are attached typically has the configuration shown in the partial structure:



X' and X'' are as defined above, preferably X' is fluoro, or more preferably hydroxy.

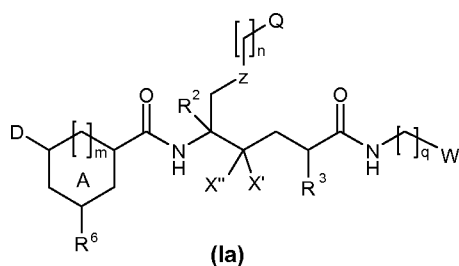
In an alternative embodiment of the invention X' and X'' are both fluoro.

In typical embodiments of the invention, the chiral centre whereto the group R³ is attached has the stereochemistry shown in the partial structure:

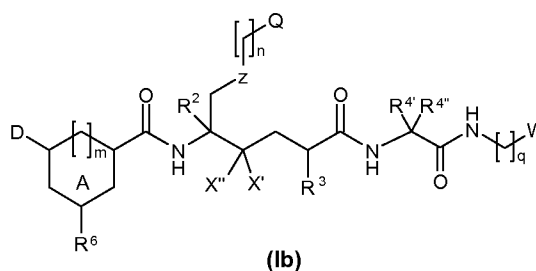


R³ is C₁-C₆alkyl, preferably sec.butyl or more preferably ethyl or isopropyl.

The invention includes compounds of general formula (I) wherein p is 0 or 1, i.e. compounds according to structures (Ia) and (Ib) respectively.

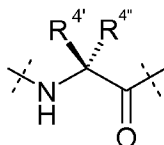


(Ia)



(Ib)

In compounds of formula (Ib), i.e. wherein p is 1, the chiral centre whereto R^{4'} and R^{4''} are attached typically has the configuration shown in the partial structure below.

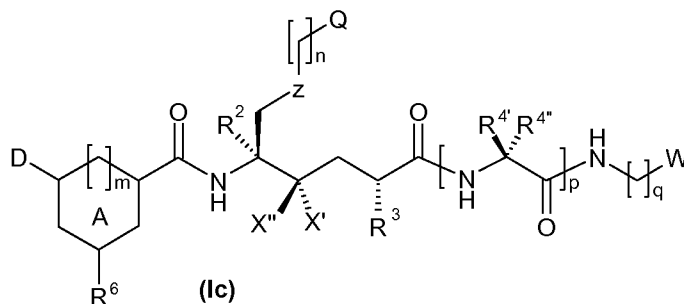


Thus, when R^{4''} is hydrogen, the configuration corresponding typically to that of an L-amino acid.

Preferably R^{4'} is C₁-C₆alkyl, such as sec.butyl or isopropyl.

R^{4''} is preferably hydrogen.

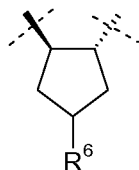
Preferred compounds of formula (I) are those having the stereochemistry indicated in formula (Ic):



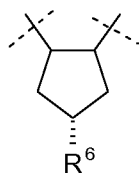
According to some embodiments of the invention ring A in general formula (I) is a six membered ring, i.e. m is 1. Representative values for ring A according to these embodiments include cyclohexyl and phenyl, preferably phenyl.

According to further embodiments of the invention ring A is a five membered ring, i.e. m is 0. Preferred values for ring A according to these embodiments include cyclopentenyl and cyclopentyl, preferably cyclopentyl.

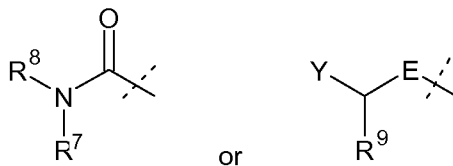
In embodiments of the invention wherein ring A is cyclopentyl, the stereochemistry is typically as indicated in the partial structures below:



The chiral centre to which R^6 is attached has typically the configuration as shown in the partial structure below:



R^6 is as defined above, typical values for R^6 include $N(C_0-C_2\text{alkyl})S(=O)_2C_1-C_4\text{alkyl}$, preferably $NHS(=O)_2CH_3$.



As indicated above, D is

or

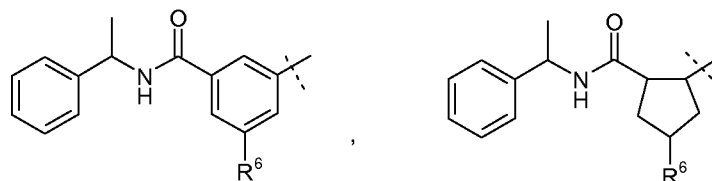
;

R^7 is as recited above. Typical values for R^7 include $C_1-C_6\text{alkyl}$, $C_1-C_3\text{alkanediylaryl}$ or $C_1-C_3\text{alkanediylheterocyclyl}$, wherein each $C_1-C_6\text{alkyl}$, cycloalkyl, aryl and heterocyclyl moiety is optionally substituted with one, two or three substituents independently selected from halo $C_1-C_4\text{alkyl}$, $C_1-C_4\text{alkyl}$, $C_1-C_4\text{alkoxy}$, hydroxy and cyano.

A further favoured configuration for R^7 includes C_1 - C_3 alkanediylaryl, wherein the C_1 - C_3 alkanediyl moiety is optionally substituted with R^7 , preferred values for R^7 include C_1 - C_4 alkyl, such as ethyl or preferably methyl.

Currently favoured values for R^7 include benzyl, 1-phenylethyl and 1-phenylpropyl, especially benzyl and 1-phenylethyl, wherein the phenyl ring is optionally substituted. Preferably the substituent(s) are in the para and/or ortho position of the phenyl ring.

Favoured compounds according to this embodiment include those having the partial structures shown below:



A further configuration for R^7 include C_1 - C_3 alkandiylaryl and C_1 - C_3 alkanediylheterocyclyl, wherein the C_1 - C_3 alkandiyl moiety is optionally substituted with C_1 - C_6 alkyl. Preferred configurations for the C_1 - C_6 alkyl according to this embodiment include C_1 - C_4 alkyl such as methyl or ethyl; halo C_1 - C_4 alkyl, such as trifluoromethyl and C_3 - C_4 cycloalkyl such as cyclopropyl.

The optional substituents to the aryl, heterocyclyl and alkyl moieties of R^7 are as defined above. Representative values include one or two substituents independently selected from C_1 - C_4 alkyl such as methyl; halo such as fluoro; halo C_1 - C_4 alkyl such as fluoromethyl and trifluoromethyl; and cyano.

Further typical values for R^7 include a carbon chain which chain is optionally interrupted by one or two oxygen atoms and which length is 5, 6 or 7 atoms. Preferred configurations for such a chain include C_5 - C_7 alkyl, C_1 - C_3 alkoxy- C_1 - C_3 alkoxy, such as methoxyethoxy, or C_1 - C_3 alkoxy- C_1 - C_3 alkyl, such as 3-methoxypropyl or 2-methoxyethyl

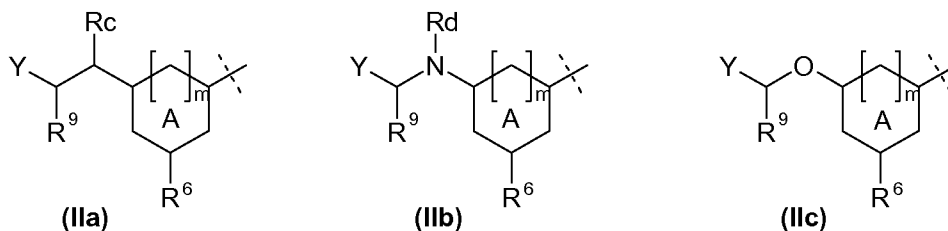
R^8 is as recited above, preferably hydrogen or methyl.

A further embodiment of the invention include compounds of formula (I) wherein R^7 and R^8 together with the nitrogen atom to which they are attached form an optionally substituted heterocyclyl group, for example optionally substituted pyrrole, piperidine or morpholine.

According to a further embodiment of the invention, R^7 and R^8 are both C_1 - C_6 alkyl, such as ethyl, propyl or butyl.

Link E between ring A and the unit $\text{CH}(\text{Y})(\text{R}^9)$ is as defined above.

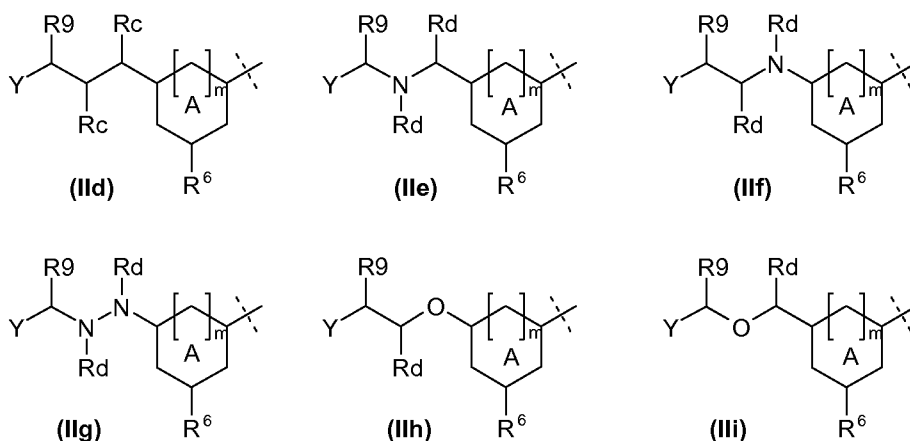
According to some embodiments of the invention, the link E is $-\text{CH}(\text{Rc})-$, $-\text{NRd}-$ or $-\text{O}-$, in which case the compounds of the invention have one of the partial structures:



wherein Rc, Rd, R^9 and Y are as defined above.

Preferably, one of R^9 and Rc in formula IIa, one of R^9 and Rd in formula IIb and R^9 in formula IIc is a carbon chain which chain is optionally interrupted by one or two oxygen atoms and which length is 5, 6 or 7 atoms. Preferred configurations for such a chain include C_5 - C_7 alkyl, C_1 - C_3 alkoxy- C_1 - C_3 alkoxy, such as methoxyethoxy, or C_1 - C_3 alkoxy- C_1 - C_3 alkyl, such as 3-methoxypropyl or 2-methoxyethyl. The other one of Rc and R^9 in formula IIa and Ra and R^7 in formula IIb is preferably hydrogen or methyl. It is to be understood that only stable configurations of the partial structures (IIa), (IIb) and (IIc) are contemplated.

According further embodiments of the invention, E is $-\text{CH}(\text{Rc})-\text{CH}(\text{Rc})-$, $-\text{NRd}-\text{CH}(\text{Rd})-$, $-\text{CH}(\text{Rd})-\text{NRd}-$, $\text{NRd}-\text{NRd}-$, $-\text{CH}(\text{Rd})-\text{O}-$ or $-\text{O}-\text{CH}(\text{Rd})-$, in which case compounds of the invention have the partial structures:



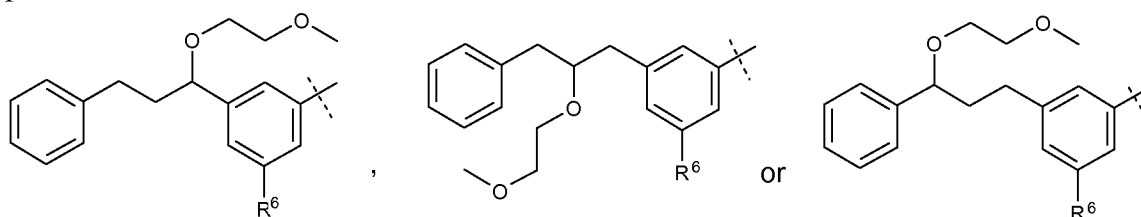
wherein Rc, Rd, R^6 , R^9 and Y are as defined above.

Conveniently, one of the moieties Rc, Rd and R^9 in each of the above partial structures is a carbon chain which chain is optionally interrupted by one or two oxygen atoms. Preferably the chain length is 5, 6 or 7 atoms. Preferred configurations for such a chain include C_1 - C_3 alkoxy-

C₁-C₃alkoxy, such as 2-methoxyethoxy, or C₁-C₃alkoxy-C₁-C₃alkyl, such as 3-methoxypropyl or 2-methoxyethyl. It is to be understood that only stable configurations of the partial structures (IIa), (IIb) and (IIc) are contemplated.

A currently preferred value for E according to this embodiment is -CHR_c-CHR_c- i.e. corresponding to partial structure (II_d), wherein one R_c is hydrogen or methyl and the other is hydrogen, C₁-C₃alkoxyC₁-C₆alkoxy such as 2-methoxyethoxy or 3-methoxypropoxy. Preferably according to this embodiment, R⁹ is phenyl and Y is hydrogen.

A preferred embodiment of the invention includes compounds of formula (I) comprising any of the partial structures:



A further preferred value for E is -CH(R_d)-NR_d-, i.e. corresponding to partial structure (II_f), wherein one of the R_d is C₁-C₆alkyl or C₁-C₃alkoxy-C₁-C₃alkyl, such as 3-methoxypropyl or 2-methoxyethyl and the other is hydrogen or methyl.

As recited above, Y is hydrogen, C₁-C₆alkyl, C₀-C₃alkanediylC₃-C₆cycloalkyl, C₀-C₃alkanediylaryl or C₀-C₃alkanediylheterocyclyl, wherein each C₁-C₆alkyl, cycloalkyl, aryl and heterocyclyl moiety is optionally substituted with one, two or three substituents independently selected from haloC₁-C₄alkyl, C₁-C₄alkyl, C₁-C₄alkoxy, hydroxy and cyano.

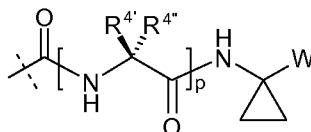
Preferred values for Y include hydrogen, C₁-C₆alkyl especially methyl, ethyl or isopropyl; optionally substituted C₀-C₃alkanediylaryl or C₀-C₃alkanediylheterocyclyl, such as optionally substituted phenyl, optionally substituted benzyl or optionally substituted pyridyl.

The optional substituents to Y are as defined above. Representative values include C₁-C₄alkyl such as methyl; halo such as fluoro; haloC₁-C₄alkyl such as fluoromethyl and trifluoromethyl; and cyano.

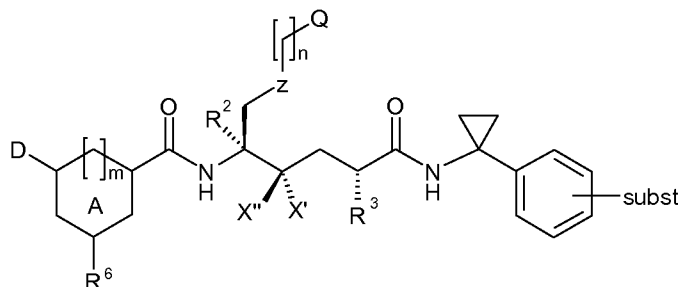
In embodiments wherein, in the definition of Y, the aryl or heterocyclyl moiety of C₀-C₃alkanediylaryl or C₀-C₃alkanediylheterocyclyl is a substituted 6-membered ring, the substituent(s) are conveniently in the para and/or ortho position. Currently favoured configurations for Y according to this embodiment include phenyl or pyridyl which is substituted in the para position.

The group W is bonded either directly to the amide nitrogen, i.e. q is 0, or W is bonded via a methylene or ethylene moiety, i.e. q is 1 or 2 respectively. In favoured embodiments of the invention W is bonded directly to the amide nitrogen or via a methylene moiety, i.e. q is 0 or 1 respectively.

Alternatively, when q is 1, the moiety linking W to the amide nitrogen may be a 1,1-cyclopropyl group, in which case compounds of the invention have the partial structure:



Preferred compounds according to this embodiment include those wherein p is 0 and W is phenyl or substituted phenyl, as shown in the structure below:



As stated above, W is hydrogen, C₁-C₆alkyl, C₃-C₆cycloalkyl, aryl or heterocyclyl which is optionally substituted with one, two or three substituents.

According to some embodiments of the invention W is an optionally substituted mono or bicyclic aryl moiety such as phenyl or naphthyl, preferably optionally substituted phenyl.

According to further embodiments of the invention, W is an optionally substituted mono- or bicyclic ring containing 1, 2 or 3 heteroatoms independently selected from nitrogen, oxygen and sulphur. Representative monocyclic rings according to this embodiment include pyridyl, thiazolyl, pyrimidyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, triazolyl, tetrazolyl, piperidyl, piperazinyl and morpholinyl and the like, representative bicyclic rings include quinolinyl, isoquinolinyl, indolyl, isoindolyl, indolinyl isoindolinyl each of which is optionally substituted wherein each of the mono and bicyclic rings is optionally substituted.

Preferably, W is a monocyclic optionally substituted 5- or 6-membered ring, such as optionally substituted phenyl.

In embodiments wherein W is a substituted 6-membered ring, the ring is preferably mono substituted with the substituent in the meta or para position.

In embodiments wherein the ring W is disubstituted the substituents are preferably in the two meta positions or in the meta and para positions.

Preferred optional substituents to W include one or two substituents independently selected from halo such as fluoro or chloro; C₃-C₄cycloalkyl such as cyclopropyl; haloC₁-C₃alkyl such as fluoromethyl and trifluoromethyl; C₁-C₄alkyl such as methyl, ethyl and isopropyl.

It is to be understood that the above defined subgroups of compounds of formulae (I) are meant to also comprise any prodrugs, *N*-oxides, addition salts, quaternary amines, metal complexes and stereochemically isomeric forms of such compounds.

As used in the foregoing and hereinafter, the scientific and technological terms and nomenclature have the same meaning as commonly understood by a person of ordinary skill in the art, in addition, the following definitions apply unless otherwise noted.

As used herein 'C₁-C₄alkyl' as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as for example methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2-methyl-1-propyl, 2-methyl-2-propyl;

'C₁-C₆alkyl' encompasses C₁-C₄alkyl radicals and the higher homologues thereof having 5 or 6 carbon atoms such as, for example, 1-pentyl, 2-pentyl, 3-pentyl, 1-hexyl, 2-hexyl, 2-methyl-1-butyl, 2-methyl-1-pentyl, 2-ethyl-1-butyl, 3-methyl-2-pentyl, and the like. Of interest amongst C₁-C₆alkyl is C₁-C₄alkyl.

The term 'C₂-C₆alkenyl' as a group or part of a group defines straight and branched chain hydrocarbon radicals having saturated carbon-carbon bonds and at least one carbon-carbon double bond, and having from 2 to 6 carbon atoms, such as, for example, ethenyl (or vinyl), 1-propenyl, 2-propenyl (or allyl), 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-2-propenyl, 2-pentenyl, 3-pentenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 2-methyl-2-butenyl, 2-methyl-2-pentenyl and the like. Of interest amongst C₂-C₆alkenyl is C₂-C₄alkenyl.

The term 'C₂-C₆alkynyl' as a group or part of a group defines straight and branched chain hydrocarbon radicals having saturated carbon-carbon bonds and at least one carbon-carbon triple bond, and having from 2 to 6 carbon atoms, such as, for example, ethynyl, 1-propynyl, 2-propynyl, 1-butylnyl, 2-butylnyl, 3-butylnyl, 2-pentylnyl, 3-pentylnyl, 2-hexynyl, 3-hexynyl and the like. Of interest amongst C₂-C₆alkynyl is C₂-C₄alkynyl.

The term C₃-C_ncycloalkyl means a non aromatic all carbon ring comprising 3 to n carbon atoms, wherein n is 3, 4 or 5, i.e. cyclopropyl, cyclobutyl or cyclopentyl. The cycloalkyl may optionally

be substituted with one or two substituents independently selected from C₁-C₃alkyl, C₂-C₃alkenyl, C₂-C₃alkynyl and halo.

‘C₀-C₃alkanediyl’ defines a bond (C₀) or a bivalent straight or branched saturated hydrocarbon chain having from 1 to 3 carbon atoms such as, for example, methylene, ethylene, 1,3-propanediyl, 1,2-propanediyl, and the like, especially methylene.

‘C₂-C₃alkenediyl’ defines a bivalent straight or branched hydrocarbon chain having one double bond and having 2 or 3 carbon atoms such as, for example, ethenylene, 1,3-propenediyl, 1,2-propenediyl, and the like, especially vinylene.

‘C₂-C₃alkynediyl’ defines a bivalent hydrocarbon chain having 2 or 3 carbon atoms and a triple bond, i.e. ethynylene and propynylene.

‘C₁-C₆alkoxy’ means a radical O-C₁-C₆alkyl wherein C₁-C₆alkyl is as defined above. C₁-C₆alkoxy of interest include but are not limited to methoxy, ethoxy n-propoxy and isopropoxy.

The term ‘halo’ is generic to fluoro, chloro, bromo and iodo. Fluoro is typically preferred in many applications.

The term ‘haloC₁-C₄alkyl’ as a group or part of a group, is meant to include mono- and polyhalo substituted C₁-C₄alkyl, in particular C₁-C₄alkyl substituted with one, two, three, four, five, six, or more halo atoms, such as methyl or ethyl with one or more fluoro atoms, for example, difluoromethyl, trifluoromethyl, trifluoroethyl. Preferred is trifluoromethyl. In case more than one halogen atom is attached to an alkyl group within the definition of haloC₁-C₆alkyl, the halogen atoms may be the same or different.

As used herein, the term ‘(=O)’ or ‘oxo’ forms a carbonyl moiety when attached to a carbon atom, a sulfoxide moiety when attached to a sulphur atom and a sulphonyl moiety when two of said terms are attached to a sulphur atom. It should be noted that an atom can only be substituted with an oxo group when the valency of that atom so permits.

‘Amino’ as a group or part of a group, unless the context suggests otherwise, includes NH₂, NHC₁-C₆alkyl or N(C₁-C₆alkyl)₂, wherein in the amino definitions each C₁-C₆alkyl is especially C₁-C₄alkyl variants. Included are also radicals wherein the two C₁-C₆alkyl groups of the N(C₁-C₆alkyl)₂ together with the nitrogen atom to which they are attached form a saturated cyclic amine such as pyrrolidiny, piperidiny, piperaziny or morpholinyl.

'Carbamoyl' includes $C(=O)NH_2$, and mono- and dialkylcarbamoyl, such as $C(=O)NHC_1-C_6alkyl$ and $C(=O)N(C_1-C_6alkyl)_2$, especially $C(=O)NHC_1-C_4alkyl$ and $C(=O)N(C_1-C_4alkyl)_2$. Included are also radicals wherein the two C_1-C_6alkyl groups of the dialkylcarbamoyl together with the nitrogen atom to which they are attached form a saturated cyclic amine such as pyrrolidinyl, piperidinyl, piperazinyl and morpholinyl.

'Amido' includes $NHC(=O)H$, alkanoylamino such as $NH(C=O)C_1-C_6alkyl$ especially $NH(C=O)C_1-C_4alkyl$, and N-alkyl alkanoylamino such as $N(C_1-C_6alkyl)(C=O)C_1-C_6alkyl$ especially $N(C_1-C_4alkyl)(C=O)C_1-C_4alkyl$. The term 'alkoxyamido' is meant to include $NHC(=O)C_1-C_6alkoxy$, such as tert.butoxycarbonylamino.

' $C_0-C_3alkanediylaryl$ ' as applied herein is meant to include an aryl moiety such as a phenyl or naphthyl or a phenyl fused to a $C_5-C_6cycloalkyl$ (for example indanyl), or a $C_5-C_6cycloalkenyl$ which aryl is directly bonded (i.e. C_0) or through an intermediate methylene, ethylene, 1,2-propanediyl or 1,3-propanediyl group as defined for $C_1-C_3alkanediyl$ above. Examples of suitable aryl groups include but are not limited to phenyl, naphthyl, tetrahydronaphthyl, indenyl and indanyl. Unless otherwise indicated the aryl and/or its fused cycloalkyl moiety is optionally substituted with one, two or where valence allows three substituents independently selected from C_1-C_4alkyl (optionally substituted with one or two substituents independently selected from $C_0-C_3alkanediylaryl^*$, amino, carbamoyl, amido and $C_1-C_4alkoxyamido$), $C_2-C_6alkenyl$, $C_2-C_6alkynyl$, $C_3-C_6cycloalkyl$, $C_1-C_4alkoxy$, $C_1-C_4alkoxyC_1-C_3alkyl$, $C_1-C_4alkoxyC_1-C_6alkoxyC_0-C_3alkyl$, halo, halo C_1-C_4alkyl , polyhalo C_1-C_4alkyl , hydroxy, hydroxy C_1-C_4alkyl , amino, amino C_1-C_4alkyl , carbamoyl, amido, cyano, azido, nitro, $C_1-C_6alkylcarbonyl$, a cyclic amine selected from pyrrolidinyl, piperidinyl, piperazinyl and morpholinyl (any of which cyclic amines being optionally substituted with C_1-C_4alkyl or fluoro), oxo, mercapto, $C_0-C_3alkanediylC_3-C_7carbocyclyl$, $C_0-C_3alkanediylaryl^*$, $C_0-C_3alkanediylheterocyclyl^*$, $C_2-C_3alkenediylC_3-C_7carbocyclyl$, $C_2-C_3alkenediylaryl^*$, $C_2-C_3alkenediylheterocyclyl^*$, $C_2-C_3alkynediylC_3-C_7carbocyclyl$, $C_2-C_3alkynediylaryl^*$, $C_2-C_3alkynediylheterocyclyl^*$, wherein the asterisked aryl or heterocyclyl moiety is optionally substituted with C_1-C_4alkyl , halo, hydroxy or amino. 'Aryl' has the corresponding meaning, i.e. where the $C_0-C_3alkanediyl$ linkage is absent.

' $C_2-C_3alkenediylaryl$ ' and ' $C_2-C_3alkynediylaryl$ ' have the corresponding meanings, adjusted just for the link to the aryl moiety as defined for ' $C_2-C_3alkenediyl$ ' and ' $C_2-C_3alkynediyl$ '

' $C_0-C_3alkanediylheterocyclyl$ ' as applied herein is meant to include a 5-6 membered saturated, partly unsaturated or unsaturated heterocyclic ring containing 1 to 3 heteroatoms each independently selected from nitrogen, oxygen and sulphur, the ring being optionally fused with a benzene ring. Examples of suitable heterocyclyl groups include but are not limited to pyranyl,

tetrahydropyranyl, tetrahydrothiopyranyl, thiopyranyl, furanyl, tetrahydrofuranyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, imidazolyl, oxazolyl, isoxazolyl, thiazinyl, isothiazinyl, thiazolyl, isothiazolyl, thiazolidinyl, thiadiazolyl, oxadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, thienyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, azetidyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, triazinyl, 1,4-dioxanyl, quinolinyl, tetrahydroquinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, quinazolinyl, tetrahydroquinazolinyl, quinoxalinyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazinyl, benzisothiazinyl, benzothiazolyl, benzoxadiazolyl, benzo-1,2,3-triazolyl, benzo-1,2,4-triazolyl, benzotetrazolyl, benzofuranyl, benzothieryl, benzopyridyl, benzopyrimidinyl, benzopyridazinyl, benzopyrazolyl, indolyl, isoindolyl, indolinyl, isoindolinyl etc, Said heterocyclyl is bonded either directly (i.e. C₀), or through an intermediate methylene, ethylene or propanediyl group as defined for C₁-C₃alkanediyl above. Unless otherwise indicated the ring system is optionally substituted with one, two or where valence allows three substituents independently selected from C₁-C₄alkyl (optionally substituted with one or two substituents independently selected from C₀-C₃alkanediylaryl*, amino, carbamoyl, amido and C₁-C₄alkoxyamido), C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₆cycloalkyl, C₁-C₄alkoxy, C₁-C₄alkoxyC₁-C₃alkyl, C₁-C₄alkoxyC₁-C₆alkoxyC₀-C₃alkyl, halo, haloC₁-C₄alkyl, polyhaloC₁-C₄alkyl, hydroxy, hydroxyC₁-C₄alkyl, amino, aminoC₁-C₄alkyl, carbamoyl, amido, cyano, azido, nitro, C₁-C₆alkylcarbonyl, a cyclic amine selected from pyrrolidinyl, piperidinyl, piperazinyl and morpholinyl (any of which cyclic amines being optionally substituted with C₁-C₄alkyl or fluoro), oxo, mercapto, C₀-C₃alkanediylC₃-C₇carbocyclyl, C₀-C₃alkanediylaryl*, C₀-C₃alkanediylheterocyclyl*, C₂-C₃alkenediylC₃-C₇carbocyclyl C₂-C₃alkenediylaryl*, C₂-C₃alkenediylheterocyclyl*, C₂-C₃alkynediylC₃-C₇carbocyclyl C₂-C₃alkynediylaryl*, C₂-C₃alkynediylheterocyclyl*, wherein the asterisked aryl or heterocyclyl moiety is optionally substituted with C₁-C₄alkyl, halo, hydroxy or amino. 'Heterocyclyl' has the corresponding meaning, i.e. where the C₀-C₃alkanediyl linkage is absent.

'C₂-C₃alkenediylheterocyclyl and 'C₂-C₃alkynediylheterocyclyl have the corresponding meanings, adjusted just for the link to the heterocyclyl moiety as defined for 'C₂-C₃alkenediyl' and 'C₂-C₃alkynediyl

'Heteroaryl' as applied herein means an aromatic heterocyclyl moiety.

Typically aryl and heterocyclyl moieties within the scope of the above definitions are thus a monocyclic ring with 5 or especially 6 ring atoms, or a bicyclic ring structure comprising a 6 membered ring fused to a 5 or 6 membered ring.

'C₀-C₃alkanediylC₃-C₆cycloalkyl' as applied herein is meant to include a C₃-C₆cycloalkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl, which is directly

bonded (i.e. C₀) or through an intermediate methylene, ethylene, 1,2-propanediyl or 1,3-propanediyl group as defined for C₁-C₃alkanediyl above. The cycloalkyl group may contain an unsaturated bond. Unless otherwise indicated the cycloalkyl moiety is optionally substituted with 1-3 substituents selected from C₁-C₄alkyl (optionally substituted with one or two substituents independently selected from C₀-C₃alkanediylaryl*, amino, carbamoyl, amido and C₁-C₄alkoxyamido), C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₆cycloalkyl, C₁-C₄alkoxy, C₁-C₄alkoxyC₁-C₃alkyl, C₁-C₄alkoxyC₁-C₆alkoxyC₀-C₃alkyl, halo, haloC₁-C₄alkyl, polyhaloC₁-C₄alkyl, hydroxy, hydroxyC₁-C₄alkyl, amino, aminoC₁-C₄alkyl, carbamoyl, amido, cyano, azido, nitro, C₁-C₆alkylcarbonyl, a cyclic amine selected from pyrrolidinyl, piperidinyl, piperazinyl and morpholinyl (any of which cyclic amines being optionally substituted with C₁-C₄alkyl or fluoro), oxo, mercapto, C₀-C₃alkanediylC₃-C₇carbocyclyl, C₀-C₃alkanediylaryl*, C₀-C₃alkanediylheterocyclyl*, C₂-C₃alkenediylC₃-C₇carbocyclyl C₂-C₃alkenediylaryl*, C₂-C₃alkenediylheterocyclyl*, C₂-C₃alkynediylC₃-C₇carbocyclyl C₂-C₃alkynediylaryl*, C₂-C₃alkynediylheterocyclyl*, wherein the asterisked aryl or heterocyclyl moiety is optionally substituted with C₁-C₄alkyl, halo, hydroxy or amino. 'C₃-C₆cycloalkyl' has the corresponding meaning, i.e. where the C₀-C₃alkanediyl linkage is absent.

'C₂-C₃alkenediylC₃-C₇carbocyclyl and 'C₂-C₃alkynediylC₃-C₇carbocyclyl have the corresponding meanings, adjusted just for the link to the carbocyclyl moiety as defined for 'C₂-C₃alkenediyl' and 'C₂-C₃alkynediyl'

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 stable.

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; pentyl includes 1-pentyl, 2-pentyl and 3-pentyl.

When any variable occurs more than one time in any constituent, each definition is independent.

Whenever used hereinafter, the term 'compounds of formula (I)', or 'the present compounds' or similar terms, it is meant to include the compounds of formula (I), their prodrugs, *N*-oxides, addition salts, quaternary amines, metal complexes, and stereochemically isomeric forms.

Preferred are pharmaceutically acceptable esters prodrugs that are hydrolysable *in vivo* and are derived from those compounds of formula (I) having a hydroxy and/or a carboxyl group. An *in vivo* hydrolysable ester is an ester, which is hydrolysed in the human or animal body to produce the parent acid or alcohol. Suitable pharmaceutically acceptable esters for carboxy include C₁-C₆alkoxymethyl esters for example methoxymethyl, C₁-C₆alkanoyloxymethyl esters for

example pivaloyloxymethyl, phthalidyl esters, C₃-C₈cycloalkoxycarbonyloxyC₁-C₆alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C₁-C₆alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl which may be formed at any carboxy group in the compounds of this invention.

An *in vivo* hydrolysable ester of a compound of the formula (I) containing a hydroxy group includes inorganic esters such as phosphate esters and α -acyloxyalkyl ethers and related compounds which as a result of the *in vivo* hydrolysis of the ester breakdown will give the parent hydroxy group. Examples of α -acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxy-methoxy. A selection of *in vivo* hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and N-(dialkylaminoethyl)-N-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl. Examples of substituents on benzoyl include morpholino and piperazino linked from a ring nitrogen atom via a methylene group to the 3- or 4-position of the benzoyl ring.

For therapeutic use, salts of the compounds of formula (I) or any subgroup of compounds of formula (I) are those wherein the counter-ion is pharmaceutically acceptable. However, salts of acids and bases which are non-pharmaceutically acceptable may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound. All salts, whether pharmaceutically acceptable or not are included within the ambit of the present invention.

The pharmaceutically acceptable acid and base addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid and base addition salt forms which the compounds of formula (I) are able to form. The pharmaceutically acceptable acid addition salts can conveniently be obtained by treating the base form with such appropriate acid. Appropriate acids comprise, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid, sulphuric, nitric, phosphoric acids and the like; or organic acids such as, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic (i.e. ethanedioic), malonic, succinic (i.e. butanedioic acid), maleic, fumaric, malic (i.e. hydroxybutanedioic acid), tartaric, citric, methanesulphonic, ethanesulphonic, benzenesulphonic, *p*-toluenesulphonic, cyclamic, salicylic, *p*-aminosalicylic, pamoic acids and the like.

Acid addition salt forms can be converted to the free base form by treatment with an appropriate base.

The compounds of formula (I) containing an acidic proton may also be converted into their non-toxic metal or amine addition salt forms by treatment with an appropriate organic or inorganic base. Appropriate base salt forms comprise, for example, the ammonium salts, the alkali and

earth alkaline metal salts, e.g. the lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. the benzathine, *N*-methyl-D-glucamine, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like.

Base addition salt forms can be converted to the free acid form by treatment with an appropriate acid.

The term addition salt as used hereinabove also comprises the solvates which the compounds of formula (I) or any of the subgroups of compounds of formula (I), as well as the salts thereof, are able to form. Such solvates are for example hydrates, alcoholates and the like.

The term 'quaternary amine' as used above and hereinafter defines the quaternary ammonium salts which the compounds of formula (I) or any of the subgroups of compounds of formula (I), are able to form by reaction between a basic nitrogen of a compound of formula (I) or any of the subgroups of compounds of formula (I), and an appropriate quaternizing agent, such as, for example, an optionally substituted alkyl halide, aryl halide or arylalkyl halide, e.g. methyl iodide or benzyl iodide. Other reactants with good leaving groups may also be used, such as alkyl trifluoromethanesulphonates, alkyl methanesulphonates, and alkyl *p*-toluenesulphonates. A quaternary amine has a positively charged nitrogen. Pharmaceutically acceptable counterions include chloro, bromo, iodo, trifluoroacetate and acetate. The counterion of choice can be introduced using ion exchange resins.

The *N*-oxide forms of the present compounds are meant to comprise the compounds of formula (I) wherein one or several nitrogen atoms are oxidized to the so-called *N*-oxide.

The compounds according to the invention may contain one or more asymmetrically substituted carbon atoms, asymmetric or chiral centre. The presence of one or more of these asymmetric centres in compounds according to the invention can give rise to stereochemically isomeric forms, stereoisomers, and in each case the invention is to be understood to extend to all such stereoisomers, both in pure form and mixed with each others, including enantiomers and diastereomers, and mixtures including racemic mixtures thereof.

Pure stereoisomeric forms of the compounds and intermediates as mentioned herein are defined as isomers substantially free of other enantiomeric or diastereomeric forms of the same basic molecular structure of said compounds or intermediates. In particular, the term 'stereoisomerically pure' concerns compounds or intermediates having a stereoisomeric excess of at least 80% (i.e. minimum 90% of one isomer and maximum 10% of the other possible isomers) up to a stereoisomeric excess of 100% (i.e. 100% of one isomer and none of the other), more in particular, compounds or intermediates having a stereoisomeric excess of 90% up to 100%, even more in particular having a stereoisomeric excess of 94% up to 100% and most in

particular having a stereoisomeric excess of 97% up to 100%. The terms 'enantiomerically pure' and 'diastereomerically pure' should be understood in a similar way, but then having regard to the enantiomeric excess, and the diastereomeric excess, respectively, of the mixture in question.

Pure stereoisomeric forms of the compounds and intermediates of this invention may be obtained by application of art-known procedures (cf. Advanced Organic Chemistry: 3rd Edition: author J March, pp 104-107). For instance, enantiomers may be separated from each other using known procedures including, for example, formation of diastereomeric mixtures by reaction with a convenient optically active auxiliary species followed by separation of the diastereomers, using for instance selective crystallisation, and finally cleavage of the auxiliary species. Examples of optically active auxiliary species are optically active acids and bases such as tartaric acid, dibenzoyltartaric acid, ditoluoyltartaric acid and camphorsulphonic acid. Alternatively, enantiomers may be separated by chromatographic techniques using chiral stationary phases. Pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. When a specific stereoisomer of a compound is desired, the compound will preferably be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

With reference to the instances where (*R*) or (*S*) is used to designate the absolute configuration of a chiral centre within a substituent, the designation is done taking into consideration the whole compound and not the substituent in isolation.

Where tautomers exist in the compounds of the invention, we disclose all individual tautomeric forms and combinations of these as individual specific embodiments of the invention.

It will be appreciated that the compounds of formula (I) may have metal binding, chelating or complex forming properties and therefore may exist as metal complexes or metal chelates. Such metalated derivatives of the compounds of formula (I) are intended to be included within the scope of the present invention.

The invention relates to the compounds of formula (I) or any subgroup of compounds of formula (I) *per se*, the prodrugs, *N*-oxides, addition salts, quaternary amines, metal complexes, and stereochemically isomeric forms thereof. One embodiment comprises the compounds of formula (I) or any subgroup of compounds of formula (I) specified herein, as well as the *N*-oxides, salts, as the possible stereoisomeric forms thereof.

The invention further relates to methods for the preparation of the compounds of formula (I) or any subgroup of compounds of formula (I), the prodrugs, *N*-oxides, addition salts, quaternary

amines, metal complexes, and stereochemically isomeric forms thereof, its intermediates, and the use of the intermediates in the preparation of the compounds of formula (I) or any subgroup of compounds of formula (I).

The invention also relates to the use of a compound of formula (I) or any subgroup of compounds of formula (I), or an prodrug, *N*-oxide, addition salt, quaternary amine, metal complex, or stereochemically isomeric form thereof, for the manufacture of a medicament. Or the invention relates to the use of a of a compound of formula (I) or any subgroup of compounds of formula (I), or a prodrug, *N*-oxide, addition salt, quaternary amine, metal complex, or stereochemically isomeric form thereof in therapy.

In the context of the present specification, the term 'therapy' also includes 'prophylaxis' unless there are specific indications to the contrary. The terms 'therapeutic' and 'therapeutically' should be construed accordingly.

The compounds of formula (I) or any of the subgroups of formula (I) have enzyme inhibiting properties, in particular they are inhibitors of aspartyl proteases such as renin and BACE.

The invention relates to a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (I) or a compound of any of the subgroups of formula (I) or a pharmaceutically acceptable salt thereof as specified herein, and a pharmaceutically acceptable adjuvant, diluent or carrier for administration to a subject in need thereof. A therapeutically effective amount in this context is an amount sufficient to act in a prophylactic way against, to stabilize or to reduce adverse conditions associated with RAS activity, such as or related to hypertension, heart failure, pulmonary hypertension, renal insufficiency or renal ischemia, or to act in a prophylactic way against or to stabilize conditions associated with BACE activity such as Alzheimer's disease in affected subjects or subjects being at risk of being affected.

The invention further relates to a process of preparing a medicament or a pharmaceutical composition as specified herein, which comprises intimately mixing a pharmaceutically acceptable adjuvant, diluent or carrier with a therapeutically effective amount of a compound of formula (I) or any of the subgroups of formula (I) as specified herein, or a pharmaceutically acceptable salt or a solvate, prodrug, *N*-oxide, quaternary amine, metal complex or stereochemically isomeric form thereof as specified herein.

In one embodiment the invention relates to use of the compounds of formula (I) in the treatment and/or prophylaxis of diseases such as or related to hypertension, congestive heart failure, pulmonary hypertension, renal insufficiency, renal ischemia, renal failure, renal fibrosis, cardiac insufficiency, cardiac hypertrophy, cardiac fibrosis, myocardial ischemia, cardiomyopathy,

glomerulonephritis, renal colic, complications resulting from diabetes such as nephropathy, vasculopathy and neuropathy, glaucoma, elevated intra-ocular pressure, atherosclerosis, restenosis post angioplasty, complications following vascular or cardiac surgery, erectile dysfunction, hyperaldosteronism, lung fibrosis, scleroderma, anxiety, cognitive disorders, complications of treatments with immunosuppressive agents, and other diseases known to be related to the renin-angiotensin system.

In a further embodiment, the invention relates to a method for the treatment and/or prophylaxis of diseases or conditions which are associated with a dysregulation of the renin-angiotensin system, in particular to a method for the treatment or prophylaxis of the above mentioned diseases, said method comprising administering to a patient a pharmaceutically active amount of a compound of formula (I) or any of the subgroups of formula (I).

The invention further provides a method of treating a disease or condition known to be related to the renin-angiotensin system (e.g. hypertension) which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I) or any of the subgroups of formula (I) or a pharmaceutically acceptable salt, solvate, prodrug, *N*-oxide, quaternary amine, metal complex, or stereochemically isomeric form thereof, as hereinbefore defined.

The invention further provides a method of treating diseases or conditions such as or related to the above mentioned (e.g. hypertension) which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I) or any of the subgroups of formula (I) or a pharmaceutically acceptable salt, or solvate thereof as hereinbefore defined.

The compounds of the present invention are also useful for the inhibition of BACE activity. Accordingly, a further embodiment of the invention relates to use of the compounds of formula (I) or any of the subgroups of formula (I) or a pharmaceutically acceptable salt, or solvate thereof as hereinbefore defined in the treatment and/or prophylaxis of Alzheimer's disease by inhibiting the activity of BACE.

The compounds of the present invention have also utility in treating, ameliorating, controlling or reducing the risk of Alzheimer's disease. For example, the compounds may be useful for the prevention of dementia of the Alzheimer's type, as well as for the treatment of early stage, intermediate stage or late stage dementia of the Alzheimer's type. The compounds may also be useful in treating, ameliorating, controlling or reducing the risk of diseases mediated by abnormal cleavage of amyloid precursor protein (also referred to as APP), and other conditions that may be treated or prevented by inhibition of β -secretase. Such conditions include mild cognitive impairment, Trisomy 21 (Down Syndrome), cerebral amyloid angiopathy,

degenerative dementia, Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type (HCHWA-D), Creutzfeld-Jakob disease, prion disorders, amyotrophic lateral sclerosis, progressive supranuclear palsy, head trauma, stroke, Down syndrome, pancreatitis, inclusion body myositis, other peripheral amyloidoses, diabetes and atherosclerosis.

In a further embodiment, the invention relates to a method for the treatment and/or prophylaxis of diseases or conditions which are associated with activity of BACE, in particular to a method for the treatment or prophylaxis of the above mentioned diseases, said method comprising administering to a patient a pharmaceutically active amount of a compound of formula (I) or any of the subgroups of formula (I).

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated. The daily dosage of the compound of formula I/salt/solvate (active ingredient) may be in the range from 0.001 mg/kg to 75 mg/kg, in particular from 0.5 mg/kg to 30 mg/kg. This daily dose may be given in divided doses as necessary. Typically unit dosage forms will contain about 1 mg to 500 mg of a compound of this invention.

The compounds of formula (I) and pharmaceutically acceptable salts, solvates, prodrugs, *N*-oxides, quaternary amines, metal complexes, or stereochemically isomeric forms thereof may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the compound of formula (I) /salt/solvate (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.10 to 70 %w/w, of active ingredient, and, from 1 to 99.95 %w/w, more preferably from 30 to 99.90 %w/w, of a pharmaceutically acceptable adjuvant, diluent or carrier, all percentages by weight being based on total composition. A representative tablet within the scope of the pharmaceutical composition of the invention could have a mass of 500 – 1500 mg with a loading of active ingredient in the range 35 – 75%, with the balance being excipients, such as binders, disintegrants, antioxidants and the like.

The pharmaceutical compositions of this invention may be administered in standard manner for the disease or condition that it is desired to treat, for example by oral, topical, parenteral, buccal, nasal, vaginal or rectal administration or by inhalation. For these purposes the compounds of this invention may be formulated by means known in the art into the form of, for example, tablets, capsules, aqueous or oily solutions, suspensions, emulsions, creams, ointments, gels, nasal sprays, suppositories, finely divided powders or aerosols for inhalation, and for parenteral use (including intravenous, intramuscular or infusion) sterile aqueous or oily solutions or

suspensions or sterile emulsions. The oral delivery route, particularly capsules or tablets is favoured.

In addition to the compounds of the present invention the pharmaceutical composition of this invention may also contain, or be co-administered (simultaneously or sequentially) with, one or more pharmacological agents of value in treating one or more of the diseases or conditions referred to hereinabove. Additionally, the compounds of the present invention may be used in combination with one or more other pharmacological agents that treat, prevent, control ameliorate or reduce the risk for side effects or toxicity of the compounds of the present invention. Such other pharmacological agents may be administered, by route and in amount commonly used therefore, contemporaneously or sequentially with the compounds of the present invention. Accordingly, the pharmaceutical compositions of the present invention include those that contain one or more active ingredients, in addition to the compounds of the present invention. The combination may be administered as part of a unit dosage form combination product, or as a kit or a treatment protocol wherein one or more additional pharmacological agents are administered in separate dosage forms as a part of a treatment regimen.

Representative examples of pharmacologically active agents directed to combinations with the compounds of the present invention useful for the treatment and/or the prophylaxis of adverse conditions associated with RAS activity as described hereinabove include ACE-inhibitors, neutral endopeptidase inhibitors, aldosterone antagonists, angiotensin II receptor antagonists, endothelin receptors antagonists, vasodilators, calcium antagonists, potassium activators, diuretics, sympatholitics, beta-adrenergic antagonists, alpha-adrenergic antagonists and/or other drugs beneficial for the prevention or the treatment of the above-mentioned diseases such as 11 β -hydroxy steroid dehydrogenase type 1 inhibitors and soluble guanylate cyclase activators.

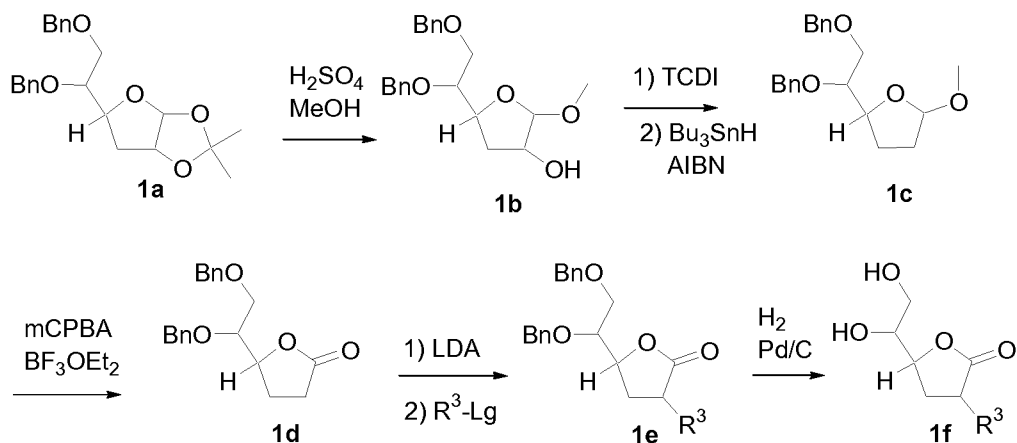
The present invention is also directed to combinations of the compounds of the invention with one or more pharmacologically active agents useful in the treatment and/or the prophylaxis of Alzheimer's disease. Examples of combinations include combinations with anti-Alzheimer's agents, for example other BACE inhibitors or γ -secretase inhibitors; HMG-CoA reductase inhibitors; NSAIDs including ibuprofen; vitamin E; anti-amyloid antibodies, including anti-amyloid humanized monoclonal antibodies; CB-1 receptor antagonists or CB-1 receptor inverse agonists; antibiotics such as doxycycline and rifampin; N-methyl-D-aspartate (NMDA) receptor antagonists, such as memantine; cholinesterase inhibitors such as galantamine, rivastigmine, donepezil, and tacrine; growth hormone secretagogues such as ibutamoren, ibutamoren mesylate, and capromorelin; histamine H3 antagonists; AMPA agonists; PDE IV inhibitors; GABAA inverse agonists; neuronal nicotinic agonists; or other drugs that affect receptors or enzymes that either increase the efficacy, safety, convenience, or reduce unwanted side effects or toxicity of

the compounds of the present invention. The foregoing list of anti-Alzheimer's agents suitable for combinations is illustrative only and not intended to be limiting in any way.

General synthetic methodology

The compounds of the present invention and intermediates useful for the synthesis of these compounds are prepared by methods and techniques known to those skilled in the art. The general schemes below illustrate typical synthetic routes to the compounds of the invention and to intermediates thereof. Alternative routes, which will be readily apparent to the ordinary skilled organic chemist, may alternatively be used to synthesize various portions of the molecules as illustrated by the general schemes and the preparative examples below.

Scheme 1 illustrates a synthetic route to a lactone which is a useful intermediate in the preparation of compounds of formula (I).

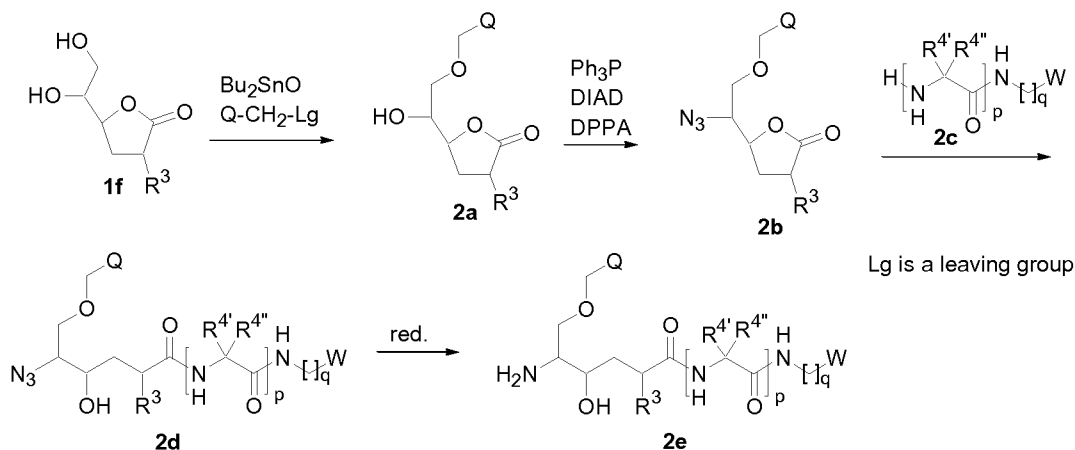


Scheme 1

The isopropylidene derivative (1a) achieved for example as described in Tetrahedron lett., 1987, 28, 1143, can be transferred into the methyl glycoside (1b) by acidic hydrolysis of the acetal group effected by treatment with a suitable acid such as sulphuric acid, in the presence of methanol. The achieved free secondary hydroxy group can then be reductively removed for instance by transformation of the hydroxy group into a thiocarbonyl group by reaction with thiocarbonyl diimidazole (TCDI) followed by reduction of the formed thiocarbonyl group using for instance tributyltin hydride in the presence of a radical initiator like azobis-(2-methylpropanenitrile) (AIBN) or the like, to give the 2,3-dideoxy glycoside (1c). Oxidative cleavage of the methyl ether can be performed for example by oxidation with *m*-chloroperoxybenzoic acid or the like in the presence of BF_3 -etherate, which gives the lactone (1d). A substituent in the position α to the carbonyl can then be introduced for example by treatment of the lactone (1d) with a base such as LDA or equivalent, followed by reaction with a suitable alkylating agent such as an alkyl halide like an alkyl bromide or alkyl iodide or a derivative of sulphonic acid such as a mesylate, triflate or tosylate or the like, thus providing the alkylated

lactone (1e). Removal of the benzyl groups using any suitable conditions well known to the skilled person, such as catalytic hydrogenation, then provides the diol (1f).

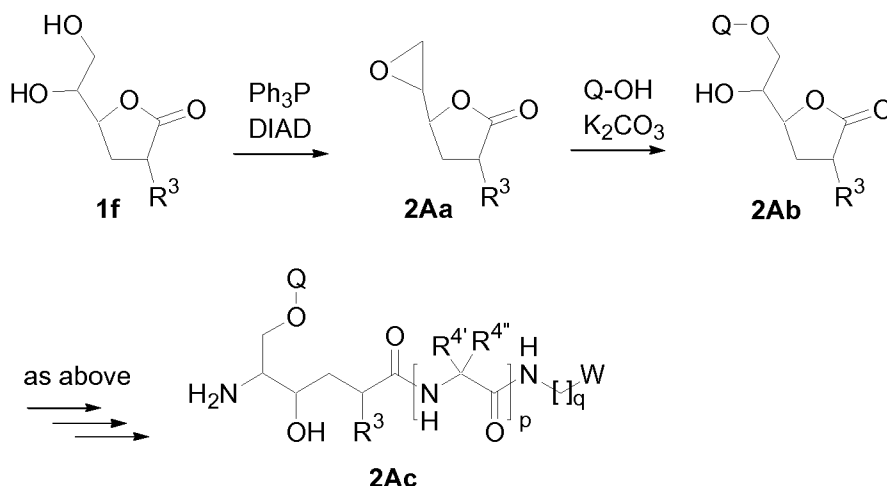
The lactone (1f) obtained in scheme 1 can then be further reacted as shown in scheme 2 to yield a linear amine which is another versatile intermediate useful for the preparation of compounds of formula (I) wherein n is 1 and Z is O.



Scheme 2

The primary hydroxy group of the lactone (1f) can be selectively alkylated for example by activation with dibutyltin oxide followed by reaction with a desired alkylating agent $Q-CH_2Lg$ wherein Lg is a suitable leaving group such as a halide like bromide or iodide in the presence of tetrabutylammonium bromide or the like thus forming the ether derivative (2a). Alternatively, the substituent $Q-CH_2$ can be introduced by using the Mitsunobu conditions (Mitsunobu, 1981, Synthesis, January, 1-28; Rano et al., Tetrahedron Lett., 1995, 36, 22, 3779-3792; Krchnak et al., Tetrahedron Lett., 1995, 36, 5, 6193-6196; Richter et al., Tetrahedron Lett., 1994, 35, 27, 4705-4706) i.e. reaction of the primary hydroxy group of the diol (1f) with an azodicarboxylate such as DIAD or the like in the presence of triphenylphosphine followed by displacement with a desired alcohol. Replacement of the secondary hydroxy group of the alcohol (2a) by azide may be effected by transforming the hydroxy group to a leaving group, for example a derivative of sulphonic acid like a triflate or tosylate or the like by subjecting the alcohol to sulfonylating conditions such as treatment with the appropriate anhydride or halide optionally in the presence of a base, for instance pyridine, followed by displacement of the leaving group with azide for example sodium azide, thus giving the azide derivative (2b). The linear amino compound (2e) can then be achieved by opening of the lactone with a desired amino derivative (2c) in the presence of for example 2-hydroxypyridine and a base like isopropyl diethylamine. Reduction of the azide using conditions compatible with the present $Q-CH_2$ group, for example hydrogenation at atmospheric pressure in the presence of Lindlar's catalyst or equivalent or treatment with Ph_3P , then provides the amine (2e).

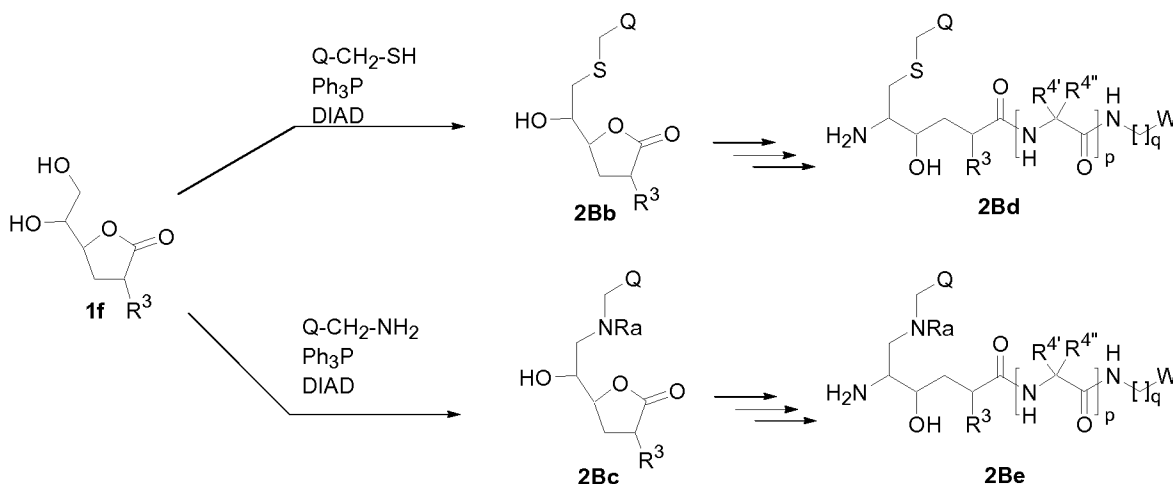
A linear intermediate amine wherein the group Q is bonded directly to the oxygen atom, useful for the preparation of compounds of formula (I) wherein Z is O and n is 0, can be prepared as shown in scheme 2A.



Scheme 2A

Treatment of the diol (1f) with triphenylphosphine and an azodicarboxylate for example DIAD provides the epoxide (2Aa). Opening of the epoxide with a desired nucleophile Q-OH in the presence of a base, such as potassium carbonate or the like, provides the ether derivative (2Ab). Subsequent replacement of the secondary hydroxy group with azide, opening of the lactone and finally reduction of the azide as described above, provides the linear amine (2Ac).

Lactones useful for the synthesis of compounds of formula (I) wherein Z is S or NH and n is 1, can be prepared from the diol 1f for example by a Mitsunobu reaction with a thiol or amino derivative respectively, as illustrated in scheme 2B.



Scheme 2B

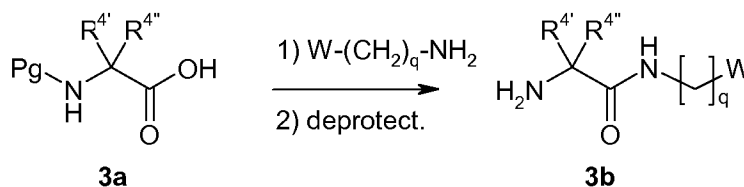
The primary hydroxy group of the lactone (1f) can be converted to a thioether or an amine for example by transforming it into a leaving group followed by displacement of the formed leaving group with the desired group Q-CH₂-S or Q-CH₂-NRa. A convenient method to effect this transformation is by way of a Mitsunobu reaction, i.e. reaction of the hydroxy group with an azodicarboxylate such as DIAD or the like in the presence of triphenylphosphine or the like followed by displacement with a desired thiol or amine to provide the thioether (2Bb) or the amine derivative (2Bc) respectively. Alternatively, the amine (2Ac) may be achieved by using an azide derivative, such as sodium azide or DPPA in the Mitsunobu reaction with the alcohol (2a), followed by reduction of the azide to the primary amine and subsequent alkylation of the amine with a suitable alkylating agent Q-CH₂-Lg, or by performing a reductive amination with a suitable aldehyde Q-CH(=O). An alternative method to obtain the amino derivative (2Bc) is to selectively oxidize the primary hydroxy group of the alcohol (1f) to the corresponding aldehyde, effected for example by treatment with Dess-Martin periodinane or by any other suitable oxidation reagent, followed by a reductive amination with the desired amino derivative Q-CH₂-NHRa in the presence of a reducing agent like NaCNBH₃. Replacement of the secondary hydroxy group with azide, opening of the lactone and finally reduction of the azide as described above, then provides the linear amines (2Bd and 2Be).

Intermediates for the preparations of compounds of formula (I) wherein the group Q is linked directly to a sulphur or nitrogen atom, i.e. Z is S or NRa and n is 0, may be prepared by transformation of the primary hydroxy group of the diol (2a) into a leaving group such as a derivative of sulphonic acid like a mesylate, triflate, tosylate or the like by treatment with the appropriate sulphonylating agent in a solvent like for instance pyridine or dichloromethane optionally in the presence of triethylamine or the like, followed by displacement of the leaving group with a desired thiol Q-SH or a amine Q-NHRa optionally in the presence of a base. An alternative method for the preparation of compounds wherein Z is S and n is 0 is to react the diol (2a) with a desired diphenyl disulphide derivative in the presence of nBu₃P. Compounds wherein Z is NRa and n is 0 may alternatively be achieved by oxidation of the primary hydroxy group of the diol (2a) followed by a reductive amination with a desired aniline derivative Q-NRa in the presence of a suitable catalyst like NaCNBH₄ or the like.

Compounds of formula (I) wherein Z is a sulphone i.e. S(=O)₂ may be obtained by oxidation of the sulphur of corresponding thioether derivative. The oxidation can be performed either at the last step of the synthesis or on any suitable intermediate. Many suitable methods for this oxidation are described in the literature for example, a peroxyacid such as AcOOH, *m*CPBA can be used.

Amino derivatives used for the opening of the lactone in scheme 2 are available commercially or they can easily be prepared by the skilled person according to literature procedures. For the

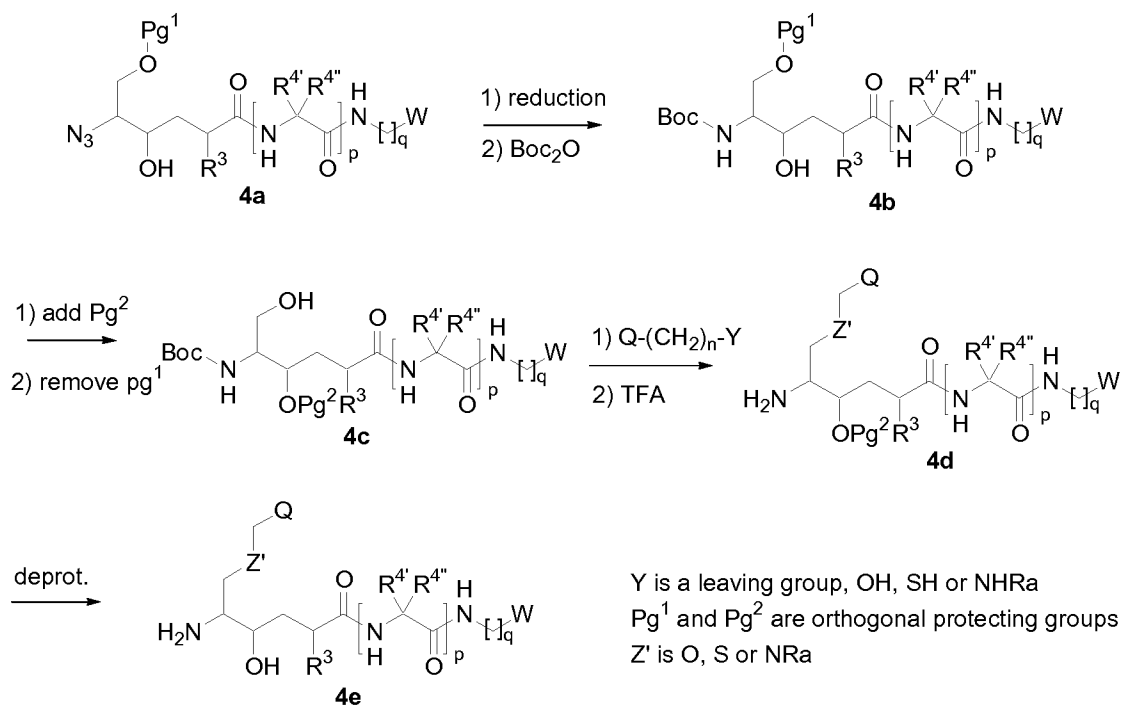
preparation of compounds of the invention wherein p is 1, the lactone 2b in scheme 2 is opened with the appropriate amino amide, which is conveniently prepared from the corresponding amino acid for example as illustrated in scheme 3.



Scheme 3

The amino acid (3a), carrying the desired side chain $\text{R}^{4'}$ and $\text{R}^{4''}$, can be coupled to the amine $\text{W}-(\text{CH}_2)_q\text{-NH}_2$ using any convenient method for peptide coupling known in the art. For example, a coupling agent like HATU or isobutylchloroformate in the presence of a tertiary amine such as ethyldiisopropylamine (DIEA) or N-methylmorpholine in a solvent like dimethyl formamide can be used. Subsequent removal of the N-protecting group using the appropriate conditions according to the protecting group used, such as acidic treatment in the case of a Boc-group, provides the amine (3b).

An alternative route to the linear amines wherein n is 1, is shown in scheme 4.



Scheme 4

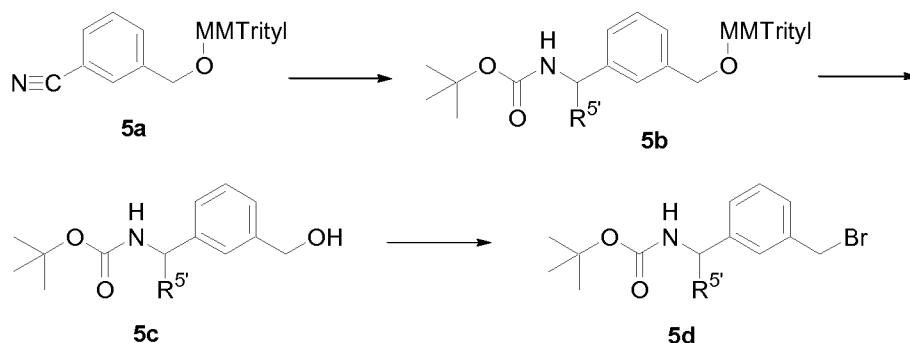
The azide derivative (4a), prepared for example as outlined in scheme 1, wherein Pg¹ is a hydroxy protecting group for example a benzyl group can be transformed to the corresponding amine by reduction of the azide using any convenient reduction method such as hydrogenation in

the presence of a suitable catalyst, such as Lindlar's catalyst or the like in the presence of Boc_2O to provide the boc protected amino derivative (4b). Protection of the secondary hydroxy group, using a protecting group (Pg^2) which is orthogonal to the one used for the primary hydroxy group (Pg^1), followed by removal of the primary hydroxy protecting group using the appropriate conditions according to the group used, such as for example catalytic hydrogenation in the case of a benzyl group, provides the primary alcohol (4c).

Suitable protecting groups for the above route will be recognized by the skilled person and a numerous of useful protecting groups are described in Greene, "Protective Groups in Organic Synthesis", John Wiley & Sons, New York (1981). For example benzyl can be used as Pg^1 and acetyl as Pg^2 . The group $\text{CH}_2\text{-Q}$ can then be introduced as described above. For example, compounds wherein Z is O and n is 1, can be prepared by reaction of the primary alcohol (4c) with an alkylating agent $\text{Q-CH}_2\text{-Lg}$ wherein Lg is a halide like a bromide, chloride or iodide or a derivative of sulphonic acid such as a triflate or mesylate or the like in the presence of a base like NaH or the like, or a trichloroacetimidate of a desired group, $\text{Q-CH}_2\text{-O-C(=NH)CCl}_3$ may be reacted with the primary alcohol (4c) in the in the presence of a Lewis acid such as BF_3OEt_2 . Trichloroacetimidates are conveniently prepared by reaction of the corresponding alcohol with trichloroacetonitrile in the presence of a base like NaH.

Compounds of formula (I) wherein n is 1 and Z is O, S or NRa may be prepared by a Mitsunobu reaction of the primary alcohol (4c) with a desired alcohol, $\text{Q-CH}_2\text{-OH}$, thiol, $\text{Q-CH}_2\text{-SH}$ or amine $\text{Q-(CH}_2\text{)}_n\text{-NHRa}$ respectively. Compounds wherein n is 0 and Z is O, S or N may be prepared by transforming the primary hydroxy group of the alcohol (4c) to a leaving group such as a halide like chloride or bromide or to a derivative of sulphonic acid such as a triflate, tosylate or the like which subsequently is displaced by a desired alcohol Q-OH , thiol Q-SH or amine Q-NHRa optionally in the presence of a base, for example as described hereinabove. An alternative method for the preparation of compounds wherein Z is S and n is 0 is to react the alcohol (4a) with a desired derivative of diphenyl disulphide in the presence of nBu_3P . Compounds wherein Z is NRa and n is 0 may alternatively be achieved by oxidation of the hydroxy group of the alcohol (4a) followed by a reductive amination with a desired aniline derivative Q-NRa in the presence of a suitable catalyst like NaCNBH_4 or the like. Removal of the Boc group according to standard procedures such as treatment with an acid, for example TFA, followed by removal of the hydroxy protecting group using the appropriate conditions, then provides the amine (4e)..

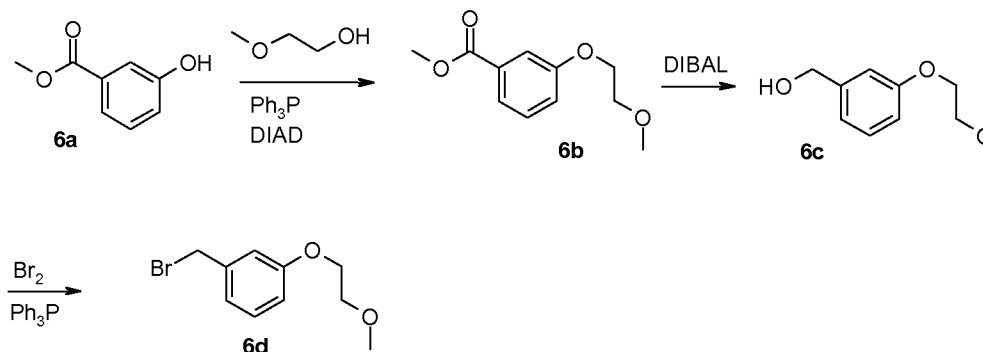
Substituted aryl and heteroaryl derivatives to be used in the coupling to the primary alcohol of the lactone 1f or linear compound 4c are commercially available or they can be prepared by the skilled person according to literature procedures. Scheme 5 illustrates a method to prepare a substituted phenyl derivative useful for the preparation of compounds of formula (I) wherein Q is phenyl substituted with aminomethyl or amidomethyl and derivatives thereof.



Scheme 5

The hydroxy protected cyanobenzyl derivative (5a) is conveniently prepared by protection of commercially available cyanobenzyl alcohol, illustrated herein as 3-cyanobenzyl alcohol, with a suitable protecting group, for example a trityl or monomethoxy trityl group using standard conditions well known in the art. Subsequent alkylation of the cyano group effected for example by way of an organometallic reaction such as a Grignard reaction or an organolithium reaction or the like, using the suitable conditions such as treatment with the desired alkyl magnesium halide in an ethereal solvent like diethyl ether or THF or the like, followed by reduction of the intermediate imine for example by LAH and finally protection of the afforded amine by treatment with the suitable agent such as di-*t*-butyldicarbonate, provides the carbamate (5b). Removal of the hydroxy protecting group using standard conditions such as treatment with acid in the case of a trityl or monomethoxy trityl group as protecting group, provides the alcohol (5c). The afforded alcohol (5c) can then be used in the coupling to the primary alcohol of the lactone 1f or the linear compound 4c employing for example the Mitsunobu conditions as described in scheme 2 and 4 respectively. Alternatively, the hydroxy group of the alcohol (5c) can be transformed into a leaving group such as a bromide for example by treatment with bromine or carbontetrabromide in the presence of triphenylphosphine or the like thus affording the bromoderivative (5d), or the hydroxy group can be transformed into a derivative of sulphonic acid by reaction with a suitable sulfonylating agent such as a sulphonic halide or anhydride optionally in the presence of a base for example pyridine. The afforded compound can then be coupled to the primary alcohol of the lactone 1f or the linear compound 4c by way of a displacement reaction.

Scheme 6 illustrates an example to another substituted phenyl derivative, useful for the preparation of compounds of formula (I) wherein Q is phenyl substituted with an alkoxy-alkoxy group.

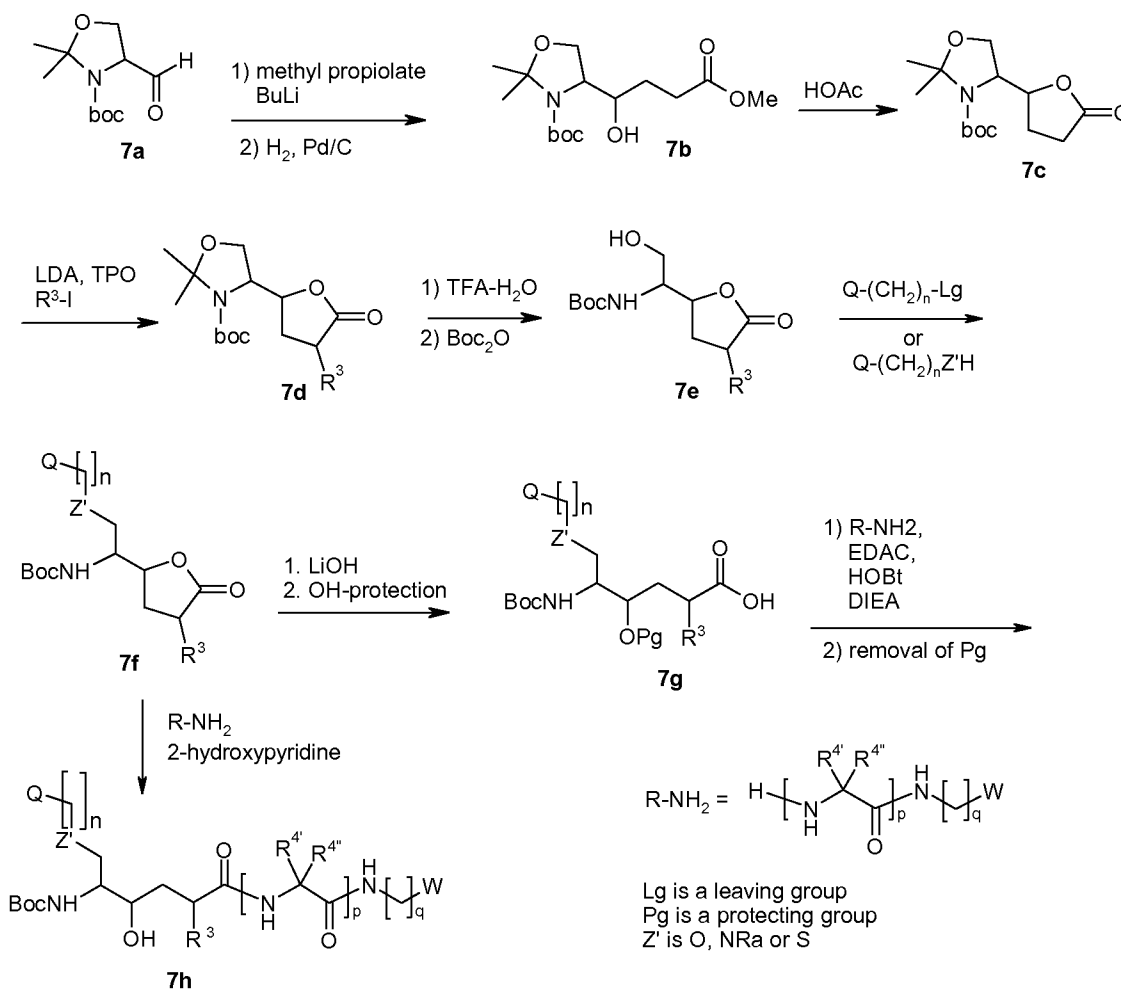


Scheme 6

Alkylation of the phenolic hydroxy group of ester (6a) using for example the Mitsunobu conditions, such as in the presence of Ph_3P , an azodicarboxylate like DIAD and the suitable alcohol, followed by reduction of the ester function using any convenient reduction method known in the art, such as treatment with DIBAL or the like, provides benzylic alcohol (6c). The afforded alcohol can then either be used directly in the coupling to the primary hydroxyl group of the lactone 1f or the linear compound 4c employing the Mitsunobu conditions, or the hydroxy group can be transferred to a leaving group, such as a halide like bromide, and subsequently coupled to the primary hydroxyl group of the lactone 1f or the linear compound 4c as described above.

Even though the strategy in scheme 6 illustrates the introduction of a methoxy-ethoxy substituent to the phenyl ring, the skilled person will easily realise that the same methodology can be applied for the introduction of other O-linked substituents, such as substituents with other chain lengths. Furthermore, despite the fact that scheme 5 and 6 are illustrated with a 1,3 substituted phenyl derivative as starting compound, the skilled person will realise that the same methodology also is applicable to other phenyl derivatives, for example the corresponding 1,2- or 1,4-disubstituted derivatives.

Scheme 7 shows an alternative route to compounds of the invention, starting from Garner's aldehyde.

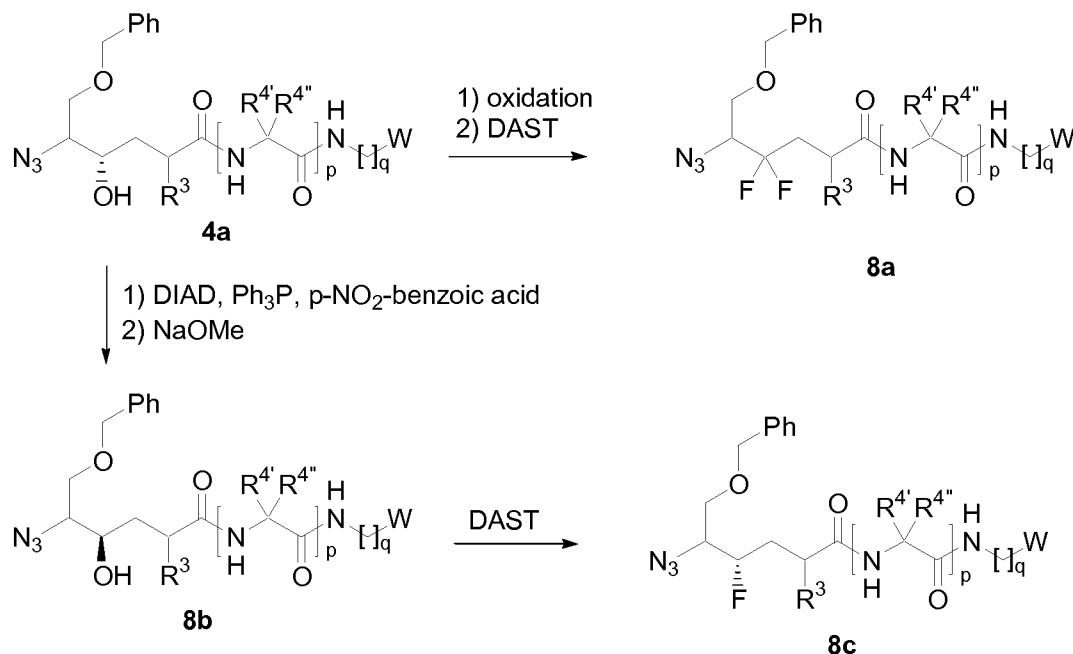


Scheme 7

α -Alkylation of the aldehyde (7a) by reaction with a suitable ester of propionic acid, for example the methyl ester, in the presence of a base like butyllithium, followed by reduction of the triple bond for example by catalytic hydrogenation using a catalyst like palladium on carbon, provides the alcohol (7b). Heating of the afforded hydroxy ester in the presence of acetic acid effects the ring closure and thus affords lactone (7c). The afforded lactone can then be alkylated at the α -carbon with a desired group R^3 for example as described above, i.e. by treatment of the lactone with a base such as LDA optionally followed by addition of tripyrrolidine phosphorus oxide and finally addition of the alkylating agent, to provide the alkylated lactone (7d). Cleavage of the cyclic aminal by treatment with acid such as TFA, followed by reaction with Boc_2O in order to reprotect the amino function affords the primary alcohol (7e). The group $Q-(CH_2)_n$ can then be introduced using any suitable method such as any of those described above. For example, a trichloroimidate of the desired group $Q-(CH_2)_n$ in the presence of TMS triflate will provide the ether derivative (7f) i.e. Z' is O. The lactone may then be opened either directly with a desired amine as described above to give the amide (7h), or alternatively, the lactone may be opened by treatment with hydroxide such as lithium hydroxide, thus affording the acid (7g). Protection of the hydroxy group, using any conventional protecting group for example a silyl group such as a tert.butyl dimethylsilyl group, followed by coupling of the acid to a suitable amine using

standard peptide coupling conditions such as using a coupling agent like EDAC in the presence of HOBT and a tertiary amine like triethylamine, and finally removal of the hydroxy protecting group provide the amide (7h).

An intermediate towards compounds of formula (I) wherein X' is F and X'' is H or X' and X'' are both F can be prepared by replacement of the hydroxy group of compound 4a with fluoro or difluoro as exemplified in scheme 8.

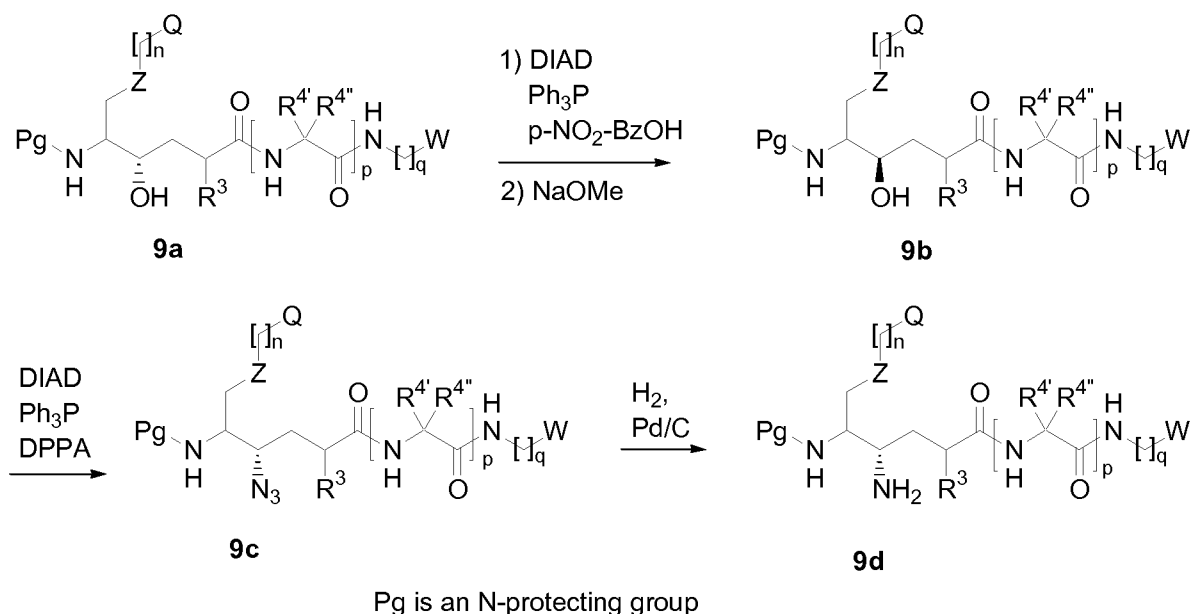


Scheme 8

The free hydroxy group of compound (4a) can be replaced by two fluoro atoms by oxidizing the hydroxy group to a keto group using any convenient method such as using a reagent like Dess Martin periodinane or oxone® (potassium monopersulphate triple salt) or any other suitable oxidizing agent, followed by treatment of the afforded keto compound with a fluorinating agent like DAST or Deoxofluor or the like in a solvent like dichloromethane, to give the difluoro compound (8a). The monofluoro compound (8c) with the desired stereochemistry can be obtained by first inverting the stereochemistry at the steric centre where the hydroxy group is attached and thereafter replace the hydroxy group with fluorine, effected for example by subjecting the afforded inverted alcohol to fluorinating conditions such as treatment with DAST or Deoxofluor in a solvent like dichloromethane as described e.g. by Singh, R. P. and Shreve, J. M. in *Synthesis*, 17, 1999, p. 2561-2578, or any other suitable fluorinating conditions. Inversion of the stereochemistry of the alcohol (4a) can be performed for example by subjecting the alcohol to a Mitsunobu reaction with for instance p-nitrobenzoic acid and reagents like DIAD and Ph₃P followed by hydrolysis of the afforded p-nitrobenzoic ester by for example treatment with sodium methoxide or the like.

Even though scheme 8 illustrates the replacement of the hydroxy group with fluoro or difluoro as the last step of the synthesis, the skilled person will realise that this transformation alternatively may be performed at any other suitable stage of the synthesis for example on any of the intermediates described above.

Compounds of formula (I) wherein X' is amino may be prepared from the corresponding alcohol. A variety of methods for the transformation of alcohols to amines are described in the literature. For example, the hydroxy group can be transformed into a leaving group which subsequently is displaced by azide and the azide is thereafter reduced to the amine, as illustrated in scheme 9.

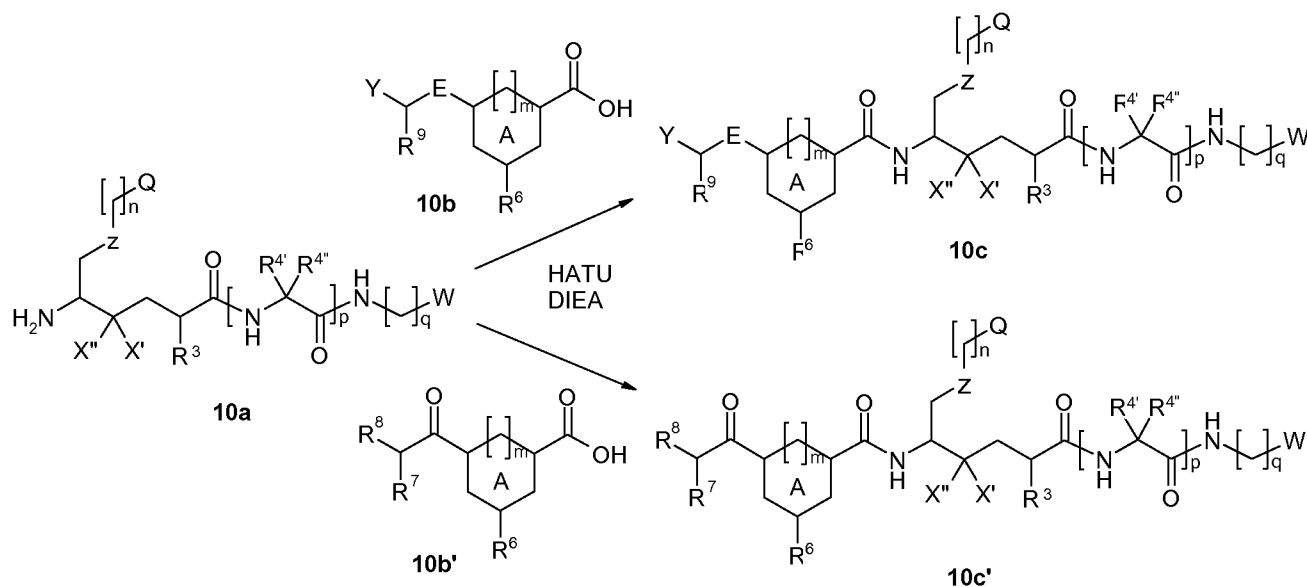


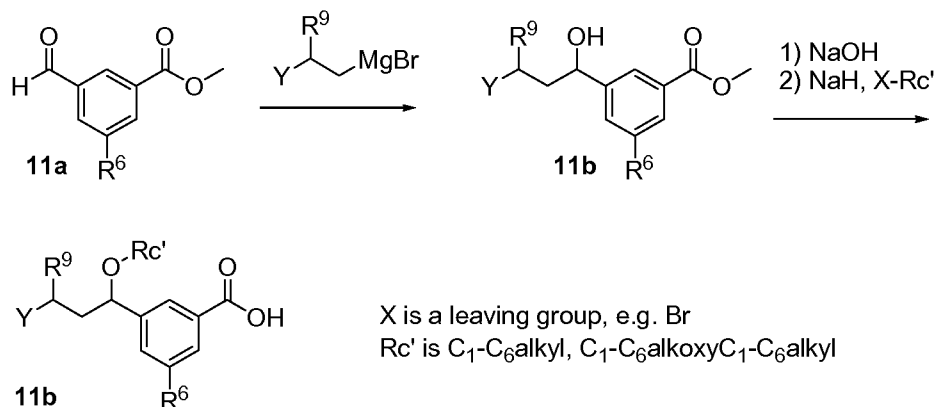
Scheme 9

In order to get the desired configuration at the steric centre where to the X' is attached in the final compound, the configuration of compound (9a), prepared as described above, has to be inverted, for example as described in scheme 8. The inverted alcohol (9b) can then be subjected to Mitsunobu conditions, i.e. treatment with an azodicarboxylate such as DIAD or the like in the presence of triphenylphosphine followed by reaction with azide, for example diphenylphosphoryl azide (DPPA) or HN_3 to give the azido derivative (9c). The azido derivative (9c) can alternatively be achieved by transformation of the hydroxy group to a derivative of sulphonic acid like a mesylate, triflate, tosylate or the like by treatment with the appropriate sulfonylating agent in a solvent like for instance pyridine or dichloromethane optionally in the presence of triethylamine or the like, followed by displacement of the leaving group with sodium azide or the like. Reduction of the azide using any conventional reduction method such as hydrogenation in the presence of a suitable catalyst, or treatment with triphenylphosphine provides the corresponding amine (9d).

Even though scheme 9 illustrates the conversion of the hydroxy group to amine as the last step of the synthesis, the skilled person will realise that this transformation is also applicable at any other suitable stage of the synthesis for example on any of the intermediates described above.

The compounds of the invention are then achieved by coupling of a suitable amine such as any of those described above, to an acid as schematically outlined in scheme 10.

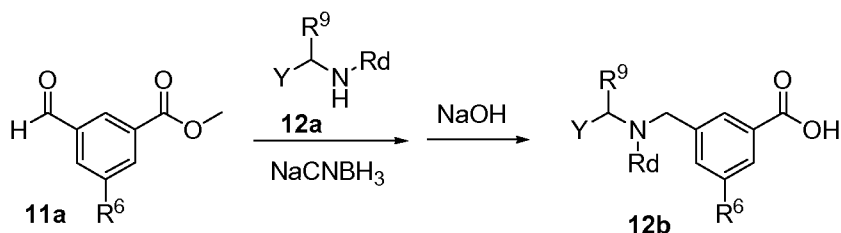




Scheme 11

Reaction of an aldehyde (11a), prepared for example according to the procedure described by S. J. Stachel et al. in *Med. Chem. Lett.*, 16 (2006) 641-644, in a Grignard reaction or equivalent with a suitable reagent such as an alkylmagnesium bromide, provides the alcohol (11b). Hydrolysis of the methyl ester using for instance sodium hydroxide or the like followed by alkylation of the tertiary hydroxy group with an alkylating agent Rc'-X, wherein Rc' is C₁-C₆alkyl or C₁-C₆alkoxyC₁-C₆alkyl and X is a leaving group for example a halogen like chloride, bromide or iodide, in the presence of a base like sodium hydride or the like gives the acid (11b).

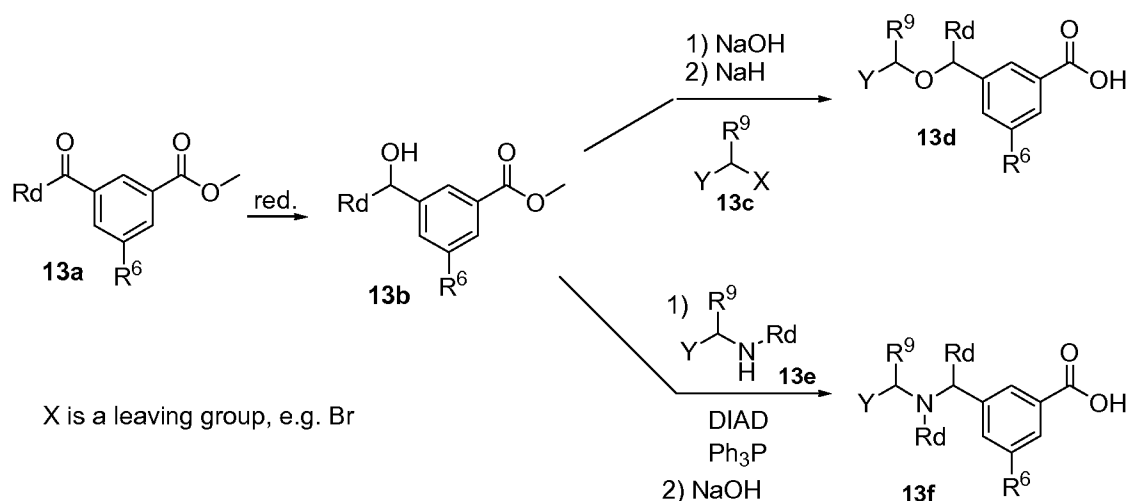
Acids (10b) wherein ring A is phenyl, E is -NRd-CH(Rd)- can be prepared as illustrated in scheme 12.



Scheme 12

Reaction of aldehyde (11a) in a reductive amination reaction with an amino derivative (12a), using a reducing agent like sodium cyanoborohydride or the like, and subsequent hydrolysis of the methyl ester provides the amine containing acid (12b). Although the method in scheme 12 illustrates the preparation of an acid wherein the benzylic carbon is unsubstituted, the skilled person will realize that acids which are substituted at the benzylic position can be obtained according to the same procedure by using the appropriate ketone instead of the aldehyde (11a) as starting material.

Scheme 13 illustrates a route to acids (10b) wherein E is -O-CH(Rd)- and Rd is hydrogen, and also an alternative route to acids wherein E is NRd-CH(Rd)-.

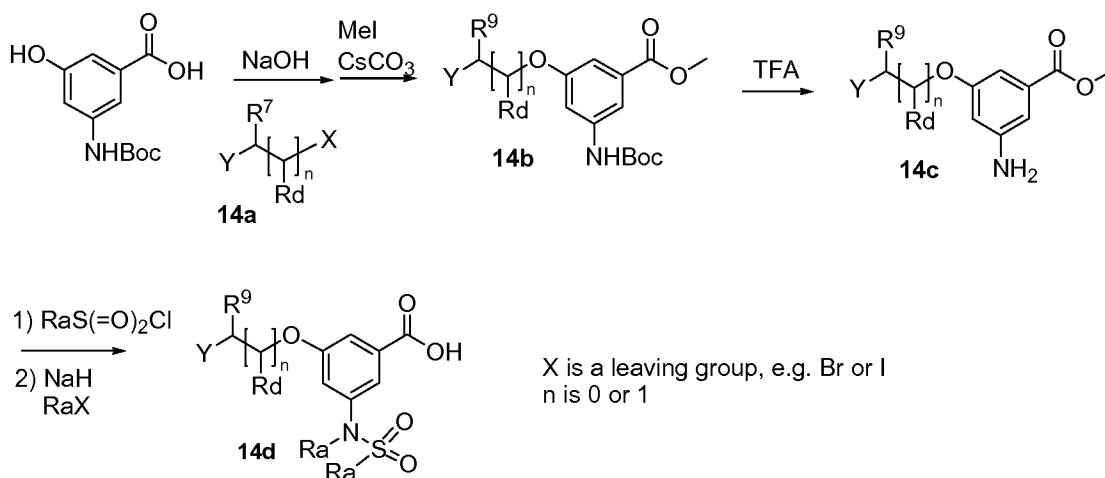


Scheme 13

The aldehyde or keto derivative (13a), prepared for example as described by S. J. Stachel et al. in *Med. Chem. Lett.*, 16 (2006) 641-644, can be reduced to the corresponding alcohol (13b) for example by treatment with sodium borohydride or any other appropriate reagent. Ether derivatives (13d) can then be achieved by hydrolysis of the methyl ester by treatment with sodium hydroxide or the like, followed by alkylation of the secondary hydroxy group using any desired alkylating agent (13c) wherein X is a leaving group such as bromide, iodide or chloride in the presence of a base like sodium hydride. Amino derivatives (13f) can be achieved by subjecting the alcohol (13b) to a Mitsunobu reaction with a desired amine (13e), followed by hydrolysis of the methyl ester as described above.

It should be appreciated that in any functional groups that optionally may be present on any of the constituent compounds are appropriately protected where necessary during the reaction sequence and deprotected afterwards.

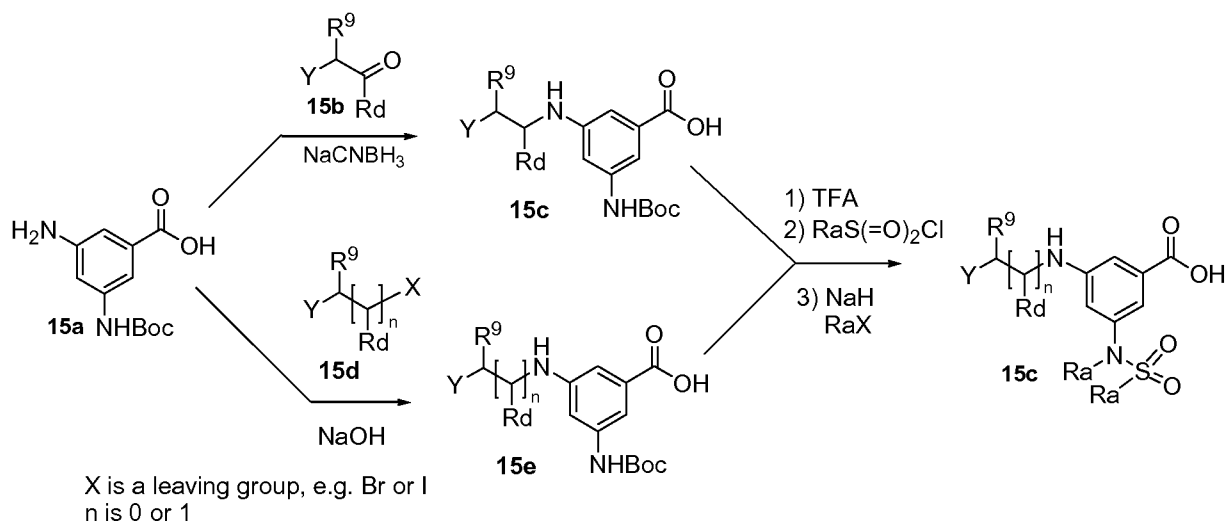
Scheme 14 illustrates a route to acids (10b) useful for the preparation of compounds wherein ring A is phenyl, R⁶ is NRaS(=O)₂CH₃ and E is -O- or -CH(Rd)-O-.



Scheme 14

Alkylation of the phenolic hydroxy group of commercially available 3-tert-butoxycarbonylamino-5-hydroxy-benzoic acid with a desired alkylating agent (14a) in the presence of a base such as NaOH, followed by transforming the acid function into an ester using standard conditions such as treatment with methyl iodide in the presence of a base like cesium carbonate, provides the ester (14b). Removal of the boc group by treatment with acid, for example TFA in dichloromethane, provides the aniline (14c). Subsequent sulphonylation of the amino group using any desired sulphonylating agent such as a sulphonylchloride, for example mesyl chloride or the like in the presence of pyridine in a solvent like dichloromethane or the like, optionally followed by alkylation of the nitrogen which can be effected by a displacement reaction with a desired alkylating agent Ra-X, wherein X is a leaving group such as a halide like bromide or iodide in the presence of a base like sodium hydride or the like, affords sulphone amide derivative (14d). Alternatively, the amino group of aniline (14c) can be reacted with a sulphamoyl chloride instead of a sulphonyl chloride thus affording compounds wherein ring A is substituted with a sulphamoyl amide group, i.e. R⁶ is NRaS(=O)₂NRaRb. Useful sulphamoyl chlorides can be prepared for example as described by W. L. Matier et al. in J. Med. Chem. 1972, 15, 4, 538-541.

Scheme 15 illustrates a route to acids (10b) useful for the preparation of compounds wherein ring A is phenyl, R⁶ is NRaS(=O)₂CH₃ and E is -CH(Rd)-NH- or -NH-.

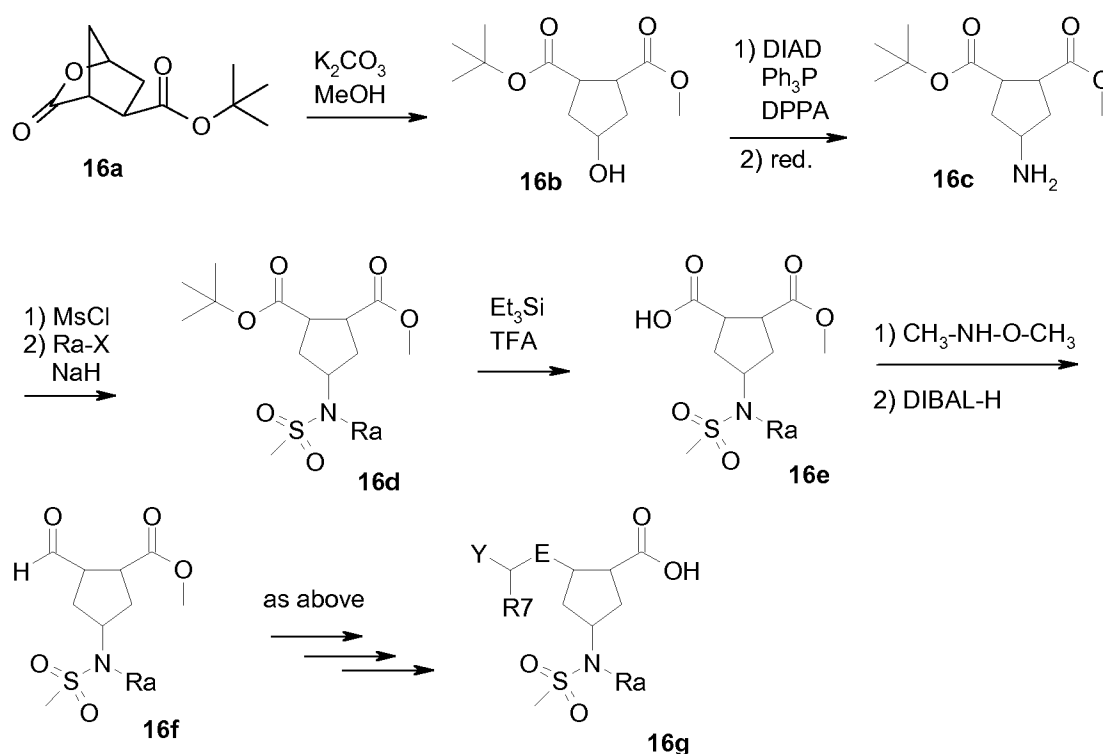


Scheme 15

The diamino benzoic acid derivative (15a) can be achieved for example by removal of the fmoc group from commercially available boc-3-amino-5-(fmoc-amino)benzoic acid using standard conditions such as treatment with piperidine or morpholine or the like. Alkylation of the free

amine effected for example by reaction with a desired aldehyde or ketone (15b) in the presence of a reducing agent like NaCNBH_3 or the like provides the amino derivative (15c). Alternatively, the amine (15a) can be alkylated by reaction with an alkylating agent (15d) wherein X is a leaving group such as a halide like bromo or chloro or a derivative of sulphonic acid like a triflate or mesylate or the like, optionally in the presence of a base, which provides the amine (15e). Alkylation of the acid followed by removal of the boc group, introduction of the sulphone amide group and finally hydrolysis of the ester as described above, then provides the acid (15c).

A typical route to acids (10b) to be coupled to the amine as schematically shown in scheme 10, wherein ring A is a cyclopentane and R^6 is $\text{NRaS(=O)}_2\text{CH}_3$ is shown in Scheme 16.

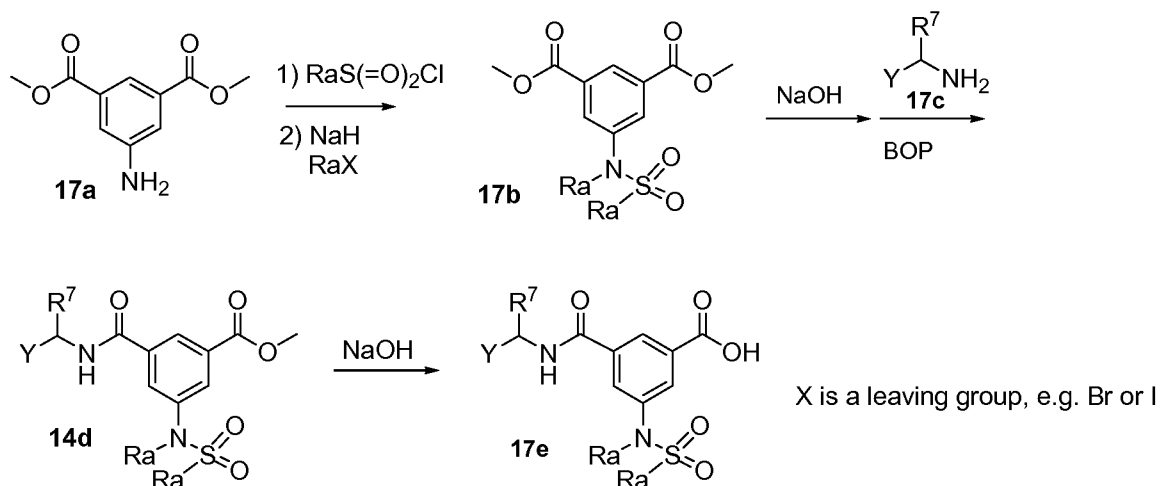


Scheme 16

The bicyclic lactone (16a), prepared from the commercially available diester 3,4-bis(methoxycarbonyl)cyclopentanone as described in WO2005/073195, can be opened by treatment with a base, such as potassium carbonate or lithium hydroxide or the like to provide the diester (16b). Conversion of the hydroxy group into an amino group can then be performed using any convenient procedure whereof many are described in the literature, for example the Mitsunobu conditions may be employed i.e. treatment of the alcohol with diisopropyl azodicarboxylate or any other suitable azodicarboxylate derivative, in combination with triphenylphosphine, followed by reaction with azide for example DPPA, subsequent reduction of the azido group effected for example by catalytic hydrogenation in the presence of a suitable catalyst, for example Lindlar's catalyst or by treatment with triphenylphosphine provides amino derivative (16c). Mesylation of the afforded amine using for example methanesulphonyl chloride

or any other corresponding sulphonylating agent in the presence of pyridine and in a solvent like dichloromethane or the like, followed optionally by alkylation of the nitrogen which can be effected by a displacement reaction with a desired alkylating agent Ra-X, wherein X is a leaving group such as a halide like bromide or iodide, in the presence of a base like sodium hydride or the like, affords sulphone amide derivative (16d). Selective removal of the tert. butyl group by subjecting the diester to acidic conditions like trifluoroacetic acid and triethylsilane in a solvent like methylene chloride then provides the acid (16e). Reduction of the acid for example by a two step process of Weinreb amide formation brought about by reaction with N,O-dimethylhydroxylamine in the presence of sodium hydrogencarbonate and subsequent Dibal reduction, gives the corresponding aldehyde (16f). The afforded aldehyde can then be reacted as described above in order to get various acids which subsequently can be coupled to a desired amino derivative as described above.

Acids (10b') to be used in the coupling with the amine (10a) are available either commercially or in the literature. Acids wherein ring A is phenyl and R⁶ is NRaS(=O)₂CH₃ can be prepared according to the procedure described by Stachel et al. in J. Med. Chem., 47, 2004, 6447-6450 as depicted in scheme 17.



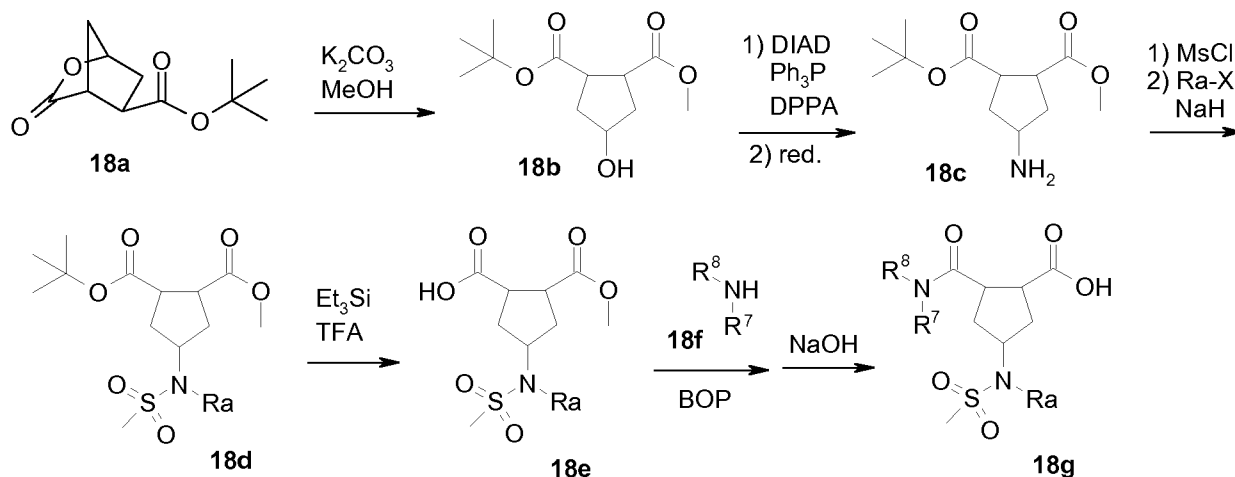
Scheme 17

Sulphonylation of the amino group of commercially available 5-amino isophthalic ester (17a) with a desired sulphonylating agent such as a sulphonyl chloride, for example methane sulphonylchloride, in the presence of pyridine in a solvent like dichloromethane or the like followed optionally by alkylation of the nitrogen effected by a displacement reaction with a desired alkylating agent Ra-X, wherein X is a leaving group such as a halide like bromide or iodide in the presence of a base like sodium hydride or the like, affords sulphone amide derivative (17b). Monohydrolysis of the bis-ester (17b) to the mono acid, for example by treatment with sodium hydroxide, followed by a peptide coupling of the amino derivative (17c)

using any convenient method such as using a reagent like BOP or the like provides the amide (17d). Subsequent hydrolysis of the methyl ester then affords the acid (17e).

Compounds of the invention wherein ring A is substituted with a sulphamoyl amide group, i.e. R^6 is $NRaS(=O)_2NRaRb$, can be prepared according to the above scheme but using sulphamoyl chloride instead of a sulphonyl chloride in the reaction of the amino group of aniline (17c). Useful sulphamoyl chlorides can be prepared for example as described by W. L. Matier et al. in J. Med. Chem. 1972, 15, 4, 538-541.

A typical route to acids 10b' to be used in the preparation of compounds of formula (I) wherein ring A is a cyclopentane, D is $C(=O)NR^7R^8$ and R^6 is $NRaS(=O)_2CH_3$ is shown in Scheme 18.



Scheme 18

The bicyclic lactone (18a), prepared from the commercially available diester 3,4-bis(methoxycarbonyl)cyclopentanone as described in WO2005/073195 can be opened by treatment with a base, such as potassium carbonate or lithium hydroxide or the like to provide the diester (18b). Conversion of the hydroxy group into an amino group can then be performed using any convenient procedure whereof many are described in the literature. For example the Mitsunobu conditions may be employed i.e. treatment of the alcohol with diisopropyl azodicarboxylate or any other suitable azodicarboxylate, in combination with triphenylphosphine, followed by reaction with azide for example DPPA and finally reduction of the azido group effected for example by catalytic hydrogenation in the presence of a suitable catalyst, for example Lindlar's catalyst or by treatment with triphenylphosphine, provides amino derivative (18c). Mesylation of the afforded amine using for example methanesulphonyl chloride or any corresponding sulphonylating agent in the presence of pyridine and in a solvent like dichloromethane or the like followed, if desired, by alkylation of the nitrogen, effected by a displacement reaction with a desired alkylating agent $Ra-X$, wherein X is a leaving group such as a halide like bromide or iodide in the presence of a base like sodium hydride or the like, affords

sulphone amide derivative (18d). Selective removal of the tert. butyl group by subjecting the diester to acidic conditions like trifluoroacetic acid and triethylsilane in a solvent like methylene chloride then provides the acid (18e). Coupling of a desired amine (18f) followed by hydrolysis of the methyl ester as described above then yields the acid (18g).

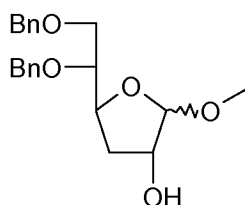
Any functional groups present on any of the constituent compounds used in the preparation of the compounds of the invention are appropriately protected where necessary. For example functionalities on the natural or non-natural amino acids are typically protected as is appropriate in peptide synthesis. Those skilled in the art will appreciate that the selection and use of appropriate protecting groups depend upon the reaction conditions. Suitable protecting groups are described in Greene, "Protective Groups in Organic Synthesis", John Wiley & Sons, New York (1981) and "The Peptides: Analysis, Synthesis, Biology", Vol. 3, Academic Press, New York (1981), the disclosure of which are hereby incorporated by reference.

Detailed Description

Various embodiments of the compounds of the invention and key intermediates towards such compounds will now be described by way of illustration only with reference to the following non-limiting examples.

Example 1

Step a



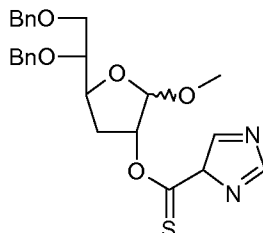
Methyl 5,6-di-O-benzyl-3-deoxy-α-D-glucofuranoside (1aα) and methyl 5,6-di-O-benzyl-3-deoxy-β-D-glucofuranoside (1aβ)

5,6-di-O-benzyl-3-deoxy-1,2-O-isopropylidene-α-D-glucofuranoside (prepared as described by Hanessian et al in Tetrahedron Lett., 1987, 28, 1142) (6.21 g, 16.2 mmol) was dissolved in methanol and cooled in an ice bath (0 °C) and conc. H₂SO₄ (2.69 mL, 48.5 mmol) was slowly added to the solution. The reaction mixture was stirred overnight at room temperature and then neutralized with NaHCO₃ and concentrated. The residue was extracted with ethyl acetate (3 x 50 mL) and H₂O (50 mL). The combined organic layers were dried, filtered and concentrated. Purification by flash column chromatography (toluene/ethyl acetate 3:1) yielded the α- and β-anomers in an 11:2 ratio (1α:1β) as transparent oils (4.69 g, 80% and 0.84 g, 14% for the α- and β-anomers, respectively).

1α: ¹H-NMR (300 MHz, CDCl₃): δ 2.0 (dd, *J* = 6.6, 13.7 Hz, 1H), 2.14 (dq, *J* = 4.7, 13.5 Hz, 1H), 3.30 (s, 3H), 3.57-3.69 (m, 2H), 3.80 (dd, *J* = 2.7, 10.2 Hz, 1H), 4.23 (t, *J* = 4.9 Hz, 1H), 4.39-4.47 (m, 1H), 4.53-4.66 (m, 3H), 4.75-4.81 (m, 2H), 7.22-7.38 (m, 10H); ¹³C-NMR (75.5

MHz, CDCl_3): δ 35.5, 54.9, 71.3, 73.2, 73.7, 76.0, 79.0, 81.8, 109.8, 127.8, 127.9, 128.1, 128.6, 128.7, 138.7, 139.0. $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 1.76-1.88 (m, 1H), 2.20-2.30 (m, 1H), 2.40 (d, $J = 11.8$ Hz, 1H), 3.47 (s, 3H), 3.56 (d, $J = 5.5$ Hz, 1H), 3.68-3.75 (m, 1H), 4.20-4.30 (m, 1H), 4.31-4.40 (m, 1H), 4.54 (s, 2H), 4.57-4.64 (m, 1H), 4.70 (d, $J = 17.9$ Hz, 1H), 4.75-4.85 (m, 1H), 7.23-7.39 (m, 10H); $^{13}\text{C-NMR}$ (75.5 MHz, CDCl_3): δ 32.8, 55.2, 70.4, 72.0, 73.3, 73.4, 76.0, 79.6, 102.5, 127.3, 127.5, 127.6, 127.7, 128.2, 128.3, 128.4, 129.0, 138.1, 138.7.

Step b

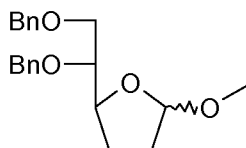


Methyl 5,6-di-O-benzyl-3-deoxy-2-O-(imidazolethiocarbonyl)-D-glucufuranoside (1b)

The alcohol 1a (α - and β -anomeric mixture) (2.24 g, 6.25 mmol) and 1,1'-thiocarbonyldiimidazole (1.67 g, 9.37 mmol) was dissolved in THF (31 mL) and the mixture was refluxed overnight. The crude residue was concentrated and purified by flash column chromatography (toluene/ethyl acetate 3:1) which gave the title compound (2.92 g, 99%).

$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 2.29-2.50 (m, 2H), 3.37 (s, 3H), 3.61-3.73 (m, 2H), 3.76-3.84 (m, 1H), 4.43-4.53 (m, 1H), 4.60 (dd $J = 7.4, 12.1$ Hz, 2H), 4.64 (d, $J = 11.5$ Hz, 1H), 4.80 (d, $J = 11.5$ Hz, 1H), 5.10 (s, 1H), 5.74 (d, $J = 4.1$ Hz, 1H), 7.05-7.07 (m, 1H), 7.27-7.39 (m, 10H), 7.60-7.62 (m, 1H), 8.33-8.34 (m, 1H); $^{13}\text{C-NMR}$ (75.5 MHz, CDCl_3): δ 32.1, 54.9, 70.1, 72.7, 73.4, 79.2, 80.8, 86.1, 106.0, 117.7, 127.7, 127.5, 127.6, 128.2, 128.3, 130.9, 136.7, 138.0, 138.3, 183.0. MS m/z 469.3 $[(M+H)^+]$ calcd for $\text{C}_{25}\text{H}_{29}\text{N}_2\text{O}_5\text{S}^+$ 469.18].

Step c



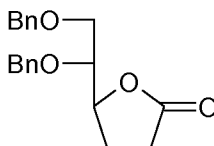
Methyl 5,6-di-O-benzyl-2,3-dideoxy-D-glucufuranoside (1c)

Tributyltin hydride (5.18 g, 17.79 mmol) was dissolved in dry toluene (35 mL) under N_2 -atmosphere and refluxed for 5 minutes. Compound 1b (5.56 g, 11.86 mmol) dissolved in dry toluene (35 mL) was added drop wise to the solution during 30 min. The combined solution was stirred at 110 $^\circ\text{C}$ and after 2 hours the mixture was concentrated. Purification by flash column chromatography (toluene/ethyl acetate 18:1) gave the title compound (2.94 g, 72%).

$^1\text{H-NMR}$ (300 MHz, CD_3OD): δ 1.87-1.98 (m, 4H), 3.25 (s, 3H), 3.55-3.66 (m, 2H), 3.81 (dd, $J = 2.2, 9.9$ Hz, 1H), 4.10 (dt, $J = 6.5, 8.2$ Hz, 1H), 4.45 (s, 1H), 4.61 (d, $J = 11.6$ Hz, 1H), 4.74 (d, $J = 11.6$ Hz, 1H), 4.80 (s, 1H), 4.92 (t, $J = 2.4$ Hz, 1H), 7.24-7.38 (m, 10H); $^{13}\text{C-NMR}$ (75.5

MHz, CD₃OD): δ 27.4, 33.5, 55.0, 71.8, 73.8, 74.4, 80.7, 82.7, 106.7, 128.6, 128.7, 128.8, 129.0, 129.2, 129.3, 139.8, 140.0. MS m/z 365.4 [(M+Na)⁺ calcd for C₂₁H₂₆NaO₄⁺ 365.17].

Step d

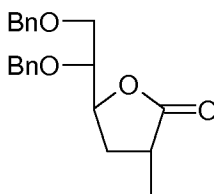


5,6-Di-O-benzyl-2,3-dideoxy-D-glucono-1,4-lactone (1d)

The methyl-glycoside 1c (2.79 g, 8.16 mmol) was dissolved in dry CH₂Cl₂ (50 mL) and cooled to 0 °C in an ice bath. BF₃OEt (0.52 mL, 2.04 mmol) and *m*-chloroperbenzoic acid (2.20 g, 9.79 mmol) were added to the solution and the mixture was kept at 0 °C for 2 hours before it was allowed to reach room temperature. After 4 hours the mixture was concentrated and extracted with ethyl acetate (3 x 50 mL) and saturated NaHCO₃ (50 mL). The combined organic layers were dried, filtered and concentrated. The crude residue was purified by flash column chromatography (toluene/ethyl acetate 18:1) to yield the title lactone (2.66 g, quant.) as white crystals.

¹H-NMR (300 MHz, CD₃OD): δ 2.14-2.25 (m, 2H), 2.44-2.50 (m, 2H), 3.60 (d, J = 5.3 Hz, 2H), 3.86 (dt, J = 3.6, 5.3 Hz, 1H), 4.49 (d, J = 12.0 Hz, 1H), 4.53 (d, J = 12.0 Hz, 1H), 4.56 (d, J = 11.5 Hz, 1H), 4.67 (d, J = 11.5 Hz, 1H), 4.68-4.75 (m, 1H), 7.25-7.34 (m, 10H); ¹³C-NMR (75.5 MHz, CD₃OD): δ 23.2, 29.3, 69.9, 74.3, 74.5, 80.0, 81.9, 128.7, 128.8, 128.9, 129.0, 129.3, 129.4, 139.4, 139.6, 180.2. MS m/z 327.3 [(M+H)⁺ calcd for C₂₀H₂₃O₄⁺ 327.39].

Step e



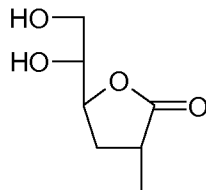
5,6-Di-O-benzyl-2,3-dideoxy-2-methyl-D-glucono-1,4-lactone (1e)

The lactone 1d (1.31 g, 4.01 mmol) was dissolved in dry THF (40 mL) and cooled to -78 °C. After 15 min a solution of 2.0 M LDA (2.47 mL, 4.01 mmol) was added drop wise. After 30 min at -78 °C methyl iodide (2.5 mL, 40.1 mmol) dissolved in dry THF (5 mL) was slowly added. After further 2 hours at -78 °C the reaction was allowed to attain room temperature and quenched with saturated ammonium chloride (4 mL). The mixture was diluted with H₂O (50 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried, filtered and concentrated. Purification by flash column chromatography (toluene/ethyl acetate 18:1) gave the title compound (899 mg, 66%).

¹H-NMR (300 MHz, CDCl₃): δ 1.23 (d, J = 7.42, 3H), 1.78-1.91 (m, 1H), 2.43-2.53 (m, 1H), 2.66-2.81 (m, 1H), 3.53-3.65 (m, 2H), 3.81-3.90 (m, 1H), 4.47-4.73 (m, 5H), 7.23-7.42 (m, 10H); ¹³C-NMR (75.5 MHz, CDCl₃): δ 16.2, 30.4, 34.0, 68.9, 73.4, 73.5, 77.5, 78.5, 127.6,

127.7, 127.8, 127.9, 128.3, 128.4, 137.7, 137.8, 180.3. MS m/z 341.4 $[(M+H)^+]$ calcd for $C_{21}H_{25}O_4^+ 341.17$.

Step f

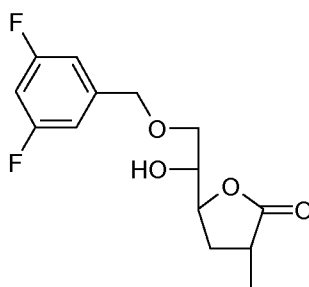


2,3-Dideoxy-2-methyl-D-glucono-1,4-lactone (1f)

Compound 1e (174 mg, 0.51 mmol) was dissolved in ethanol (2.5 mL, 95%) and Pd-C (~5 mg) was added. The reaction was preformed under H_2 -atmosphere, which was refilled until the reaction was complete. The mixture was filtered though a pad of celite and concentrated. This gave after co-concentration with methanol and toluene the title diol (83 mg, quant.) as white crystals.

^1H -NMR (300 MHz, CD_3OD): δ 1.23 (d, $J = 7.4$ Hz, 3H), 1.85-1.98 (m, 1H), 2.45-2.57 (m, 1H), 2.72-2.86 (m, 1H), 3.52-3.59 (m, 2H), 3.74-3.84 (m, 1H), 4.53-4.61 (m, 1H); ^{13}C -NMR (75.5 MHz, CD_3OD): δ 15.3, 30.0, 34.3, 62.7, 72.4, 78.7, 181.8. HRMS m/z 183.0631 $[(M+Na)^+]$ calcd for $C_7H_{12}NaO_4^+ 183.0628$.

Step g



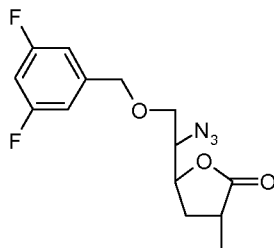
2,3-Dideoxy-6-O-(3,5-difluorobenzyl)-2-methyl-D-glucono-1,4-lactone (1g)

The diol 1f (201 mg, 1.25 mmol) and dibutyltin oxide (405 mg, 1.63 mmol) was dissolved in toluene (7 mL). The mixture was refluxed for 5 hours before the temperature was lowered to 90 °C and tetrabutylammonium bromide (464 mg, 1.44 mmol) and 3,5-difluoro benzyl bromide (0.186 ml, 1.44 mmol) were added. The mixture was allowed to stir at 90 °C overnight and thereafter concentrated. Purification by flash column chromatography (toluene/ethyl acetate 6:1) gave the title compound (291 mg, 81%) as an colourless oil.

^1H -NMR (300 MHz, CD_3OD): δ 1.22 (d, $J = 7.3$ Hz, 3H), 1.92 (dt, $J = 8.6, 13.0$ Hz, 1H), 2.52 (ddd, $J = 3.6, 9.5, 13.0$ Hz, 1H), 2.79 (ddq, $J = 7.3, 8.6, 9.5$ Hz, 1H), 3.54 (dd, $J = 5.7, 10.8$ Hz, 1H), 3.58 (dd, $J = 5.0, 10.8$ Hz, 1H), 3.95 (dt, $J = 4.7, 5.7$ Hz, 1H), 4.55 (s, 2H), 4.59 (ddd, $J = 3.6, 4.7, 8.6$ Hz, 1H), 6.78-6.86 (m, 1H), 6.92-7.00 (m, 2H); ^{13}C -NMR (75.5 MHz, CD_3OD): δ 16.4, 31.3, 35.3, 71.9, 72.5, 72.9, 79.7, 103.4 (t, $J_{CF} = 25.8$ Hz), 110.9 (d, $J_{CF} = 25.5$ Hz, 2C),

144.4 (t, $J_{\text{CF}} = 8.9$ Hz), 164.3 (d, $J_{\text{CF}} = 247.5$ Hz), 164.5 (d, $J_{\text{CF}} = 247.5$ Hz), 182.8. MS m/z 287.2 [(M+H)⁺ calcd for C₁₄H₁₇F₂O₄⁺ 287.11].

Step h

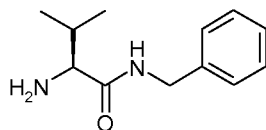


5-Azido-2,3,5-trideoxy-6-O-(3,5-difluorobenzyl)-2-methyl-L-iodono-1,4-lactone (1h)

The alcohol 1g (150 mg, 0.53 mmol) was dissolved in dry THF (5 mL) and cooled to -15 °C (ice/acetone 1:1). Triphenylphosphine (207 mg, 0.79 mmol) and diisopropyl azodicarboxylate (0.156 mL, 0.79 mmol) were added. After 10 min the mixture was allowed to reach 0 °C and diphenylphosphoryl azide (217 mg, 0.79 mmol) was added. After 30 min of stirring at 0 °C the mixture was allowed to attain room temperature and was stirred overnight. The solvent was evaporated, and the crude mixture was purified by flash column chromatography (toluene/ethyl acetate 18:1) which gave the title compound (152 mg, 93%) as a colourless oil.

¹H-NMR (300 MHz, CD₃OD): δ 1.22 (d, $J = 7.4$ Hz, 3H), 2.05 (dt, $J = 8.4, 13.2$ Hz, 1H), 2.42 (ddd, $J = 4.1, 9.6, 13.2$ Hz, 1H), 2.83 (ddq, $J = 7.4, 8.4, 9.6$ Hz, 1H), 3.73 (dd, $J = 8.0, 9.9$ Hz, 1H), 3.79 (dd, $J = 4.0, 9.9$ Hz, 1H), 3.80-3.88 (m, 1H), 4.58 (s, 2H), 4.65 (dt, $J = 4.1, 8.4$ Hz, 1H), 6.77-6.86 (m, 1H), 6.91-6.99 (m, 2H); ¹³C-NMR (75.5 MHz, CD₃OD): 16.4, 33.5, 34.9, 65.4, 71.6, 72.8, 72.9, 103.6 (t, $J_{\text{CF}} = 25.8$ Hz), 110.9 (d, $J_{\text{CF}} = 25.2$ Hz, 2C), 143.9 (t, $J_{\text{CF}} = 8.9$ Hz), 164.4 (d, $J_{\text{CF}} = 247.2$ Hz), 164.6 (d, $J_{\text{CF}} = 247.2$ Hz), 182.0.

Step i



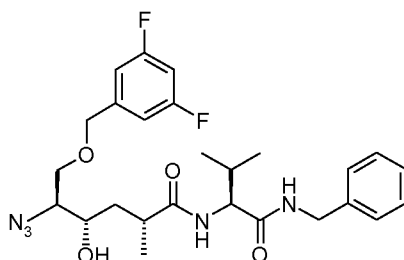
(S)-2-amino-N-benzyl-3-methyl-butamide (1i)

Boc-Val-OH (500 mg, 2.30 mmol), benzylamine (321 mg, 2.99 mmol) and DIPEA (0.52 mL, 2.99 mmol) were dissolved in DMF (12 mL) and cooled (0 °C). HATU (137 mg, 2.99 mmol) was added and the mixture was allowed to attain room temperature and was stirred for 2 hours. The DMF was removed under reduced pressure and the crude residue was purified by flash column chromatography (toluene/ethyl acetate 6:1) to yield ((S)-1-benzylcarbamoyl-2-methyl-propyl)-carbamic acid *tert*-butyl ester (666 mg, 95 %).

¹H-NMR (CDCl₃): δ 0.94 (m, 6H), 1.42 (s, 9H), 2.18 (m, 1H), 3.90 (m, 1H), 4.42 (m, 2H), 5.10 (s, 1H), 6.43 (s, 1H), 7.30 (m, 5H); ¹³C NMR: δ 19.0, 28.1, 30.8, 42.9, 59.9, 79.2, 126.9, 127.3, 128.2, 138.1, 155.9, 172.0.

The Boc-derivative (666 mg, 2.17 mmol) was dissolved in CH_2Cl_2 (7.3 ml) and cooled to 0 °C in an ice bath. Et_3SiH (0.52 mL, 3.27 mmol) and TFA (3.5 mL) was added and the mixture were allowed to attain room temperature. After 3 hours the solution was co-evaporated with toluene (3 x 20 mL), which gave the TFA salt of the title compound as a white powder (448 mg, quant.). $^1\text{H-NMR}$ (CDCl_3): δ 0.94 (m, 6H), 2.0-2.15 (m, 1H), 3.90 (d, $J = 6.32$, 1H), 4.15-4.40 (m, 2H), 7.05-7.15 (m, 5H), 8-8.15 (m, 3H); $^{13}\text{C-MNR}$ (CDCl_3): δ 17.7, 17.9, 30.3, 43.6, 59.1, 125.3, 127.4, 127.6, 128.2, 128.6, 129.0, 168.7.

Step j

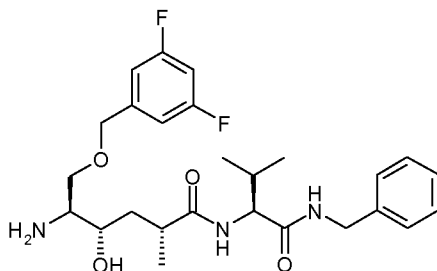


(2R,4S,5S)-5-Azido-6-(3,5-difluorobenzyloxy)-4-hydroxy-2-methyl-hexanoic acid ((S)-1-benzylcarbamoyl-2-methyl-propyl)-amide (1j)

The title compound (133 mg, 54%) was synthesized by opening the lactone 1h (141 mg, 0.51 mmol) with the amine 1g according to the method described in example 2 step c.

$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 0.90-0.99 (m, 6H), 1.16 (d, $J = 7.01$ Hz, 3H), 1.67-1.77 (m, 2H), 2.06-2.19 (m, 1H), 2.58-2.72 (m, 1H), 3.05 (bs, 1H), 3.39-3.47 (m, 1H), 3.64-3.78 (m, 3H), 4.17-4.24 (m, 1H), 4.32-4.50 (m, 2H), 4.52 (s, 2H), 6.30-6.38 (m, 1H), 6.41-6.49 (m, 1H), 6.67-6.77 (m, 1H), 6.81-6.89 (m, 2H), 7.20-7.36 (m, 5H); $^{13}\text{C-NMR}$ (75.5 MHz, CDCl_3): δ 17.0, 17.2, 17.9, 29.7, 36.5, 37.2, 42.1, 58.3, 65.1, 68.1, 69.8, 70.9, 101.5 (t, $J_{\text{CF}} = 25.2$ Hz), 108.9 (d, $J_{\text{CF}} = 25.2$ Hz, 2C), 126.2, 126.5, 127.5, 137.5, 141.9 (t, $J_{\text{CF}} = 8.8$ Hz), 162.4 (d, $J_{\text{CF}} = 251.2$ Hz), 162.6 (d, $J_{\text{CF}} = 251.2$ Hz), 171.5, 176.7. MS m/z 518.4 $[(\text{M}+\text{H})^+]$ calcd for $\text{C}_{26}\text{H}_{34}\text{F}_2\text{N}_5\text{O}_4^+$ 518.26].

Step k



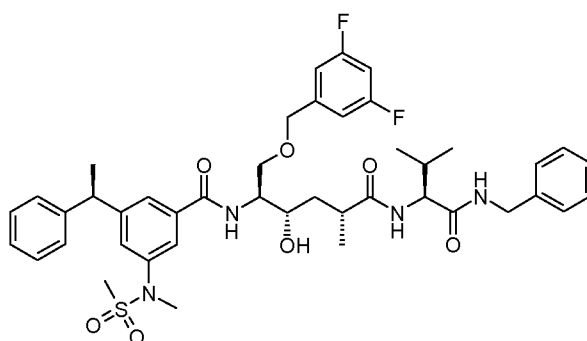
(2R,4S,5S)-5-Amino-6-(3,5-difluorobenzyloxy)-4-hydroxy-2-methyl-hexanoic acid ((S)-1-benzylcarbamoyl-2-methyl-propyl)-amide (1k)

The azide 1j (42 mg, 0.08 mmol) and triphenyl phosphine (32 mg, 0.12 mmol) was dissolved in MeOH (4 mL). Three drops of water were added and the reaction mixture was stirred overnight

at room temperature. Removal of the solvent and purification by LC/MS (50% MeOH, 6 min ramp time to 100% MeOH, 10 min) gave the amine as white crystals (34.8 mg, 87%).

$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 0.88-1.01 (m, 6H), 1.15 (d, $J = 7.01$ Hz, 3H), 1.42-1.54 (m, 1H), 1.85-1.97 (m, 1H), 1.99-2.11 (m, 1H), 2.69-2.84 (m, 1H), 3.09-3.19 (m, 1H), 3.53-3.73 (m, 3H), 4.16 (d, $J = 7.76$ Hz, 1H), 4.37 (d, $J = 2.68$ Hz, 2H), 4.56 (s, 2H), 6.80-6.90 (m, 1H), 6.95-7.05 (m, 2H), 7.20-7.34 (m, 5H); $^{13}\text{C-NMR}$ (75.5 MHz, CDCl_3): δ 17.9, 18.1, 18.6, 30.6, 37.1, 37.8, 42.8, 56.2, 59.4, 67.0, 68.4, 71.9, 102.5 (t, $J_{\text{CF}} = 26.1$ Hz), 110.1 (d, $J_{\text{CF}} = 25.5$ Hz, 2C), 127.0, 127.4, 128.3, 138.6, 142.6 (t, $J_{\text{CF}} = 8.9$ Hz), 163.3 (d, $J_{\text{CF}} = 247.4$ Hz), 163.5 (d, $J_{\text{CF}} = 247.4$ Hz), 172.4, 177.5. MS m/z 477.9 $[(\text{M}+\text{H})^+]$ calcd for $\text{C}_{25}\text{H}_{34}\text{F}_2\text{N}_3\text{O}_4^+$ 478.3].

Step 1



N-[(1*S*,2*S*,4*R*)-4-((*S*)-1-Benzylcarbamoyl-2-methylpropylcarbamoyl)-1-(3,5-difluorobenzyloxymethyl)-2-hydroxypentyl]-5-(methanesulphonyl-methylamino)-*N'*-((*R*)-1-phenyl-ethyl)-isophthalamide (11)

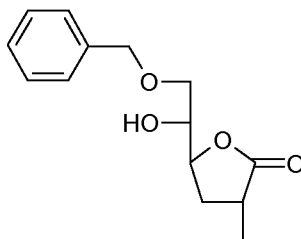
The amine 1k (17 mg, 0.034 mmol) was dissolved in DMF (2 mL) and cooled to 0 °C. 5-Methanesulphonyl-methyl-amino)-*N'*-(1-phenyl-ethyl)-isophthalic acid (prepared as described in J. Med. Chem., 47, 2004, 6447-6450) (25 mg, 0.064 mmol), diisopropylethylamine (12 μL , 0.067 mmol) and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (25 mg, 0.067 mmol) were added and the reaction was stirred at room temperature overnight. The crude product was purified with LC/MS (50% MeOH, 15 min ramp time to 100% MeOH, 10 min) which gave the title compound (10 mg, 35%) as white crystals after lyophilization.

$^1\text{H-NMR}$ (300 MHz, CD_3OD): δ 0.86 (d, $J = 6.8$ Hz, 3H), 0.87 (d, $J = 6.8$ Hz, 3H), 1.14 (d, $J = 6.9$ Hz, 3H), 1.48-1.57 (m, 1H), 1.58 (d, $J = 7.0$ Hz, 3H), 1.84-2.05 (m, 2H), 2.70-2.81 (m, 1H), 2.95 (s, 3H), 3.36 (s, 3H), 3.68 (dd, $J = 7.0, 9.8$ Hz, 1H), 3.77 (dd, $J = 6.3, 9.8$ Hz, 1H), 3.85-3.91 (m, 1H), 4.14 (d, $J = 7.7$ Hz, 1H), 4.32-4.40 (m, 1H), 4.33 (d, $J = 15.0$ Hz, 1H), 4.39 (d, $J = 15.0$ Hz, 1H), 4.56 (s, 2H), 5.25 (q, $J = 7.1$ Hz, 1H), 6.76-6.84 (m, 1H), 6.91-6.96 (m, 2H), 7.19-7.42 (m, 10H), 8.02-8.07 (m, 2H), 8.27 (t, $J = 1.58$ Hz, 1H); $^{13}\text{C-NMR}$ (75.5 MHz, CDCl_3): δ 17.6, 18.3, 19.3, 21.7, 30.8, 35.5, 37.7, 37.9, 38.5, 43.5, 49.7, 52.9, 59.0, 69.7, 71.2, 72.3, 103.2 (t, $J_{\text{CF}} = 25.2$ Hz), 110.0 (d, $J_{\text{CF}} = 24.9$ Hz, 2C), 124.2, 126.2, 127.5, 127.5, 127.6, 127.8, 128.0, 128.6, 128.7, 135.3, 135.9, 137.8, 141.6 (t, $J_{\text{CF}} = 8.6$ Hz), 142.3, 142.9, 163.0 (d, $J_{\text{CF}} = 249.4$ Hz).

Hz), 163.2 (d, $J_{CF} = 249.4$ Hz), 164.6, 166.0, 171.2, 176.9. HRMS m/z 850.3675 $[(M+H)^+]$ calcd for $C_{44}H_{54}F_2N_5O_8S^+$ 850.3656].

Example 2

Step a

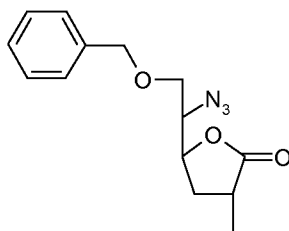


2,3-Dideoxy-6-O-benzyl-2-methyl-D-glucono-1,4-lactone (2a)

The title compound (413 mg, 79%) was synthesized from the lactone 1f (336 mg, 2.09 mmol) according to the method described for the preparation of compound 8, but using benzyl bromide was instead of 3,5-difluoro benzyl bromide.

^1H -NMR (300 MHz, $CDCl_3$): δ 1.23 (d, $J = 7.28$ Hz, 3H), 1.86 (dt, $J = 8.3, 13.0$ Hz, 1H), 2.49 (ddd, $J = 3.9, 9.4, 13.0$ Hz, 1H), 2.72 (ddq, $J = 7.3, 8.5, 9.4$, 1H), 2.94 (bs, 1H), 3.51 (dd, $J = 5.2, 9.8$ Hz, 1H), 3.58 (dd, $J = 4.5, 9.8$ Hz, 1H), 3.90 (dt, $J = 4.5, 5.6$ Hz, 1H), 4.47 (ddd, $J = 3.9, 5.6, 8.3$ Hz, 1H), 4.51 (d, $J = 11.8$ Hz, 1H), 4.56 (d, $J = 11.8$ Hz, 1H), 7.28-7.38 (m, 5H); ^{13}C -NMR (75.5 MHz, $CDCl_3$): δ 16.0, 30.6, 33.7, 70.5, 70.7, 73.4, 77.5, 127.7, 127.8, 128.4, 137.5, 180.3.

Step b

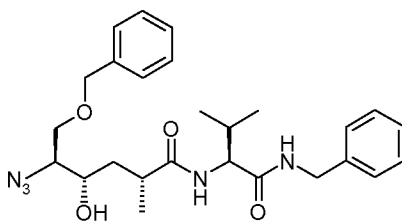


5-Azido-2,3,5-trideoxy-6-O-benzyl-2-methyl-L-idono-1,4-lactone (2b)

The title compound (403 mg, 90%) was synthesized from compound (408 mg, 1.63 mmol) according to the method described for the preparation of 1h.

^1H -NMR (300 MHz, CD_3OD): δ 1.22 (d, $J = 7.4$ Hz, 3H), 2.02 (dt, $J = 8.4, 13.1$ Hz, 1H), 2.39 (ddd, $J = 4.1, 9.6, 13.1$ Hz, 1H), 3.83 (ddq, $J = 7.4, 8.4, 9.6$ Hz, 1H), 3.67-3.82 (m, 3H), 4.51-4.66 (m, 3H), 7.26-7.38 (m, 5H); ^{13}C -NMR (75.5 MHz, CD_3OD): δ 16.4, 33.5, 35.0, 65.4, 71.1, 74.4, 78.2, 128.8, 129.4, 139.2, 182.1.

Step c

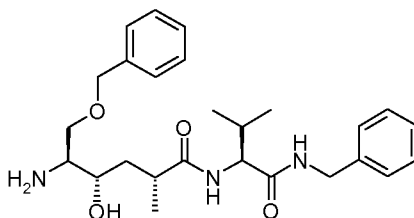


(2R,4S,5S)-5-Azido-6-benzyloxy-4-hydroxy-2-methyl-hexanoic acid ((S)-1-benzylcarbamoyl-2-methyl-propyl)-amide (2c)

The lactone 2b (59 mg, 0.21 mmol) and (S)-2-amino-N-benzyl-3-methyl-butylamide (1i) (71 mg, 0.34 mmol) were dissolved in dry THF (2 mL). DIPEA (74 μ L, 0.43 mmol) and 2-hydroxypyridine (81 mg, 0.86 mmol) were added and the mixture was refluxed for 4 days. Purification by HPLC chromatography (80% MeOH, 20% H₂O + 0.2% TFA) gave the title compound as a colourless oil (37 mg, 36%).

¹H-NMR (300 MHz, CD₃OD): δ 0.92 (d, J = 6.8 Hz, 3H), 0.94 (d, J = 6.8 Hz, 3H), 1.13 (d, J = 7.0 Hz, 3H), 1.55 (ddd, J = 3.9, 10.2, 13.9 Hz, 1H), 1.82 (ddd, J = 2.9, 10.4, 13.9 Hz, 1H), 1.98-2.11 (m, 1H), 2.70 (ddd, J = 3.9, 7.0, 10.4 Hz, 1H), 3.42-3.49 (m, 1H), 3.59 (ddd, J = 2.9, 3.9, 10.2 Hz, 1H), 3.64 (dd, J = 7.2, 10.1 Hz, 1H), 3.70 (dd, J = 4.6, 10.1 Hz, 1H), 4.12-4.19 (m, 1H), 4.35 (dd, J = 5.8, 15.0 Hz, 1H), 4.55 (dd, J = 6.0, 15.0 Hz, 1H), 4.55 (s, 2H), 7.20-7.37 (m, 10H); ¹³C-NMR (75.5 MHz, CD₃OD): δ 19.0, 19.1, 19.8, 31.8, 38.5, 39.2, 44.1, 60.7, 67.2, 70.3, 71.4, 74.3, 128.2, 128.6, 128.7, 128.8, 129.4, 129.5, 139.4, 139.8, 173.8, 179.0. MS m/z 482.4 [(M+H)⁺ calcd for C₂₆H₃₆N₅O₄⁺ 482.6].

Step d

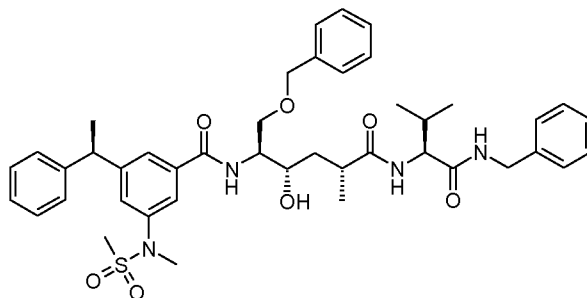


(2R,4S,5S)-5-Amino-6-benzyloxy-4-hydroxy-2-methyl-hexanoic acid ((S)-1-benzylcarbamoyl-2-methyl-propyl)-amide (2d)

The title compound (35 mg, quant.) was synthesized by reduction of the azide of compound 2c (37 mg, 0.077 mmol) according to the method described for the preparation of compound 1k.

¹H-NMR (300 MHz, CD₃OD): δ 0.91 (d, J = 6.8 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H), 1.11 (d, J = 7.0 Hz, 3H), 1.48 (ddd, J = 4.1, 10.2, 13.9 Hz, 1H), 1.84 (ddd, J = 3.3, 10.3, 13.9 Hz, 1H), 1.98-2.10 (m, 1H), 2.63-2.81 (m, 2H), 3.43 (dd, J = 6.3, 9.4 Hz, 1H), 3.50-3.58 (m, 2H), 4.16 (d, J = 7.8 Hz, 1H), 4.34 (d, J = 14.9 Hz, 1H), 4.40 (d, J = 14.9 Hz, 1H), 4.50 (s, 2H), 7.23-7.34 (m, 10H); ¹³C-NMR (75.5 MHz, CD₃OD): δ 19.0, 19.8, 31.8, 38.6, 39.3, 44.0, 56.4, 60.5, 70.6, 72.9, 74.3, 128.2, 128.6, 128.8, 128.9, 129.4, 129.5, 139.6, 139.8, 173.7, 179.1. MS m/z 456.4 [(M+H)⁺ calcd for C₂₆H₃₇N₃O₄⁺ 456.3].

Step e



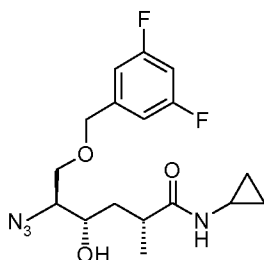
N-[(1*S*,2*S*,4*R*)-4-((*S*)-1-Benzylcarbamoyl-2-methyl-propylcarbamoyl)-1-benzyloxymethyl-2-hydroxy-pentyl]-5-(methanesulphonyl-methyl-amino)-*N'*-((*R*)-1-phenyl-ethyl)-isophthalamide (2e)

The title compound (27 mg, 77%) was synthesized by coupling of amine 2d (20 mg, 0.044 mmol) to 5-methanesulphonyl-methyl-amino)-*N'*-(1-phenyl-ethyl)-isophthalic acid according to the method described for the preparation of compound 11.

¹H-NMR (300 MHz, CD₃OD): δ 0.92 (d, 6.8 Hz, 3H), 0.93 (d, 6.8 Hz, 3H), 1.18 (d, *J* = 6.9 Hz, 3H), 1.51-1.62 (m, 1H), 1.61 (d, *J* = 7.1 Hz, 3H), 1.89-1.99 (m, 1H), 2.00-2.10 (m, 1H), 2.74-2.84 (m, 1H), 3.00 (s, 3H), 3.40 (s, 3H), 3.69-3.82 (m, 2H), 3.90-3.97 (m, 1H), 4.19 (d, *J* = 7.7 Hz, 1H), 4.38 (d, *J* = 15.0 Hz, 1H), 4.38-4.44 (m, 1H), 4.44 (d, *J* = 15.0 Hz, 1H), 4.57 (d, *J* = 11.9 Hz, 1H), 4.62 (d, *J* = 11.9 Hz, 1H), 5.30 (q, *J* = 7.0 Hz, 1H), 7.25-7.48 (m, 15 H), 8.07-8.11 (m, 2H), 8.31 (t, *J* = 1.58 Hz, 1H); ¹³C-NMR (75.5 MHz, CD₃OD): δ 18.4, 19.0, 19.8, 22.1, 31.9, 36.0, 38.4, 38.5, 39.5, 44.0, 50.9, 55.0, 60.4, 69.7, 70.4, 74.1, 126.0, 127.3, 128.2, 128.6, 128.7, 128.9, 129.4, 129.5, 129.6, 137.2, 137.4, 139.5, 139.8, 143.8, 145.0, 167.7, 168.9, 173.7, 179.0. HRMS *m/z* 814.3847 [(*M*+H)⁺ calcd for C₄₄H₅₆N₅O₈S⁺ 814.3844].

Example 3

Step a

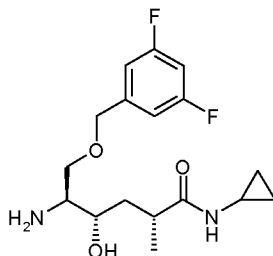


(2*R*,4*S*,5*S*)-5-Azido-6-(3,5-difluorobenzoyloxy)-4-hydroxy-2-methyl-hexanoic acid cyclopropylamide (3a)

Cyclopropylamine (49 μL, 0.71 mmol) was dissolved in CH₂Cl₂ (2 mL) and 2 M Me₃Al (710 μL, 1.41 mmol) was added drop wise to the solution. The reaction was stirred for 15 min before the lactone 1h (110 mg, 0.35 mmol) dissolved in CH₂Cl₂ (1 mL) was added slowly. The reaction mixture was stirred at 40 °C for 1 hour and then quenched with 1M HCl to pH 5. The crude mixture was extracted with H₂O (10 ml) and ethyl acetate (3 x 10 mL). The combined organic layers were dried, filtered and concentrated. Purification by flash column chromatography (toluene/ethyl acetate 2:1) gave the title compound (69 mg, 53%) as an colourless oil.

$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 0.98 (d, $J = 6.9$ Hz, 3H), 1.17 (s, 2H), 1.25 (s, 2H), 1.51-1.62 (m, 1H), 1.64-1.78 (m, 2H), 2.38-2.48 (m, 1H), 2.43 (bs, 1H), 3.54 (ddd, $J = 3.6, 4.7, 6.6$ Hz, 1H), 3.75 (dd, $J = 4.7, 9.9$ Hz, 1H), 3.79 (dd, 6.6, 9.9 Hz, 1H), 3.86-3.92 (m, 1H), 4.56 (s, 2H), 6.68-6.77 (m, 1H), 6.84-6.92 (m, 2H); $^{13}\text{C-NMR}$ (75.5 MHz, CDCl_3): δ 16.0, 25.6, 29.1, 36.8, 40.4, 65.1, 69.7, 71.4, 72.3, 73.3, 103.0 (t, $J_{\text{CF}} = 25.2$ Hz), 109.9 (d, $J_{\text{CF}} = 25.2$ Hz, 2C), 141.8 (t, $J_{\text{CF}} = 8.9$ Hz), 163.0 (d, $J_{\text{CF}} = 249.0$ Hz), 163.2 (d, $J_{\text{CF}} = 249.0$ Hz), 184.7.

Step b

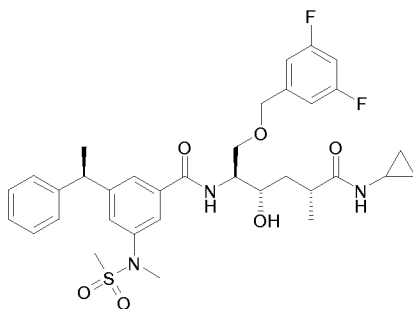


(2R,4S,5S)-5-Amino-6-(3,5-difluorobenzoyloxy)-4-hydroxy-2-methyl-hexanoic acid cyclopropylamide (3b)

The title compound (58 mg, 92%) was prepared by reduction of the azide of compound 3a (69 mg, 0.19 mmol) according to the method described for the preparation of compound 17.

$^1\text{H-NMR}$ (300 MHz, CD_3OD): δ 0.99 (d, $J = 6.9$ Hz, 3H), 1.05-1.12 (m, 1H), 1.11 (s, 2H), 1.19 (s, 2H), 1.23-1.35 (m, 2H), 1.58-1.66 (m, 1H), 1.83-1.92 (m, 1H), 3.67-3.73 (m, 2H), 3.81-3.88 (m, 1H), 4.59 (s, 2H), 6.82-6.90 (m, 1H), 6.97-7.04 (m, 2H); $^{13}\text{C-NMR}$ (75.5 MHz, CD_3OD): δ 17.1, 24.8, 28.8, 37.5, 42.2, 56.9, 68.8, 69.3, 73.1, 73.9, 103.7 (t, $J_{\text{CF}} = 25.7$ Hz), 110.3 (d, $J_{\text{CF}} = 25.2$ Hz, 2C), 144.0 (t, $J_{\text{CF}} = 8.8$ Hz), 163.5 (d, $J_{\text{CF}} = 247.2$ Hz), 163.7 (d, $J_{\text{CF}} = 247.2$ Hz), 178.4.

Step c



N-((1S,2S,4R)-1-Benzoyloxymethyl-4-cyclopropylcarbamoyl-2-hydroxy-pentyl)-5-(methanesulphonyl-methyl-amino)-N'-(R)-1-phenyl-ethyl-isophthalamide (3c)

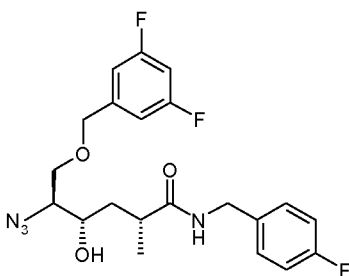
The title compound (13 mg, 17%) was synthesized by coupling the amine 3b (36 mg, 0.105 mmol) to 5-methanesulphonyl-methyl-amino)-N'-(1-phenyl-ethyl)-isophthalic acid according to the method described for the preparation of compound 11. Compound 31 was collected as white powder after lyophilization.

$^1\text{H-NMR}$ (300 MHz, CD_3OD): δ 0.99 (d, $J = 6.9$ Hz, 3H), 1.11 (d, $J = 11.1$ Hz, 4H), 1.23-1.33 (m, 2H), 1.58 (d, $J = 7.1$ Hz, 3H), 1.59-1.68 (m, 1H), 1.83-1.92 (m, 1H), 2.96 (s, 3H), 3.37 (s,

3H), 3.68 (dd, $J = 6.8, 9.6$ Hz, 1H), 3.77 (dd, $J = 6.7, 9.6$ Hz, 1H), 4.01-4.09 (m, 1H), 4.41 (dt, $J = 2.4, 6.6$ Hz, 1H), 4.55 (d, $J = 12.9$ Hz, 1H), 4.61 (d, $J = 12.9$ Hz, 1H), 5.25 (q, $J = 7.1$ Hz, 1H), 6.77-6.82 (m, 1H), 6.90-6.99 (m, 2H), 7.22-7.44 (m, 5H), 8.02 (d, $J = 1.6$ Hz, 2H), 8.21 (t, $J = 1.6$ Hz, 1H); ^{13}C -NMR (75.5 MHz, CD_3OD): δ 15.7, 22.1, 26.3, 27.4, 35.9, 37.4, 38.3, 42.1, 50.9, 53.6, 70.3, 71.3, 72.6, 73.8, 103.4 (t, $J_{\text{CF}} = 25.8$ Hz), 110.9 (d, $J_{\text{CF}} = 25.2$ Hz, 2C), 125.8, 127.3, 128.2, 129.2, 129.3, 129.6, 137.2, 137.5, 143.8, 144.6, 145.0, 164.4 (d, $J_{\text{CF}} = 247.5$ Hz), 164.6 (d, $J_{\text{CF}} = 247.5$ Hz), 167.8, 167.9, 168.9. HRMS m/z 760.3196 [(M+H) $^+$ calcd for $\text{C}_{37}\text{H}_{48}\text{F}_2\text{N}_5\text{O}_8\text{S}^+$ 760.3186].

Example 4

Step a

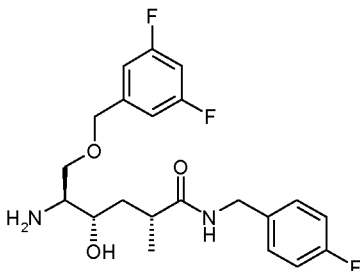


(2R,4S,5S)-5-Azido-6-(3,5-difluorobenzyloxy)-4-hydroxy-2-methyl-hexanoic acid 4-fluorobenzylamide (4a)

The title compound (188 mg, 88%) was prepared by opening of the lactone 1h (152 mg, 0.49 mmol) according to the method described for the preparation of compound 2c but using the amine 4-fluorobenzylamine instead of the amine (*S*)-2-Amino-*N*-benzyl-3-methyl-butylamide. The title compound was collected as white crystals after purification.

^1H -NMR (300 MHz, CDCl_3): δ 1.21 (d, $J = 6.7$ Hz, 3H), 1.56-1.59 (m, 1H), 1.70-1.79 (m, 2H), 2.52-2.67 (m, 1H), 2.89-2.95 (m, 1H), 3.41-3.48 (m, 1H), 3.61-3.79 (m, 2H), 4.40 (d, $J = 5.8$, 2H), 4.54 (s, 2H), 6.69-6.78 (m, 1H), 6.82-6.91 (m, 2H), 6.95-7.04 (m, 2H), 7.20-7.26 (m, 3H). ^{13}C -NMR (75.5 MHz, CDCl_3): δ 18.3, 37.7, 38.4, 42.9, 65.8, 69.1, 71.5, 72.4, 103.3 (t, $J_{\text{CF}} = 25.3$ Hz, 1C), 110.1 (d, $J_{\text{CF}} = 25.3$ Hz, 2C), 115.7 (d, $J_{\text{CF}} = 21.5$ Hz, 2C), 129.5 (d, $J_{\text{CF}} = 8.0$ Hz, 2C), 134.3 (d, $J_{\text{CF}} = 3.3$ Hz, 1C), 141.9 (t, $J_{\text{CF}} = 8.9$ Hz, 1C), 162.3 (d, $J_{\text{CF}} = 245.9$ Hz, 1C), 163.2 (d, $J_{\text{CF}} = 248.8$ Hz, 1C), 163.4 (d, $J_{\text{CF}} = 248.8$ Hz, 1C), 176.7. MS m/z 437.1 [(M+H) $^+$ calcd for $\text{C}_{21}\text{H}_{24}\text{F}_3\text{N}_4\text{O}_3^+$ 437.2].

Step b

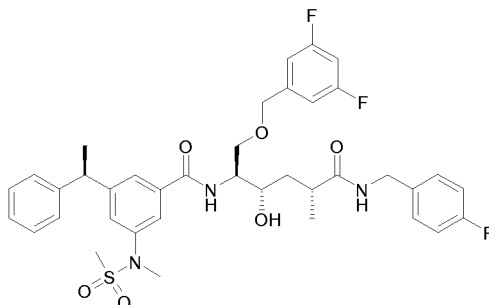


(2*R*,4*S*,5*S*)-5-Amino-6-(3,5-difluorobenzyloxy)-4-hydroxy-2-methyl-hexanoic acid 4-fluoro-benzylamide (4b)

The title compound (96.5 mg, 62%) was synthesized by reduction of the azide of compound 4a (149 mg, 0.57 mmol) according to the method described for the preparation of compound 1k.

¹H-NMR (300 MHz, CDCl₃): δ 1.16 (d, *J* = 6.9, 3H), 1.43-1.54 (m, 1H), 1.66-1.87 (m, 1H), 2.32-2.53 (m, 3H), 2.53-2.67 (m, 1H), 2.73-2.82 (m, 1H), 3.30-3.42 (m, 2H), 3.48 (dd, *J* = 4.1, 9.4 Hz, 1H), 4.36 (t, *J* = 5.4 Hz, 1H), 4.44 (s, 2H), 6.41-6.50 (m, 1H), 6.66-6.75 (m, 1H), 6.77-6.86 (m, 2H), 6.88-7.02 (m, 2H), 7.14-7.31 (m, 2H). ¹³C-NMR (75.5 MHz, CDCl₃): δ 18.6, 37.8, 39.1, 42.9, 55.4, 69.2, 72.3, 73.6, 103.2 (t, *J*_{CF} = 25.4 Hz, 1C), 110.1 (d, *J*_{CF} = 25.1, 2C), 115.6 (d, *J*_{CF} = 21.5 Hz, 2C), 129.6 (d, *J*_{CF} = 8.2 Hz, 2C), 134.6 (d, *J*_{CF} = 3.3 Hz, 1C), 142.3 (t, *J*_{CF} = 8.8 Hz, 1C), 162.3 (d, *J*_{CF} = 246.2 Hz, 1C), 163.2 (d, *J*_{CF} = 248.9 Hz, 1C), 163.4 (d, *J*_{CF} = 248.9 Hz, 1C), 176.6. MS *m/z* 411.1 [(M+H)⁺ calcd for C₂₁H₂₆F₃N₂O₃⁺ 411.2].

Step c



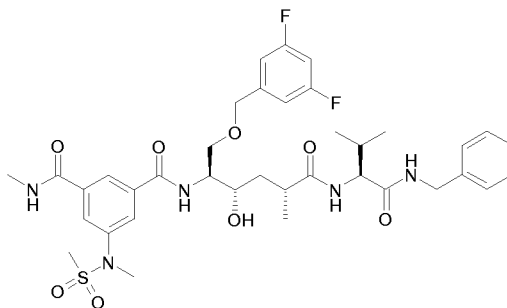
N-[(1*S*,2*S*,4*R*)-1-(3,5-Difluorobenzyloxymethyl)-4-(4-fluoro-benzylcarbamoyl)-2-hydroxy-pentyl]-5-(methanesulphonyl-methyl-amino)-*N'*-((*R*)-1-phenyl-ethyl)-isophthalamide (4c)

The title compound (9.4 mg, 18%) was synthesized by coupling the amine 4b (27.9 mg, 0.068 mmol) to 5-methanesulphonyl-methyl-amino)-*N'*-(1-phenyl-ethyl)-isophthalic acid according to the method described for the preparation of compound 1l. The title compound was collected as white powder after lyophilization.

¹H-NMR (300 MHz, CD₃OD): δ 1.17 (d, *J* = 7.1 Hz, 3H), 1.21-1.54 (m, 3H), 1.58 (d, *J* = 6.9 Hz, 3H), 1.86-1.99 (m, 1H), 2.65 (s, 3H), 2.95 (s, 3H), 3.61-3.86 (m, 4H), 4.19-4.40 (m, 2H), 4.49-4.62 (m, 2H), 5.19-5.32 (m, 1H), 6.74-6.86 (m, 1H), 6.87-7.04 (m, 4H), 7.06-7.50 (m, 10H), 7.95-8.09 (m, 2H), 8.20-8.23 (m, 1H). ¹³C-NMR (75.5 MHz, CD₃OD): δ 17.8, 20.9, 34.7, 37.1, 37.6, 38.0, 42.1, 49.8, 54.2, 68.5, 69.5, 71.5, 102.3 (t, *J*_{CF} = 28.8 Hz, 1C), 109.8 (d, *J*_{CF} = 25.5 Hz, 2C), 114.9 (d, *J*_{CF} = 21.8 Hz, 2C), 124.7, 126.1, 127.0, 128.0, 128.1, 128.4, 129.1 (d, *J*_{CF} = 8.0 Hz, 2C), 135.0, 136.1, 142.6, 143.3 (t, *J*_{CF} = 9.2 Hz, 1C), 143.8, 162.1 (d, *J*_{CF} = 243.9, 1C), 163.2 (d, *J*_{CF} = 247.1, 1C), 163.4 (d, *J*_{CF} = 247.1, 1C), 166.5, 167.8, 177.7. HRMS *m/z* 769.2868 [(M+H)⁺ calcd for C₃₉H₄₄F₃N₄O₇S⁺ 769.2877].

Example 5

58



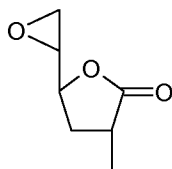
N-[(1*S*,2*S*,4*R*)-4-((*S*)-1-Benzylcarbamoyl-2-methyl-propylcarbamoyl)-1-(3,5-difluoro-benzyloxymethyl)-2-hydroxy-pentyl]-5-(methanesulphonyl-methyl-amino)-*N'*-methyl-isophthalamide (5)

The title compound (18 mg, 52%) was prepared by coupling of amine 1k (25 mg, 0.051 mmol) to 5-(methanesulphonyl-methyl-amino)-*N*-methyl-isophthalamic acid according to the method described for the preparation of compound 11. The title compound was collected as white powder after lyophilization.

$^1\text{H-NMR}$ (300 MHz, CD_3OD): δ 0.87 (d, $J = 6.8$ Hz, 6H), 1.14 (d, $J = 6.9$ Hz, 3H), 1.48-1.58 (m, 1H), 1.83-1.92 (m, 1H), 1.93-2.05 (m, 1H), 2.72-2.80 (m, 1H), 2.92 (s, 3H), 2.95 (s, 3H), 3.37 (s, 3H), 3.69 (dd, $J = 7.0, 9.8$ Hz, 1H), 3.78 (dd, $J = 6.3, 9.8$ Hz, 1H), 3.85-3.92 (m, 1H), 4.14 (d, $J = 7.7$ Hz, 1H), 4.33 (d, $J = 15.0$ Hz, 1H), 4.41 (d, $J = 15.0$ Hz, 1H), 4.34-4.45 (m, 1H), 4.56 (s, 2H), 6.76-6.84 (m, 1H), 6.92-6.97 (m, 2H), 7.21-7.32 (m, 5H), 8.02-8.05 (m, 2H), 8.23-8.25 (m, 1H); $^{13}\text{C-NMR}$ (75.5 MHz, CD_3OD): δ 18.5, 19.0, 19.8, 27.0, 31.9, 35.9, 38.4, 39.5, 40.4, 44.0, 55.0, 60.4, 69.5, 70.7, 72.6, 103.4 (t, $J_{\text{CF}} = 25.8$ Hz), 111.0 (d, $J_{\text{CF}} = 25.5$ Hz, 2C), 125.9, 128.2, 128.6, 129.1, 129.5, 137.1, 137.2, 139.8, 143.8, 144.5 (t, $J_{\text{CF}} = 9.0$ Hz), 162.9 (d, $J_{\text{CF}} = 247.3$ Hz), 166.1 (d, $J_{\text{CF}} = 247.1$ Hz), 168.9, 173.7, 180.0. HRMS m/z 676.2863 $[(\text{M}+\text{H})^+]$ calcd for $\text{C}_{37}\text{H}_{48}\text{F}_2\text{N}_5\text{O}_8\text{S}^+$ 676.2542].

Example 6

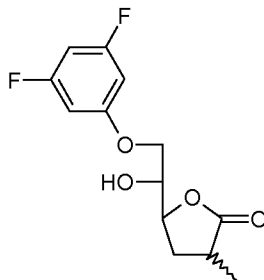
Step a



5,6-Anhydro-2,3-dideoxy-2-methyl-D-glucono-1,4-lactone (6a)

The diol 1f (119 mg, 0.75 mmol) was dissolved in chloroform (37 mL), triphenylphosphine (293 mg, 1.12 mmol) and diisopropyl azodicarboxylate (220 μL , 1.12 mmol) were added. The mixture was refluxed overnight whereafter the solvent was evaporated. The crude mixture was purified by flash column chromatography (toluene/ethyl acetate 9:1) to give the title epoxide (66 mg, 63%) as a colourless oil.

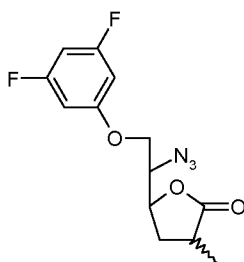
$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 1.13 (d, $J = 6.32$ Hz, 3H), 1.76-1.87 (m, 1H), 2.06-2.17 (m, 1H), 2.50-2.56 (m, 1H), 2.57-2.68 (m, 1H), 2.74 (t, $J = 4.67$ Hz, 1H), 3.06-3.12 (m, 1H), 4.40-4.49 (m, 1H); $^{13}\text{C-NMR}$ (75.5 MHz, CDCl_3): δ 15.3, 30.2, 33.3, 44.2, 51.5, 76.5, 179.1.

Step b

2,3-Dideoxy-6-O-(3,5-difluorophenyl)-2-methyl-D-glucono-1,4-lactone and 2,3-dideoxy-6-O-(3,5-difluorophenyl)-2-methyl-D-manono-1,4-lactone (6b)

To the epoxide 6a (66 mg, 0.47 mmol) in DMF (2.4 mL) 3,5-difluorophenol (92 mg, 0.71 mmol) and K_2CO_3 (37 mg, 0.24 mmol) were added. The reaction mixture was heated to 110 °C for 4 hours. The DMF was removed by co-evaporation with toluene (3 x 15 mL). The crude residue was purified by flash column chromatography (toluene/ethyl acetate 9:1) to yield a diastereomeric mixture of the title compound (116 mg, 91%) as an colourless oil.

^1H -NMR (300 MHz, CD_3OD): δ 1.21-1.29 (m, 3H), 1.87-2.02 (m, 1H), 2.41-2.63 (m, 1H), 2.64-2.85 (m, 1H), [3.31 (d, $J = 4.94$ Hz, 0.5H) & 3.47 (d, $J = 5.22$ Hz, 0.5 Hz, 0.5H)], 3.98-4.04 (m, 2H), 4.10-4.20 (m, 1H), [4.46-4.53 (m, 0.5H), 4.55-4.63 (m, 0.5H)], 6.38-6.48 (m, 3H); ^{13}C -NMR (75.5 MHz, CD_3OD): δ [15.4 & 16.4], [31.5 & 32.8], [35.3 & 36.5], 70.8, [71.2 & 71.4], 79.3, 97.2 (t, $J_{CF} = 25.7$ Hz), 99.5 (d, $J_{CF} = 28.9$ Hz, 2C), 162.3 (t, $J_{CF} = 13.7$ Hz), 165.0 (d, $J_{CF} = 247.1$ Hz), 165.5 (d, $J_{CF} = 247.1$ Hz), [181.7 & 182.6]. MS m/z 272.8 $[(M+H)^+]$ calcd for $C_{13}H_{15}F_2O_4^+$ 273.09].

Step c

5-Azido-2,3,5-trideoxy-6-O-(3,5-difluorobenzyl)-2-methyl-L-idono-1,4-lactone (6c-(R)) and 5-azido-2,3,5-trideoxy-6-O-(3,5-difluorobenzyl)-2-methyl-L-gulono-1,4-lactone (6c-(S))

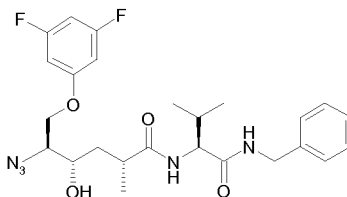
The diastereomeric mixture 6b (116 mg, 0.42 mmol) and triphenyl phosphine (168 mg, 0.64 mmol) were dissolved in dry THF (4.3 mL). The mixture was cooled to -15 °C (acetone/ice 1:1) and diisopropyl azodicarboxylate (126 μ L, 0.64 mmol) were added. The mixture was stirred for 30 min at -15 °C (acetone/ice 1:1) before the temperature was raised to 0 °C and diphenylphosphoryl azide (142 μ L, 0.64 mmol) was added. The reaction mixture was allowed to attain room temperature and was stirred overnight. The solvent was evaporated and the crude diastereomeric mixture was purified by flash column chromatography (toluene/ethyl acetate

18:1). The two diastereomers 6c-(*R*) (40 mg, 32%) and 6c-(*S*) (53 mg, 42%) were separated and collected as transparent oils. 6c-(*R*):

$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 1.29 (d, $J = 7.1$ Hz, 3H), 2.02-2.16 (m, 1H), 2.40-2.53 (m, 1H), 2.82-2.98 (m, 1H), 3.86-3.95 (m, 1H), 4.21 (d, $J = 6.3$ Hz, 2H), 4.63-4.71 (m, 1H), 6.38-6.52 (m, 3H); $^{13}\text{C-NMR}$ (75.5 MHz, CDCl_3): δ 16.2, 32.6, 33.4, 63.3, 68.4, 75.2, 97.4 (t, $J_{\text{CF}} = 25.8$ Hz), 98.5 (d, $J_{\text{CF}} = 28.9$ Hz, 2C), 159.6 (t, $J_{\text{CF}} = 13.7$ Hz), 163.5 (d, $J_{\text{CF}} = 247.2$ Hz), 163.7 (d, $J_{\text{CF}} = 247.2$ Hz) 179.1. $[\alpha]_D^{22} = +63.5^\circ$ (chloroform). MS m/z 319.6 $[(\text{M}+\text{Na})^+]$ calcd for

$\text{C}_{13}\text{H}_{13}\text{F}_2\text{N}_3\text{NaO}_3^+ 320.08$. 6c-(*S*): $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 1.33 (d, $J = 4.1$ Hz, 3H), 1.87-2.01 (m, 1H), 2.43-2.56 (m, 1H), 2.66-2.80 (m, 1H), 3.80-3.87 (m, 1H), 4.17 (m, 2H), 4.52-4.62 (m, 1H), 6.41-6.52 (m, 3H); $^{13}\text{C-NMR}$ (75.5 MHz, CDCl_3): δ 15.1, 32.9, 35.0, 62.0, 68.2, 76.0, 97.4 (t, $J_{\text{CF}} = 26.1$ Hz), 98.5 (d, $J_{\text{CF}} = 29.2$ Hz, 2C), 163.5 (d, $J_{\text{CF}} = 247.4$ Hz), 163.8 (d, $J_{\text{CF}} = 247.4$ Hz), 177.9. $[\alpha]_D^{22} = +46.3^\circ$ (chloroform). MS m/z 319.6 $[(\text{M}+\text{Na})^+]$ calcd for $\text{C}_{13}\text{H}_{13}\text{F}_2\text{N}_3\text{NaO}_3^+ 320.08$.

Step d

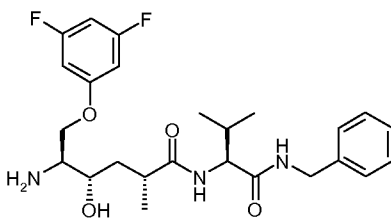


(2*R*,4*S*,5*S*)-5-Azido-6-(3,5-difluoro-phenoxy)-4-hydroxy-2-methyl-hexanoic acid ((*S*)-1-benzylcarbamoyle-2-methyl-propyl)-amide (6d)

The title compound (94 mg, 70%) was synthesized by opening of the lactone 6c-(*R*) (77 mg, 0.26 mmol) with the amine 1i according to the method described for the preparation of compound 2c. The title compound was collected as crystals after purification by flash column chromatography (toluene/ethyl acetate 1:1).

$^1\text{H-NMR}$ (300 MHz, $\text{CD}_3\text{OD}/\text{CDCl}_3$ (1:1, v/v)): δ 0.92 (d, $J = 6.8$ Hz, 3H), 0.93 (d, $J = 6.6$ Hz, 3H), 1.14 (d, $J = 6.9$ Hz, 3H), 1.56-1.68 (m, 1H), 1.78-1.91 (m, 1H), 1.97-2.10 (m, 1H), 2.62-2.75 (m, 1H), 3.60-3.70 (m, 2H), 4.02-4.20 (m, 3H), 4.33 (d, $J = 14.9$ Hz, 1H), 4.40 (d, $J = 14.9$ Hz, 1H), 6.39-6.52 (m, 3H), 7.16-7.31 (m, 5H); $^{13}\text{C-NMR}$ (75.5 MHz, $\text{CD}_3\text{OD}/\text{CDCl}_3$ (1:1, v/v)): δ 18.2, 18.3, 19.1, 30.8, 37.6, 38.1, 43.2, 59.2, 65.4, 68.8, 68.9, 96.6 (t, $J_{\text{CF}} = 26.1$ Hz), 98.5 (d, $J_{\text{CF}} = 28.6$ Hz, 2C), 127.3, 127.5, 128.5, 138.3, 160.6 (t, $J_{\text{CF}} = 13.7$ Hz), 163.8 (d, $J_{\text{CF}} = 264.1$ Hz), 164.0 (d, $J_{\text{CF}} = 264.1$ Hz), 172.3, 177.5. MS m/z 504.5 $[(\text{M}+\text{H})^+]$ calcd for $\text{C}_{25}\text{H}_{32}\text{F}_2\text{N}_5\text{O}_4^+ 504.24$.

Step e

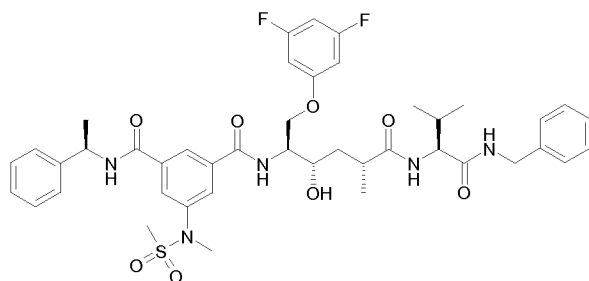


(2R,4S,5S)-5-Amino-6-(3,5-difluorophenoxy)-4-hydroxy-2-methyl-hexanoic acid ((S)-1-benzylcarbamoyl-2-methyl-propyl)-amide (6e)

The title compound (77 mg, 82%) was synthesized by reduction of the azide of compound 6d (97 mg, 0.19 mmol) according to the method described for the preparation of compound 1k. The title compound was collected as a white powder after purification.

$^1\text{H-NMR}$ (300 MHz, CD_3OD): δ 0.93 (d, $J = 6.7$ Hz, 3H), 0.95 (d, $J = 6.7$ Hz, 3H), 1.14 (d, $J = 7.14$ Hz, 3H), 1.51-1.63 (m, 1H), 1.82-1.93 (m, 1H), 1.98-2.12 (m, 1H), 2.66-2.79 (m, 1H), 2.90-2.98 (m, 1H), 3.58-3.65 (m, 1H), 3.85 (dd, $J = 6.3, 9.3$ Hz, 1H), 3.99 (dd, $J = 5.8, 9.3$ Hz, 1H), 4.19 (d, $J = 7.7$ Hz, 1H), 4.37 (d, $J = 2.48$ Hz, 2H), 6.44-6.60 (m, 3H), 7.16-7.32 (m, 5H); $^{13}\text{C-NMR}$ (75.5 MHz, CD_3OD): δ 17.8, 18.7, 30.7, 37.5, 38.0, 42.9, 54.5, 59.3, 69.0, 70.4, 95.8 (t, $J_{\text{CF}} = 26.3$ Hz), 98.3 (d, $J_{\text{CF}} = 28.9$ Hz, 2C), 127.0, 127.4, 128.3, 138.6, 161.3 (t, $J_{\text{CF}} = 13.7$ Hz), 163.9 (d, $J_{\text{CF}} = 244.8$ Hz), 164.1 (d, $J_{\text{CF}} = 244.8$ Hz), 172.5, 177.9. MS m/z 477.9 $[(\text{M}+\text{H})^+]$ calcd for $\text{C}_{25}\text{H}_{34}\text{F}_2\text{N}_3\text{O}_4^+$ 478.25].

Step f



N-[(1S,2S,4R)-4-((S)-1-Benzylcarbamoyl-2-methyl-propylcarbamoyl)-1-(3,5-difluorophenoxymethyl)-2-hydroxy-pentyl]-5-(methanesulphonyl-methyl-amino)-N'-(1-phenyl-ethyl)-isophthalamide (6f)

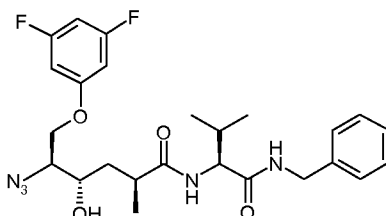
The title compound (34 mg, 74%) was synthesized by coupling of the amine 6e (26 mg, 0.055 mmol) with 5-methanesulphonyl-methyl-amino)-N'-(1-phenyl-ethyl)-isophthalic acid according to the method described for the preparation of compound 1l. The title compound was collected as a white powder after lyophilization.

$^1\text{H-NMR}$ (300 MHz, $\text{CD}_3\text{OD}/\text{CDCl}_3$ (1:1, v/v)): δ 0.84 (d, $J = 6.9$ Hz, 3H), 0.87 (d, $J = 6.9$ Hz, 3H), 1.13 (d, $J = 6.9$ Hz, 3H), 1.56 (d, $J = 7.2$ Hz, 3H), 1.50-1.64 (m, 1H), 1.77-1.88 (m, 1H), 1.90-2.03 (m, 1H), 2.62-2.75 (m, 1H), 2.92 (s, 3H), 3.33 (s, 3H), 3.89-3.97 (m, 1H), 4.05-4.20 (m, 3H), 4.29-4.37 (m, 2H), 4.40-4.45 (m, 1H), 5.25 (q, $J = 6.9$ Hz, 1H), 6.34-6.51 (m, 3H), 7.16-7.39 (m, 10H), 7.99 (t, $J = 1.6$ Hz, 1H), 8.01 (t, $J = 1.6$ Hz, 1H), 8.26 (t, $J = 1.6$ Hz, 1H); $^{13}\text{C-NMR}$ (75.5 MHz, $\text{CD}_3\text{OD}/\text{CDCl}_3$ (1:1, v/v)): δ 17.7, 18.2, 19.1, 21.4, 31.0, 35.6, 37.6, 37.9, 38.5, 43.3, 49.8, 53.4, 59.1, 67.4, 67.7, 96.5 (t, $J_{\text{CF}} = 26.1$ Hz), 98.5 (d, $J_{\text{CF}} = 28.9$ Hz, 2C),

125.0, 126.3, 127.3, 127.4, 127.6, 128.5, 128.6, 128.7, 135.6, 136.3, 138.2, 142.4, 143.5, 160.8 (t, $J_{\text{CF}} = 14.0$ Hz), 163.8 (d, $J_{\text{CF}} = 245.9$ Hz), 164.0 (d, $J_{\text{CF}} = 245.9$ Hz), 166.0, 167.3, 172.2, 177.5. HRMS m/z 836.4376 [(M+H)⁺ calcd for C₄₃H₅₂F₂N₅O₈S⁺ 836,3499].

Example 7

Step a

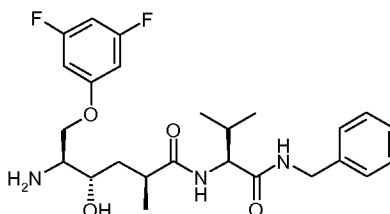


(2*S*,4*S*,5*S*)-5-Azido-6-(3,5-difluorophenoxy)-4-hydroxy-2-methyl-hexanoic acid ((*S*)-1-benzylcarbamoyl-2-methyl-propyl)-amide (7a)

The title compound (93 mg, 62%) was synthesized by opening of the lactone 6c-(*S*) (86 mg, 0.29 mmol) with the amine 1i according to the method described for the preparation of compound 2c. The title compound was collected as crystals after purification by flash column chromatography (toluene/ethyl acetate 1:1).

¹H-NMR (300 MHz, CD₃OD/CDCl₃ (1:1, v/v)): δ 0.91 (d, $J = 6.9$ Hz, 3H), 0.92 (d, $J = 6.9$ Hz, 3H), 1.15 (d, $J = 6.9$ Hz, 3H), 1.49-1.60 (m, 1H), 1.82-1.96 (m, 1H), 2.05-2.19 (m, 1H), 2.50-2.64 (m, 1H), 3.61-3.70 (m, 1H), 3.70-3.79 (m, 1H), 3.99 (m, 3H), 4.35 (s, 2H), 6.38-6.51 (m, 3H), 7.15-7.32 (m, 5H); ¹³C-NMR (75.5 MHz, CD₃OD/CDCl₃ (1:1, v/v)): δ 17.7, 17.8, 19.1, 30.5, 37.7, 43.3, 58.9, 65.1, 69.1, 69.2, 96.7 (t, $J_{\text{CF}} = 26.1$ Hz), 98.6 (d, $J_{\text{CF}} = 28.9$ Hz, 2C), 127.3, 127.6, 128.6, 138.3, 160.6 (t, $J_{\text{CF}} = 13.5$ Hz), 163.8 (d, $J_{\text{CF}} = 246.3$ Hz), 164.0 (d, $J_{\text{CF}} = 246.3$ Hz), 172.4, 178.2. MS m/z 504.5 [(M+H)⁺ calcd for C₂₅H₃₂F₂N₅O₄⁺ 504.24].

Step b



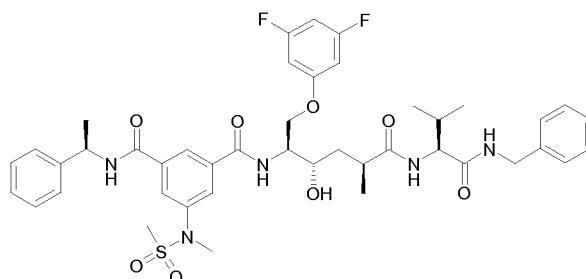
(2*S*,4*S*,5*S*)-5-Amino-6-(3,5-difluorophenoxy)-4-hydroxy-2-methyl-hexanoic acid ((*S*)-1-benzylcarbamoyl-2-methyl-propyl)-amide (7b)

The title compound (66 mg, 99%) was synthesized by reduction of the azide of compound 7a (70 mg, 0.14 mmol) according to the method described for the preparation of compound 1k. The title compound was collected as a white powder after purification.

¹H-NMR (300 MHz, CD₃OD): δ 0.94 (d, $J = 6.9$ Hz, 6H), 1.16 (d, $J = 6.9$ Hz, 3H), 1.52-1.63 (m, 1H), 1.80-1.92 (m, 1H), 2.07-2.21 (m, 1H), 2.59-2.71 (m, 1H), 2.93-3.01 (m, 1H), 3.67-3.75 (m, 1H), 3.84 (dd, $J = 9.1, 6.6$ Hz, 1H), 3.96 (dd, $J = 9.1, 5.2$ Hz, 1H), 4.20 (d, $J = 6.9$ Hz, 1H), 4.36 (s, 2H), 6.44-6.60 (m, 3H), 7.16-7.32 (m, 5H); ¹³C-NMR (75.5 MHz, CD₃OD): δ 17.3, 18.6,

30.4, 37.6, 37.8, 42.9, 54.5, 59.0, 69.6, 70.5, 95.8 (t, J_{CF} = 26.6 Hz), 98.3 (d, J_{CF} = 29.2 Hz, 2C), 127.0, 127.4, 128.3, 138.3, 161.4 (t, J_{CF} = 13.7 Hz), 163.9 (d, J_{CF} = 244.7 Hz), 164.1 (d, J_{CF} = 244.7 Hz), 172.6, 178.7. MS m/z 477.9 [(M+H)⁺ calcd for C₂₅H₃₄F₂N₃O₄⁺ 478.25].

Step c



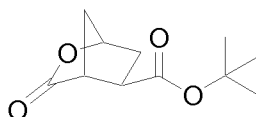
N-[(1S,2S,4S)-4-((S)-1-Benzylcarbamoyl-2-methyl-propylcarbamoyl)-1-(3,5-difluorophenoxymethyl)-2-hydroxy-pentyl]-5-(methanesulphonyl-methyl-amino)-N'-((R)-1-phenyl-ethyl)-isophthalamide (7c)

The title compound (28 mg, 64%) was synthesized by coupling of the amine 7b (25 mg, 0.052 mmol) to 5-methanesulphonyl-methyl-amino)-N'-(1-phenyl-ethyl)-isophthalic acid according to the method described for the preparation of compound 11. The title compound was collected as a white powder after lyophilization.

¹H-NMR (300 MHz, CD₃OD/CDCl₃ (1:1, v/v)): δ 0.92 (d, J = 6.8 Hz, 6H), 1.14 (d, J = 6.9 Hz, 3H), 1.48-1.56 (m, 1H), 1.58 (d, J = 7.0 Hz, 3H), 1.85-1.97 (m, 1H), 2.05-2.19 (m, 1H), 2.55-2.67 (m, 1H), 2.93 (s, 3H), 3.33 (s, 3H), 3.96-4.03 (m, 1H), 4.05-4.12 (m, 2H), 4.13-4.22 (m, 1H), 4.28-4.32 (m, 2H), 4.40-4.47 (m, 1H), 5.25 (q, J = 7.0 Hz, 1H), 6.36-6.55 (m, 3H), 7.11-7.41 (m, 10H), 7.98-8.01 (m, 2H), 8.23 (t, J = 1.58 Hz, 1H); ¹³C-NMR (75.5 MHz, CD₃OD/CDCl₃ (1:1, v/v)): δ 17.7, 18.2, 19.0, 21.3, 30.5, 35.4, 37.7, 38.0, 38.1, 43.2, 49.8, 53.6, 58.9, 67.6, 68.3, 96.4 (t, J_{CF} = 26.1 Hz), 98.5 (d, J_{CF} = 28.9 Hz, 2C), 124.8, 126.2, 127.2, 127.3, 127.5, 128.4, 128.5, 128.6, 128.7, 135.7, 136.3, 138.3, 142.4, 143.6, 160.9 (t, J_{CF} = 13.6 Hz), 163.8 (d, J_{CF} = 245.9 Hz), 164.0 (d, J_{CF} = 245.9 Hz), 165.6, 166.2, 167.6, 178.4. HRMS m/z 836.3502 [(M+H)⁺ calcd for C₄₃H₅₂F₂N₅O₈S⁺ 836,3499].

Example 8

Step a

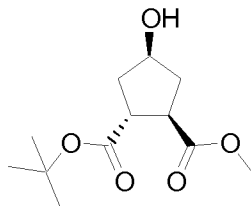


3-Oxo-2-oxa-bicyclo[2.2.1]heptane-5-carboxylic acid tert-butyl ester (8a)

The 3-Oxo-2-oxa-bicyclo[2.2.1]heptane-5-carboxylic acid (0.75 g, 4.8 mmol) was dissolved in DCM (48 mL). *tert*-Butyl 2,2,2-trichloroacetimidate (3.2 g, 14.5 mmol) was added and the reaction mixture was stirred for 23 h. The solution was concentrated and purified using flash column chromatography (toluene/ethyl acetate 9:1), which gave the title compound as white crystals (0.73 g, 71 %).

$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 1.41 (s, 9H), 1.87 (d, $J = 10.5$ Hz, 1H), 2.08-2.14 (m, 3H), 2.74-2.79 (m, 1H), 3.05 (s, 1H), 4.91 (bs, 1H); $^{13}\text{C-NMR}$ (75.5 MHz, CDCl_3): δ 28.1, 33.3, 38.0, 40.8, 46.2, 80.7, 81.9, 171.8, 176.8.

Step b

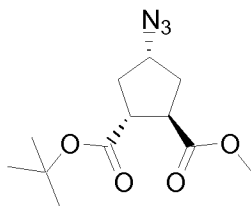


(1R,2R,4S)-1-tert-butyl 2-methyl 4-hydroxycyclopentane-1,2-dicarboxylate (8b)

3-Oxo-2-oxa-bicyclo[2.2.1]heptane-5-carboxylic acid *tert*-butyl ester (72 mg, 0.34 mmol) was dissolved in methanol (3 mL) and cooled to 0 °C. Potassium carbonate (70 mg, 0.50 mmol) was added and the reaction mixture was stirred for 30 min. Then the solution was neutralized with 1 M HCl and concentrated. Purification using flash column chromatography (toluene/ethyl acetate 3:1) gave the title compound as an oil (82 mg, 99 %).

$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 1.42 (s, 9H), 1.86-1.99 (m, 2H), 2.02-2.11 (m, 1H), 2.17-2.27 (m, 1H), 2.29 (s, 1H), 3.10-3.17 (m, 1H), 3.23-3.32 (m, 1H), 3.70 (s, 3H), 4.32-4.38 (m, 1H); $^{13}\text{C-NMR}$ (75.5 MHz, CDCl_3): δ 28.1, 38.8, 39.9, 45.4, 46.8, 52.3, 73.1, 80.9, 173.9, 176.5.

Step c

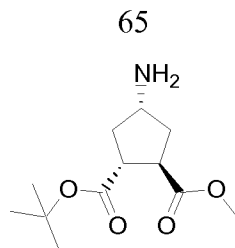


(1R,2R,4R)-1-tert-butyl 2-methyl 4-azidocyclopentane-1,2-dicarboxylate (8c)

(1R,2R,4S)-1-*tert*-butyl 2-methyl 4-hydroxycyclopentane-1,2-dicarboxylate (648 mg, 2.65 mmol) was dissolved in dry THF (20 mL) and the solution was cooled to 0 °C. PPh_3 (1.04 g, 3.96 mmol) and DIAD (1.3 mL, 6.6 mmol) were added and the mixture was stirred for 10 min. Then, DPPA (0.86 mL, 4.0 mmol) was added drop wise and the reaction mixture was stirred for 2 h and 20 min. The solution was concentrated and purified by flash column chromatography (toluene/ethyl acetate 39:1). which gave the title compound as as an oil (663 mg, 93 %).

$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 1.45 (s, 9H), 1.99-2.08 (m, 3H), 2.24-2.35 (m, 1H), 3.05-3.13 (m, 1H), 3.31 (q, $J = 8.4$ Hz, 1H), 3.70 (s, 3H), 4.07 (quintet, $J = 5.1$ Hz, 1H); $^{13}\text{C-NMR}$ (75.5 MHz, CDCl_3): δ 28.1, 35.3, 36.3, 44.9, 46.8, 52.3, 61.7, 81.3, 172.6, 174.9.

Step d

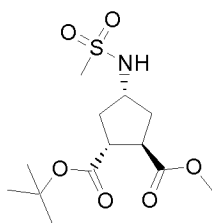


(1R,2R,4R)-1-tert-Butyl 2-methyl 4-aminocyclopentane-1,2-dicarboxylate (8d)

(1R,2R,4R)-1-tert-butyl 2-methyl 4-azidocyclopentane-1,2-dicarboxylate (80 mg, 0.30 mmol) was dissolved in methanol (4 mL). PPh₃ (128 mg, 0.49 mmol) and H₂O (3 drops) were added and the reaction mixture was stirred for 23 h. The solution was concentrated and purified by flash column chromatography (methanol/ethyl acetate 1:9 + 1 % TEA) which gave the title compound as an oil, which crystallized upon cooling (69 mg, 96 %).

¹H-NMR (300 MHz, CDCl₃): δ 1.43 (s, 9H), 1.54-1.64 (m, 1H), 1.71-1.80 (m, 1H), 2.02-2.11 (m, 1H), 2.21-2.31 (m, 1H), 3.04 (q, *J* = 8.4 Hz, 1H), 3.29 (q, *J* = 8.2 Hz, 1H), 3.47 (quintet, *J* = 6.3 Hz, 1H), 3.68 (s, 3H). ¹³C-NMR (75.5 MHz, CDCl₃): δ 28.1, 39.8, 40.0, 45.2, 47.3, 52.1, 52.5, 80.8, 174.0, 175.7.

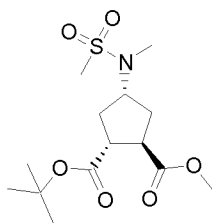
Step c



(1R,2R,4R)-4-Methanesulphonylamino-cyclopentane-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (8e)

(1R,2R,4R)-1-tert-butyl 2-methyl 4-aminocyclopentane-1,2-dicarboxylate (155 mg, 0.64 mmol) was dissolved in DCM/pyridine (2.1:0.7 mL) and cooled to 0 °C. Methanesulphonyl chloride (50 µL, 0.64 mmol) was added and the reaction mixture was allowed to reach room temperature. The mixture was stirred over night, concentrated and purified by flash column chromatography (toluene/ethyl acetate 3:1), which gave the title compound as white crystals (154 mg, 75 %).

Step f

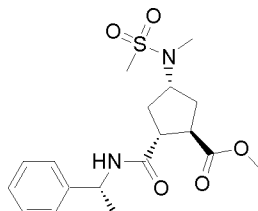


(1R,2R,4R)-4-(Methanesulphonyl-methyl-amino)-cyclopentane-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (8f)

Compound 8e (145 mg, 0.45 mmol) was dissolved in DMF (1.5 mL). Sodium hydride (18 mg, 60 %-solution) and methyl iodide (56 µL, 0.9 mmol) were added and the reaction mixture was

stirred for 1 h and 20 min. The reaction was quenched with H₂O (6 mL) and extracted twice with ethyl acetate (6 mL). The organic layers were pooled, dried with MgSO₄ and concentrated. Purification by flash column chromatography (toluene/ethyl acetate 3:1) gave the title compound as white crystals (143 mg, 95 %).

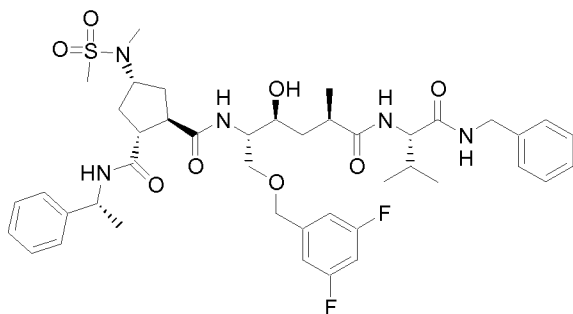
Step g



(1R,2R,4S)-4-(Methanesulphonyl-methyl-amino)-2-((R)-1-phenyl-ethylcarbamoyl)-cyclopentanecarboxylic acid methyl ester (8g)

(1R,2R,4R)-4-(Methanesulphonyl-methyl-amino)-cyclopentane-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (38 mg, 0.11 mmol) was dissolved in DCM (1.5 mL). Triethylsilane (36 µL, 0.22 mmol) and TFA (0.7 mL) were added. The reaction mixture was stirred for 1 h, concentrated and re-dissolved in DMF (0.9 mL). (R)-(+)-1-phenylethylamine (17 µL, 0.13 mmol), TEA (50 µL, 0.36 mmol) and HOBT (23 µL, 0.18 mmol) were added and the solution was cooled to 0 °C. EDC (35 mg, 0.18 mmol) was added and the reaction mixture was stirred for 2.5 h. Brine (3 mL) was added and the solution was extracted twice with ethyl acetate. The combined organic phases were dried with MgSO₄, filtered and concentrated. Purification by flash column chromatography (toluene/ethyl acetate 1:2) gave the title compound as an oil (40.6 mg, 93 %).

Step h



(1R,2R,4S)-4-(Methanesulphonyl-methyl-amino)-cyclopentane-1,2-dicarboxylic acid 1-[(1S,2S,4R)-4-((S)-1-benzylcarbamoyl-2-methyl-propylcarbamoyl)-1-(3,5-difluorobenzyloxymethyl)-2-hydroxy-pentyl]-amide} 2-[(R)-1-phenyl-ethyl]-amide (8h)

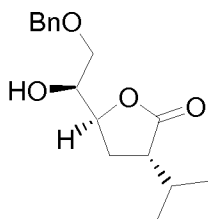
Compound 1g (20 mg, 0.05 mmol) was dissolved in MeOH (1 mL) and LiOH (63 µL, 40 mg/mL) was added. The reaction mixture was stirred over night, concentrated and purified using flash column chromatography (toluene/ethyl acetate 1:2 + 2 % AcOH). The carboxylic acid (25 mg, 0.007 mmol) was re-dissolved in DMF (1 mL). The amine 1k (26 mg, 0.05 mmol), DIPEA

(28 μ L, 0.16 mmol) and HATU (33 mg, 0.09 mmol) were added and the reaction mixture was stirred for 1 h. The solution is co-evaporated with toluene and purified using HPLC. The product (27 mg, 61%) was collected as crystals.

$^1\text{H-NMR}$ (300 MHz, DMSO- d_6): δ 0.77 (d, J = 6.6 Hz, 6H), 0.95 (d, J = 6.6 Hz, 3H), 1.21 (m, 1H), 1.29 (d, J = 6.9 Hz, 3H), 1.49-1.1.57 (m, 1H), 1.71-2.12 (m, 6H), 2.56-2.65 (m, 1H), 2.70 (s, 3H), 2.84 (s, 3H), 2.87-3.05 (m, 2H), 3.19 (dd, J = 5.9, 9.2 Hz, 1H), 3.41 (t, J = 8.7 Hz, 1H), 3.61-3.67 (m, 1H), 3.79-3.88 (m, 1H), 4.12-4.3 (m, 3H), 4.39 (d, J = 3.9 Hz, 2H), 4.66 (d, J = 5.7 Hz, 1H), 4.87 (quintet, J = 7.2 Hz, 1H), 6.95-6.97 (m, 2H), 7.05-7.30 (m, 11H), 7.42 (d, J = 9 Hz, 1H), 7.60 (d, J = 9.3 Hz, 1H), 8.18 (d, J = 8.1 Hz, 1H), 8.38 (t, J = 5.9 Hz, 1H); $^{13}\text{C-NMR}$ (75.5 MHz, DMSO- d_6): δ 18.9, 19.3, 19.9, 23.1, 29.0, 31.3, 33.1, 33.4, 36.9, 37.3, 39.2, 42.7, 46.0, 46.2, 48.5, 53.1, 56.9, 58.4, 67.1, 69.6, 71.4, 103.2 (t, J_{CF} = 25.9 Hz), 110.5 (d, J_{CF} = 24.7 Hz, 2C), 126.5, 127.1, 127.4, 127.8, 128.8, 128.9, 140.0, 144.0 (t, J_{CF} = 8.9 Hz), 145.2, 163.0 (d, J_{CF} = 246.1 Hz), 163.1 (d, J_{CF} = 246.1 Hz), 171.8, 172.7, 174.2, 176.0.

Example 9

Step a

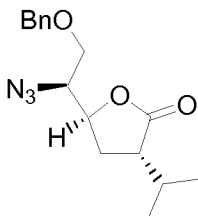


2,3-dideoxy-6-O-benzyl-2-isopropyl-D-glucono-1,4-lactone (9a)

2,3-Dideoxy-2-isopropyl-D-glucono-1,4-lactone (300 mg, 1.6 mmol) and dibutyltin oxide (520 mg, 2.08 mmol) were slurried in benzene (50 ml) and the mixture was refluxed through a Dean-Stärke tube for 3 h. Then the temperature was adjusted to 80 °C and benzyl bromide (220 μ l, 1.84 mmol) and tetrabutylammonium bromide (590 mg, 1.84 mmol) were added and the mixture was stirred over night. The suspension was filtered and the filtrate evaporated. Silica gel column chromatography (gradient 0 - $\frac{1}{2}$ - 1% EtOH/DCM) gave title product (350 mg, 79%). MS m/z 296.2 ($\text{M}+\text{NH}_4$) $^+$.

$^1\text{H-NMR}$ (CDCl_3): 7.38-7.31 (m, 5H), 4.53 (dd, 2H), 4.42 (m, 1H), 3.86 (m, 1H), 3.62 (dd, 1H), 3.55 (dd, 1H), 2.60 (m, 1H), 2.54 (d, 1H) OH, 2.32 (m, 1H), 2.15 (octette, 1H), 2.06 (m, 1H), 1.02 (d, 3H), 0.93 (d, 3H).

Step b

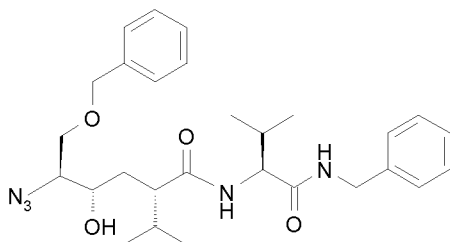


5-azido-2,3,5-trideoxy-6-O-benzyl-2-isopropyl-D-glucono-1,4-lactone (9b)

A stirred solution of 2,3-dideoxy-6-O-benzyl-2-isopropyl-D-glucono-1,4-lactone (350 mg, 1.26 mmol) and pyridine (0.16 ml) in DCM (11 ml), cooled at 0 °C, was treated with triflic anhydride (424 μ l, 2.52 mmol) dissolved in DCM (1 ml) by dropwise addition under nitrogen and the mixture was stirred at 0 °C for 1 h. The mixture was poured into a chilled 5% NaHSO₄ solution and extracted with DCM. The organic extract was dried through sodium sulfate and evaporated on rotavapor below r.t. The residue was dissolved in dimethylformamide (DMF, 11 ml) and then sodium azide (328 mg, 5.05 mmol) was added and the mixture was stirred at 70 °C for 1 h. The solvent was removed by evaporation on rotavapor and the residue was partitioned between DCM and water. The organic extract was dried thorough sodium sulfate and evaporated. Silica gel column chromatography (gradient 10%EtOAc / hexane – 15%EtOAc / hexane) gave title product (257 mg, 67%). MS m/z 321.3 (M+NH₄)⁺.

¹H-NMR (CDCl₃): 7.38-7.31 (m, 5H), 4.53 (d, 2H), 4.54 (m, 1H), 3.75 (d, 2H), 3.65 (m, 1H), 2.72 (m, 1H), 2.21-2.08 (m, 3H), 1.02 (d, 3H), 0.93 (d, 3H).

Step c



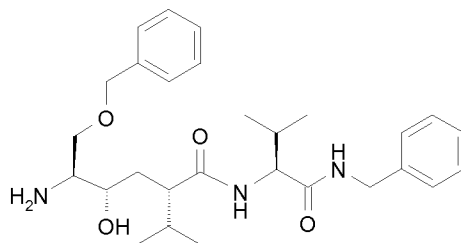
(2R,4S,5S)-5-azido-6-benzoyloxy-4-hydroxy-2-isopropyl-hexanoic acid ((S)-1-benzylcarbamoyl-2-methyl-propyl)amide (9c)

5-azido-2,3,5-trideoxy-6-O-benzyl-2-isopropyl-D-glucono-1,4-lactone (50 mg, 0.165 mmol), 2-hydroxypyridine (17 mg, 0.182 mmol) and (S)-2-amino-N-benzyl-3-methylbutyramide (37 mg, 0.182 mmol) were dissolved in DMF (1-2 ml), which was then evaporated on rotavapor.

Diisopropylethylamine (115 μ l) was added to the oily residue and the mixture was vigorously stirred at 70 °C for 88 h (3-4 days). The volatile matter was removed by evaporation on rotavapor and the residue was partitioned between dichloromethane (DCM) and saturated aqueous sodium bicarbonate. The organic extract was then extracted with 5% citric acid, dried through sodium sulfate and evaporated. Silica gel column chromatography (gradient 0 - 1 – 1½ - 2%EtOH/DCM) gave title product (52 mg, 61%). MS m/z 510.3 (M+H)⁺.

¹H-NMR (CDCl₃): 7.36-7.20 (m, 10H), 6.65 (t, 1H) NH, 6.51 (d, 1H) NH, 4.53 (dd, 2H), 4.40 (dd, 1H), 4.32 (dd, 1H), 4.25 (t, 1H), 3.70 (m, 2H), 3.63 (m, 1H), 3.39 (m, 1H), 3.08 (d, 1H) OH, 2.18 (m, 1H), 2.12 (octette, 1H), 1.82-1.64 (m, 3H), 0.94-0.82 (8xs, 12H).

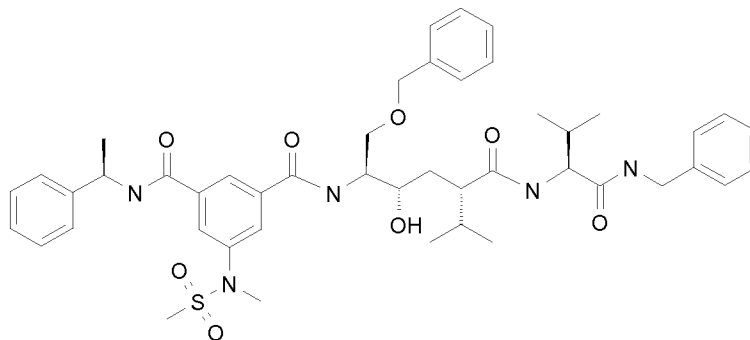
Step d



(2*R*,4*S*,5*S*)-5-amino-6-benzyloxy-4-hydroxy-2-isopropyl-hexanoic acid ((*S*)-1-benzylcarbamoyl-2-methyl-propyl)amide (9d)

(2*R*,4*S*,5*S*)-5-azido-6-benzyloxy-4-hydroxy-2-isopropyl-hexanoic acid ((*S*)-1-benzyl carbamoyl-2-methyl-propyl)amide (52 mg, 0.102 mmol) was dissolved in EtOH (2.5 ml). 5% Pd on calcium carbonate (Lindlar's catalyst, 105 mg) was added and the mixture was stirred under atmospheric pressure of hydrogen for 5 h. The mixture was filtered through Celite and the filtrate evaporated on rotavapor. An additional filtration of the residue redissolved in EtOH was done through a 0.2 μ m PTFE filter. Evaporation gave title product as a solid (47 mg, 95%). MS m/z 484.3 ($M+H$)⁺. The crude product was used directly in the next step.

Step c



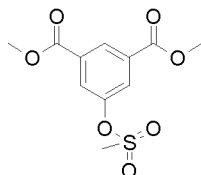
N-[(1*S*,2*S*,4*R*)-4-((*S*)-1-benzylcarbamoyl-2-methylpropylcarbamoyl)-1-benzyloxymethyl-2-hydroxy-5-methylhexyl]-5-(methanesulphonylmethylamino)-*N'*-((*R*)-1-phenylethyl)isophthalamide (9e)

5-(Methanesulphonylmethylamino)-*N*-((*R*)-1-phenylethyl)isophthalamide (5.5 mg, 0.015 mmol) was dissolved in DMF (60 μ l). Then diisopropylamine (10 μ l, 0.058 mmol) was added followed by addition of HATU (5.8 mg, 0.0152 mmol) and the mixture was stirred at r.t. for 10 min. Then (2*R*,4*S*,5*S*)-5-amino-6-benzyloxy-4-hydroxy-2-isopropyl-hexanoic acid ((*S*)-1-benzylcarbamoyl-2-methyl-propyl)amide (7.0 mg, 0.015 mmol) dissolved in DMF (60 μ l) was added and the mixture was stirred at r.t. for 30 min. The reaction was quenched with one drop of saturated aqueous sodium bicarbonate, the solvent evaporated on rotavapor and the residue was partitioned between DCM and saturated aqueous sodium bicarbonate and then between DCM and 5% citric acid. The organic extract was dried through sodium sulfate and evaporated. Silica gel column chromatography (gradient 1/2 - 1 - 1 1/2 - 2 - 3 - 4% EtOH/DCM) gave 11 mg of unpure title product, which was further purified using preparative HPLC (ACE-8, gradient 10 - 90% acetonitrile / water) which gave the pure title compound (6.66 mg, 55%). MS m/z 842.3 ($M+H$)⁺.

$^1\text{H-NMR}$ (CDCl_3): 8.28 (s, 1H), 8.00 (m, 2H), 7.36-7.15 (m, 16H) arom., NH, 7.04 (d, 1H) NH, 6.62 (t, 1H) NH, 6.43 (d, 1H) NH, 5.28 (pentette, 1H) CH, 4.51 (s, 2H), 4.38 (dd, 1H), 4.30 (dd, 1H), 4.25 (m, 2H), 3.88 (br, d, 1H), 3.79 (dd, 1H), 3.71 (dd, 1H), 3.70 (br, s, 1H) OH, 3.33 (s, 3H), 2.84 (s, 3H), 2.32 (m, 1H), 2.10 (octette, 1H), 1.85-1.64 (m, 3H), 1.56 (d, 3H), 0.92-0.84 (8xs, 12H).

Example 10

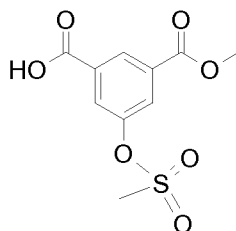
Step a



5-Methanesulphonyloxy-isophthalic acid dimethyl ester (10a)

To a solution of 5-hydroxy-isophthalic acid dimethyl ester (4.2 g, 20 mmol) and pyridine (3 mL, 37.2 mmol) in CH_2Cl_2 (40 mL) was added methanesulphonyl chloride (2 mL, 25.8 mmol) and the resulting solution was stirred at r.t. until full conversion of starting material to product was achieved. The reaction mixture was then diluted with CH_2Cl_2 and washed with H_2O . The organic phase was dried (Na_2SO_4) and the solvent evaporated to give a residue that was triturated into $^t\text{BuOMe}$ to give the title compound as a white solid (5.4 g, 93%).

Step b

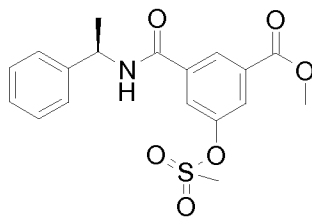


5-Methanesulphonyloxy-isophthalic acid monomethyl ester (10b)

A suspension of 5-methanesulphonyloxy-isophthalic acid dimethyl ester (1 g, 3.47 mmol) in $\text{THF}:\text{MeOH}$ (1:1, 24 mL) was treated with 2.1 M NaOH (1.7 mL, 3.63 mmol) and the resulting mixture was stirred at r.t. for 20 h. The reaction mixture was diluted with H_2O and CH_2Cl_2 and the organic phase was washed with H_2O . The aqueous phase was acidified with HCl and then extracted with CH_2Cl_2 . The organic phase was extracted with sat. aq. NaHCO_3 and the aqueous extracts acidified with HCl . Extraction with CH_2Cl_2 , drying (Na_2SO_4) and evaporation of the solvent afforded the title compound as white foam (0.3 g, 32%).

Step c

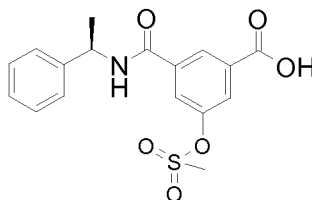
71



5-Methanesulphonyloxy-N-(1-phenyl-ethyl)-isophthalamic acid methyl ester (10c)

A solution of 5-methanesulphonyloxy-isophthalic acid monomethyl ester (381 mg, 1.39 mmol), HATU (528 mg, 1.39 mmol) and EtNⁱPr₂ (606 μ L, 3.48 mmol) in DMF (2 mL) was stirred at r.t. for 2 min before adding 1-phenethylamine (179 μ L, 1.39 mmol). The reaction mixture was allowed to stir for 5 min and then it was concentrated under vacuum and the residue was purified by flash chromatography on silica gel (eluent: Hex:EtOAc, 2.5:1) to give the title compound as a colourless syrup (344 mg, 66%).

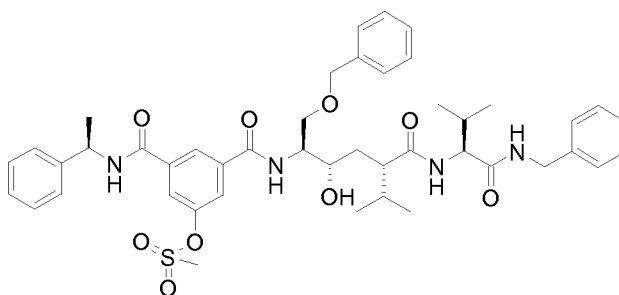
Step d



5-Methanesulphonyloxy-N-(1-phenyl-ethyl)-isophthalamic acid (10d)

A solution of 5-methanesulphonyloxy-N-(1-phenyl-ethyl)-isophthalamic acid methyl ester (344 mg, 0.91 mmol) in MeOH:THF (1:1, 4 mL) was treated with 1.8 M NaOH (0.5 mL, 0.9 mmol). The resulting mixture was stirred at r.t. for 17 h and then it was concentrated under vacuum. The residue was taken into H₂O and the solution was acidified with HCl and then the pH was adjusted to just about 8 with solid NaHCO₃. The product was extracted into CH₂Cl₂ and the volatiles were evaporation under vacuum which gave the title compound as a white solid (130 mg, 39%).

Step e



Methanesulphonic acid 3-[4-(1-benzylcarbamoyl-2-methyl-propylcarbamoyl)-1-benzyloxymethyl-2-hydroxy-5-methyl-hexylcarbamoyl]-5-(1-phenyl-ethylcarbamoyl)-phenyl ester (10e)

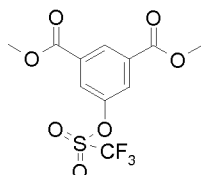
HATU (7.4 mg, 0.019 mmol) was added to a solution of the acid 10d (7 mg, 0.019 mmol) and EtNⁱPr₂ (10 μ L, 0.06 mmol) in DMF (1 mL) and the resulting mixture was stirred for 2 min

before adding 5-amino-6-benzyloxy-4-hydroxy-2-isopropyl-hexanoic acid (1-benzylcarbamoyl-2-methyl-propyl)-amide (9 mg, 0.019 mmol). The reaction mixture was stirred 5 min at r.t. and then concentrated under vacuum. The residue was purified by preparative HPLC (20% acetonitrile in H₂O to 100% acetonitrile) which gave the title compound (3.7 mg, 23%).

¹H-NMR (CDCl₃) δ (ppm): 0.87, 0.91, 1.64-1.72, 1.75-1.93, 2.10, 2.27, 3.19, 3.62, 3.69-3.75, 3.77-3.84, 3.86-3.92, 4.16-4.43, 4.52, 5.31, 6.28, 6.40, 7.02-7.12, 7.17-7.40, 7.19, 8.33.

Example 11

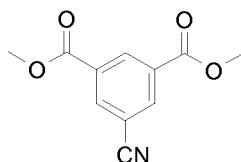
Step a



5-Trifluoromethanesulphonyloxy-isophthalic acid dimethyl ester (11a)

To a solution of 5-hydroxy-isophthalic acid dimethyl ester (2 g, 9.5 mmol) and pyridine (2 mL, 24.8 mmol) in CH₂Cl₂ (10 mL) was carefully added triflic anhydride (2 mL, 25.8 mmol) and the resulting solution was stirred at r.t. until full conversion of starting material to product was achieved. The reaction mixture was then diluted with CH₂Cl₂ and washed with H₂O. The organic phase was dried (Na₂SO₄) and the solvent evaporated to give a residue that was purified by flash chromatography on silica gel (eluent: Hex:EtOAc, 5:1) which gave the title compound as white crystals (1.8 g, 56%).

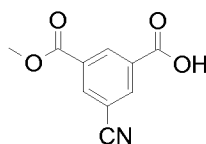
Step b



5-Cyano-isophthalic acid dimethyl ester (11b)

A mixture of 5-trifluoromethanesulphonyloxy-isophthalic acid dimethyl ester (0.34 g, 1 mmol), Pd(PPh₃)₄ (231 mg, 0.2 mmol) and Zn(CN)₂ (235 mg, 2 mmol) in DMF (2 mL) was heated at 60 °C under nitrogen for 3 days. The reaction mixture was concentrated under vacuum and the product purified by flash chromatography on silica gel (eluent: Hex:EtOAc, 10:1) which gave the title compound as a white solid (123 mg, 57%).

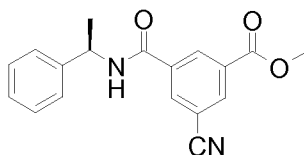
Step c



5-Cyano-isophthalic acid monomethyl ester (11c)

A solution of 5-cyano-isophthalic acid dimethyl ester (123 mg, 0.56 mmol) in THF:MeOH (1:1, 4 mL) was treated with NaOH (22 mg, 0.56 mmol) in H₂O (0.5 mL) at r.t. The reaction mixture was stirred 17 h and concentrated under vacuum. The residue was taken into EtOAc and 2M HCl, the phases were separated and the organic phase dried (Na₂SO₄). Evaporation of the solvent afforded the title compound (49 mg, 43 %).

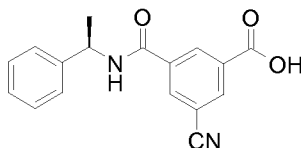
Step d



5-Cyano-N-(1-phenyl-ethyl)-isophthalamic acid methyl ester (11d)

The acid 11c was coupled to 1-phenethylamine according to the procedure described for the preparation of compound 10c, which gave the title compound in 66% yield.

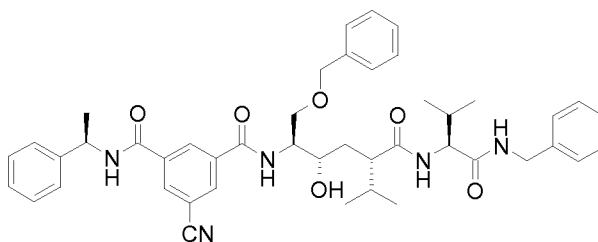
Step e



5-Cyano-N-(1-phenyl-ethyl)-isophthalamic acid (11e)

The methyl ester of compound 11d was hydrolyzed as described in Example 10, step d, which gave the title compound in 33% yield.

Step f



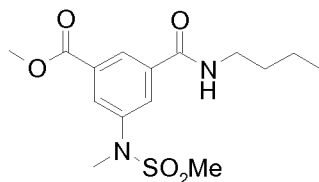
N-[4-(1-Benzylcarbamoyl-2-methyl-propylcarbamoyl)-1-benzyloxymethyl-2-hydroxy-5-methyl-hexyl]-5-cyano-N'-(1-phenyl-ethyl)-isophthalamide (11f)

The title compound was prepared in 9% yield by coupling of the acid 11e to 5-Amino-6-benzyloxy-4-hydroxy-2-isopropyl-hexanoic acid (1-benzylcarbamoyl-2-methyl-propyl)-amide according to the procedure described in Example 10 step e.

¹H-NMR (CD₃OD) δ (ppm): 0.86, 0.88, 0.91, 1.57, 1.68-1.88, 2.29-2.38, 3.61-3.80, 4.14, 4.25-4.41, 4.47-4.63, 5.23, 7.20-7.44, 8.30, 8.53.

Example 12

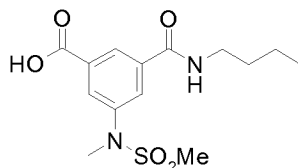
Step a



N-Butyl-5-(methanesulphonyl-methyl-amino)-isophthalamic acid methyl ester (12a)

HATU (132 mg, 0.348 mmol) was added to a solution of 5-(methanesulphonyl-methyl-amino)-isophthalic acid methyl ester (100 mg, 0.348 mmol) and EtNⁱPr₂ (150 μ L, 0.86 mmol) in DMF (1 mL) and the resulting mixture was stirred for 2 min before adding n-butylamine (34 μ L, 0.34 mmol). The reaction mixture was stirred 5 min at r.t. and then concentrated under vacuum. The residue was purified by flash chromatography on silica gel (eluent: Hex:EtOAc, 1:2) which gave the title compound as a white solid, (109 mg (91%).

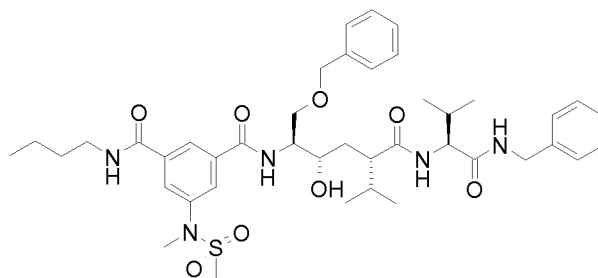
Step b



N-Butyl-5-(methanesulphonyl-methyl-amino)-isophthalamic acid (12b)

The methyl ester of compound 12a was hydrolyzed as described in Example 10 step d, which gave the title compound in 53% yield.

Step c



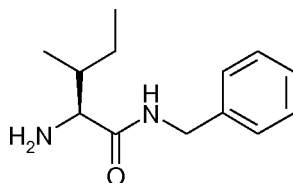
N-[4-(1-Benzylcarbamoyl-2-methyl-propylcarbamoyl)-1-benzyloxymethyl-2-hydroxy-5-methyl-hexyl]-N'-butyl-5-(methanesulphonyl-methyl-amino)-isophthalamide (12c)

The title compound was prepared in 55% yield by coupling of the acid 12b to 5-amino-6-benzyloxy-4-hydroxy-2-isopropyl-hexanoic acid (1-benzylcarbamoyl-2-methyl-propyl)-amide according to the procedure described in Example 10, step e.

¹H-NMR (CDCl₃) δ (ppm): 0.81-0.97, 1.38, 1.56, 2.13, 2.27, 2.86, 3.36, 3.38, 3.69-3.75, 3.77-3.84, 3.91, 4.22, 4.29-4.48, 4.54, 6.40, 6.66, 6.83, 7.20-7.36, 7.96, 8.02, 8.25.

Example 13

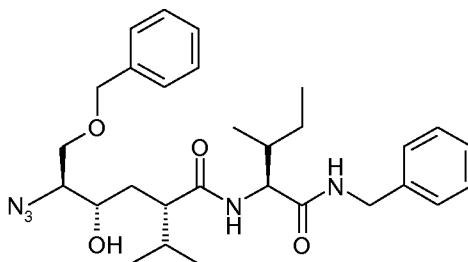
Step a



(1-Benzylcarbamoyl-2-methyl-butyl)-amine (13a)

To a solution pre-cooled to 0 °C of Boc-Ile-OH (0.5 g, 2.16 mmol), benzylamine (0.38 ml, 3.46 mmol), di-isopropyl-ethylamine (3.6 ml) in DMF (10 ml) was added 1080 mg of HATU. The solution was stirred at 0 °C for 30 min, then 2 hours at room temperature. The reaction mixture was evaporated, distributed between water and ethyl acetate. The organic phase was washed with water, brine, dried over sodium sulfate, evaporated and purified by column chromatography (hexane/ethyl acetate 3:1) which gave a pure product (520 mg, 79%). The solid was dissolved in TFA/DCM (1:1) and the resulting solution was stirred at r.t. for 1h. The solvent was evaporated and the afforded oil that was taken into CH₂Cl₂ and washed with 1 M NaOH. The organic phase was dried (Na₂SO₄) and concentrated which gave the title compound as a colourless oil (99%). LC-MS: 221 (M+1)

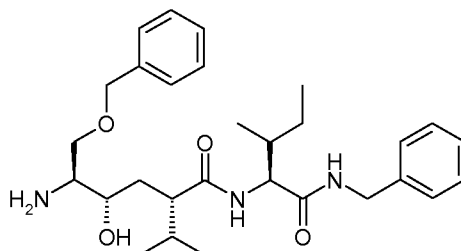
Step b



5-Azido-6-benzyloxy-4-hydroxy-2-isopropyl-hexanoic acid (1-benzylcarbamoyl-2-methyl-butyl)-amide (13b)

A mixture of the lactone 9b (54 mg, 0.178 mmol), the amine 13a (143 mg, 0.653 mmol), 2-hydroxypyridine (62 mg, 0.653 mmol) and EtNⁱPr₂ (100 μL, 0.575 mmol) was heated to 70 °C for 3 days. The reaction mixture was cooled to r.t. and taken into EtOAc/1 M HCl. The organic phase was washed with 1 M HCl, dried (Na₂SO₄) and evaporated to give a yellow solid which was triturated into hot ^tBuOMe to give the title compound as a white solid (65 mg, 70%). LC-MS: 524 (M+1).

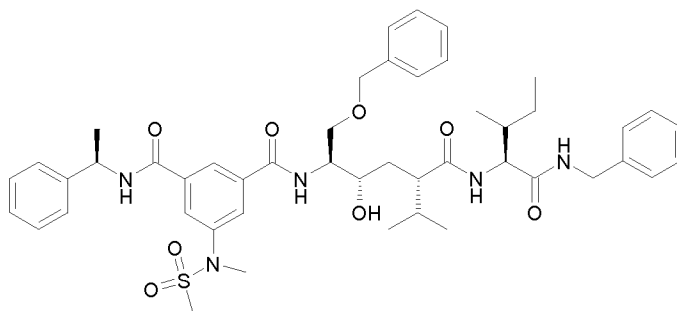
Step c



5-Amino-6-benzyloxy-4-hydroxy-2-isopropyl-hexanoic acid (1-benzylcarbamoyl-2-methyl-propyl)-amide (13c)

A solution of the azide derivative 13b in EtOAc:MeOH (50:1, 8 mL) was hydrogenated in the presence of Pd Lindlar. Filtration of the reaction mixture and evaporation of the solvent afforded an oil that was used without further purification. Yield 130 mg (95%) LC-MS: 498 (M+1).

Step d

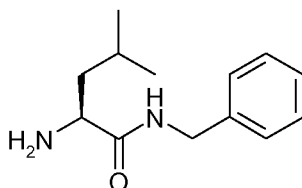


N-[4-(1-Benzylcarbamoyl-2-methyl-butylcarbamoyl)-1-benzyloxymethyl-2-hydroxy-5-methyl-hexyl]-5-(methanesulphonyl-methyl-amino)-N'-(1-phenyl-ethyl)-isophthalamide (13d)

A solution of acid (2*R*,4*S*,5*S*)-5-amino-6-benzyloxy-4-hydroxy-2-isopropyl-hexanoic acid ((*S*)-1-benzylcarbamoyl-2-methyl-propyl)amide (24 mg, 0.0625 mmol), EtNⁱPr₂ (0.2 ml) and HATU (24 mg, 0.0625 mmol) in DMF (0.2 ml) were stirred for 5 min at 0 °C whereafter a solution of the amine 13c (31mg, 0.0625 mmol) in DMF (0.7ml) was added. The reaction mixture was stirred for 20 min and concentrated *in vacuo*. Purification by preparative HPLC (20% acetonitrile in H₂O with 0.1% TFA to 70% acetonitrile) gave the title compound (2.25 mg, 25%). LC-MS: 856 (M+1).

Example 14

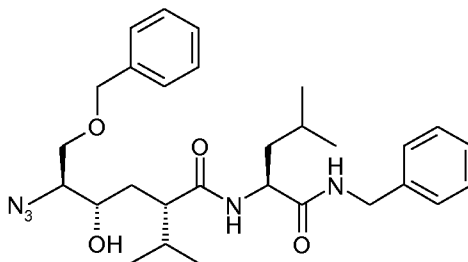
Step a



(1-Benzylcarbamoyl-3-methyl-butyl)-amine (14a)

The title compound was prepared in 75% yield according to the method described in Example 13 step a but using Boc-Leu-OH instead of Boc-Ile-OH. LC-MS: 221 (M+1).

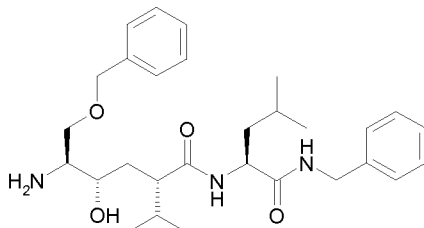
Step b



5-Azido-6-benzyloxy-4-hydroxy-2-isopropyl-hexanoic acid (1-benzylcarbamoyl-2-methyl-butyl)-amide (14b)

The lactone 9b was opened with the amine 14a according to the method described in Example 13, step b, which gave the title compound in 75% yield. LC-MS: 524 (M+1).

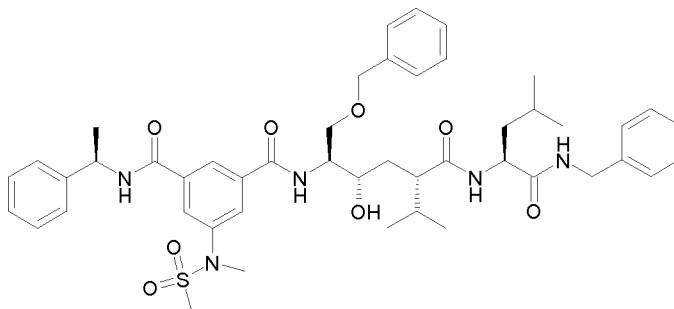
Step c



5-Amino-6-benzyloxy-4-hydroxy-2-isopropyl-hexanoic acid (1-benzylcarbamoyl-2-methyl-propyl)-amide (14c)

The azide group of compound 14b was reduced according to the method described in Example 13 step c, which gave the title compound in 94% yield. LC-MS: 498 (M+1).

Step d

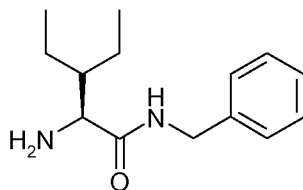


N-[4-(1-Benzylcarbamoyl-3-methyl-butylcarbamoyl)-1-benzyloxymethyl-2-hydroxy-5-methyl-hexyl]-5-(methanesulphonyl-methyl-amino)-N'-(1-phenyl-ethyl)-isophthalamide (14d)

The amine 14c was coupled to (2*R*,4*S*,5*S*)-5-amino-6-benzyloxy-4-hydroxy-2-isopropyl-hexanoic acid ((*S*)-1-benzylcarbamoyl-2-methyl-propyl)amide according to the method described in Example 13 step d, which gave the title compound in 43% yield. LC-MS: 856 (M+1).

Example 15

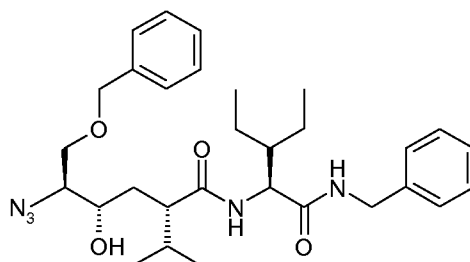
Step a



(1-Benzylcarbamoyl-2-ethyl-butyl)-amine (15a)

The title compound was prepared in 78% yield according to the method described in Example 13 step a but using 2-tert-butoxycarbonylamino-3-ethyl-pentanoic acid instead of Boc-Ile-OH. LC-MS: 235 (M+1).

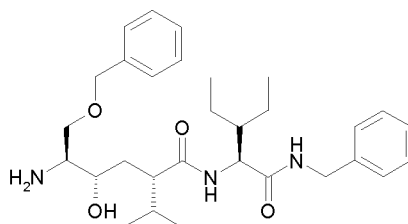
Step b



5-Azido-6-benzyloxy-4-hydroxy-2-isopropyl-hexanoic acid (1-benzylcarbamoyl-2-ethyl)-amide (15b)

The lactone 9b was opened with the amine 15a according to the method described in Example 13, step b, which gave the title compound in 74% yield. LC-MS: 538 (M+1).

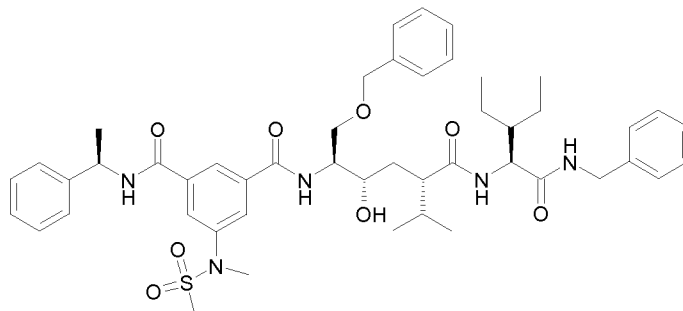
Step c



5-Amino-6-benzyloxy-4-hydroxy-2-isopropyl-hexanoic acid (1-benzylcarbamoyl-2-ethyl-propyl)-amide (15c)

The azide group of compound 15b was reduced according to the method described in Example 13 step c, which gave the title compound in 95% yield. LC-MS: 512 (M+1).

Step d

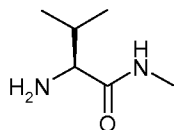


N-[4-(1-Benzylcarbamoyl-2-ethyl-butylcarbamoyl)-1-benzyloxymethyl-2-hydroxy-5-methyl-hexyl]-5-(methanesulphonyl-methyl-amino)-N'-(1-phenyl-ethyl)-isophthalamide (15d)

The amine 15c was coupled to (2*R*,4*S*,5*S*)-5-amino-6-benzyloxy-4-hydroxy-2-isopropyl-hexanoic acid ((*S*)-1-benzylcarbamoyl-2-methyl-propyl)amide according to the method described in Example 13 step d, which gave the title compound in 65% yield. LC-MS: 870 (M+1).

Example 16

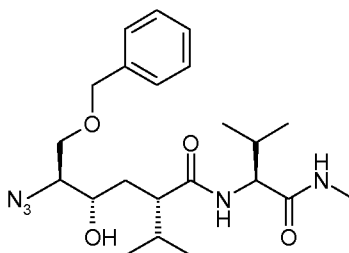
Step a



(1-Methylcarbamoyl-2-methyl-propyl)-amine (16a)

The title compound was prepared in 76% yield according to the method described in Example 13 step a but using a 40% water solution of methylamine instead of Boc-Ile-OH. LC-MS: 131 (M+1).

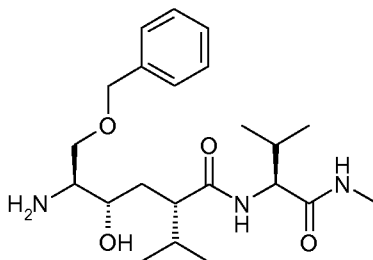
Step b



5-Azido-6-benzyloxy-4-hydroxy-2-isopropyl-hexanoic acid (1-methylcarbamoyl-2-methyl-propyl)-amide (16b)

The lactone 9b was opened with the amine 16a according to the method described in Example 13, step b, which gave the title compound in 63% yield. LC-MS: 434 (M+1).

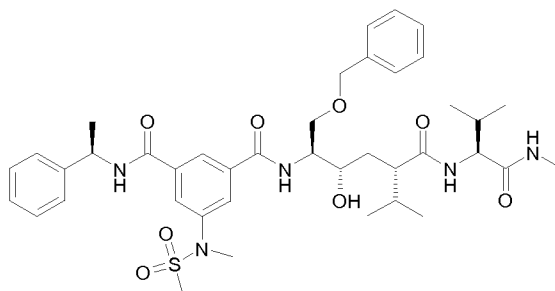
Step c



5-Amino-6-benzyloxy-4-hydroxy-2-isopropyl-hexanoic acid (1-benzylcarbamoyl-2-methyl-propyl)-amide (16c)

The azide group of compound 16b was reduced according to the method described in Example 13 step c, which gave the title compound in 94% yield. LC-MS: 408 (M+1).

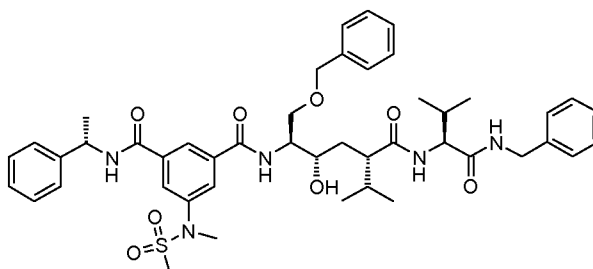
Step d



N-[4-(1-Benzylcarbamoyl-2-methyl-propylcarbamoyl)-1-benzyloxymethyl-2-hydroxy-5-methyl-hexyl]-5-(methanesulphonyl-methyl-amino)-N'-(1-phenyl-ethyl)-isophthalamide (16d)

The amine 16c was coupled to (2*R*,4*S*,5*S*)-5-amino-6-benzyloxy-4-hydroxy-2-isopropyl-hexanoic acid ((*S*)-1-benzylcarbamoyl-2-methyl-propyl)amide according to the method described in Example 13 step d, which gave the title compound in 58% yield. LC-MS: 766 (M+1).

Example 17



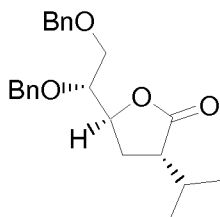
N-[(1*S*,2*S*,4*R*)-4-((*S*)-1-benzylcarbamoyl-2-methylpropylcarbamoyl)-1-benzyloxymethyl-2-hydroxy-5-methylhexyl]-5-(methanesulphonylmethylamino)-N'-((*S*)-1-phenylethyl)isophthalamide (17)

HATU (3.2 mg, 8.4 μ mol) was added to a solution of the acid 5-(methanesulphonylmethylamino)-*N*'-((*S*)-1-phenylethyl)isophthalamide [prepared according to the method described by Stachel et al. in J. Med. Chem., 47, (2004), 6447-6450] (3.1 mg, 8.4 μ mol) and Et₃N (3 μ L, 16.8 μ mol) in DMF (0.25 mL) and the resulting mixture was stirred for

2 min before adding 5-amino-6-benzyloxy-4-hydroxy-2-isopropyl-hexanoic acid (1-benzylcarbamoyl-2-methyl-propyl)-amide (5 mg, 8.4 μmol). The reaction mixture was stirred 5 min at r.t. and then concentrated under vacuum. The residue was purified by preparative HPLC (20% acetonitrile in H_2O to 100% acetonitrile) which gave the title compound (3.3 mg, 48%). MS 842 ($\text{M}+\text{H}$)⁺.

Example 18

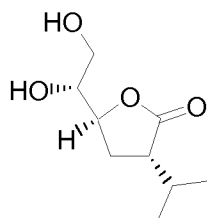
Step a



5-(1,2-Bis-benzyloxyethyl)-3-isopropylidihydrofuran-2-one (18a)

A solution of compound 1d (3.1 g, 9.51 mmol) in THF (30 mL) was added to a 1 M solution of LDA in THF (20 mL, 20 mmol) at $-60\text{ }^{\circ}\text{C}$ under N_2 . The reaction mixture was then treated with tris(pyrrolidinophosphine) oxide (15 mL) followed by iodopropane (3.8 mL, 38.1 mmol). Stirring at $-60\text{ }^{\circ}\text{C}$ was continued for 1 h and the reaction mixture was quenched with aq. NH_4Cl . The phases were separated and the aqueous phase was extracted with $^t\text{BuOMe}$. The combined organic extracts were dried (Na_2SO_4) and the solvent evaporated. The residue was purified by flash chromatography on silica gel (Hex:EtOAc 10:1) which gave the title compound (1.2 g, 34%) as a colourless oil.

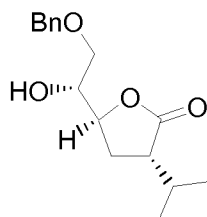
Step b



5-(1,2-Dihydroxyethyl)-3-isopropylidihydrofuran-2-one (18b)

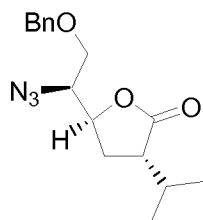
A solution of compound 18e (2.58 g, 7.01 mmol) in MeOH (50 mL) was hydrogenated in the presence of 10% Pd/C at 3 bar H_2 pressure. Filtration of the catalyst and evaporation of the solvent afforded the title compound (1.2 g, 92%) as a white solid.

Step c

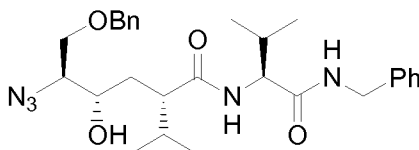


5-(1-Hydroxy-2-benzyloxyethyl)-3-isopropyl-dihydrofuran-2-one (18c)

A solution of compound 1f (0.6 g, 3.19 mmol) and Bu_2SnO (1.0 g, 4.0 mmol) in toluene (50 mL) was refluxed with a Dean-Stark trap for 4 h. The reaction mixture was cooled down to 90 °C and benzyl bromide (0.43 mL, 3.66 mmol) and Bu_4NBr (1.18 g, 3.66 mmol) were added. Stirred further 22 h at 90 °C, concentrated under vacuum and the residue purified by flash chromatography on silica gel (Hex:EtOAc 10:1 to 2.5:1) to give the title compound (0.7 g) as a colourless oil.

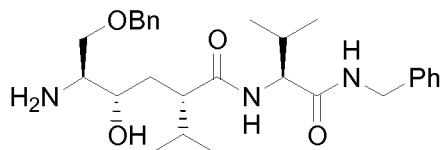
Step d5-(1-Azido-2-benzyloxyethyl)-3-isopropyl-2-oxotetrahydrofuran (18d)

A solution of compound 18c (278 mg, 1 mmol) and pyridine (140 μL , 1.7 mmol) in CH_2Cl_2 (5 mL) was treated with TiF_4 (220 μL , 1.3 mmol) at room temperature. Stirred for 30 min and quenched with H_2O . The product was extracted into CH_2Cl_2 and the combined extracts were dried (Na_2SO_4) and the solvent evaporated to give a yellow oil that was dissolved in DMF (1 mL). Sodium azide (325 mg, 5 mmol) was added and the resulting suspension was stirred at 60 °C for 1 h. The reaction mixture was concentrated under vacuum and the residue was purified by flash chromatography on silica gel (Hex:EtOAc 2.5:1) which gave the title compound (180 mg, 59%) as a colourless oil.

Step e5-Azido-6-benzyloxy-4-hydroxy-2-isopropylhexanoic acid (1-benzylcarbamoyl-2-methylpropyl)-amide (18e)

A mixture of the lactone 18d (200 mg, 0.66 mmol), the amine 1i (665 mg, 3.2 mmol), 2-hydroxypyridine (296 mg, 3.1 mmol) and Et_3N (200 μL , 1.15 mmol) was heated to 70 °C for 3 days. The reaction mixture was cooled down to room temperature and taken into EtOAc/1 M HCl. The organic phase was washed with 1 M HCl, dried (Na_2SO_4) and evaporated to give a yellow solid that was triturated into hot BuOMe which gave the title compound (235 mg, 70%) as a white solid.

Step f

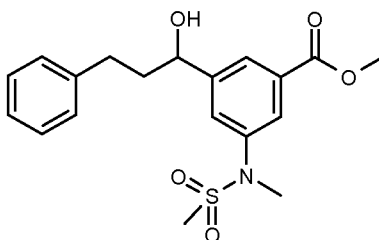


5-Amino-6-benzyloxy-4-hydroxy-2-isopropyl-hexanoic acid (1-benzylcarbamoyl-2-methylpropyl)-amide (18f)

A solution of the azide 18e in EtOAc:MeOH (50:1, 8 mL) was hydrogenated in the presence of Pd Lindlar. Filtration of the product and evaporation of the solvent afforded an oil that was purified by preparative HPLC (5% acetonitrile in H₂O with 0.1% TFA to 30% acetonitrile) which gave the title compound (52 mg, 38%) as its TFA salt.

¹H-NMR (*d*₆-DMSO) δ (ppm): 0.77-0.86, 1.45, 1.62-1.72, 1.89, 2.30, 3.10, 3.44-3.57, 4.16-4.24, 4.29, 4.32, 4.45, 4.51, 5.29, 7.17-7.38, 7.72, 7.77, 8.47.

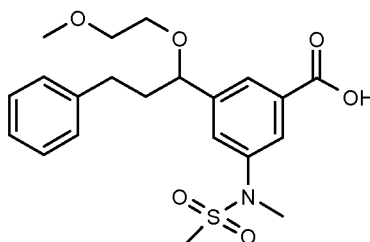
Step g



3-(1-Hydroxy-3-phenyl-propyl)-5-(methanesulphonyl-methyl-amino)-benzoic acid methyl ester (18g)

The Grignard reagent phenylethylmagnesium chloride (1.0 M in THF, 0.32 mL, 0.32 mmol) was added dropwise to a cooled solution (-78 °C) of the aldehyde 3-formyl-5-[methanesulphonyl(methyl)amino]benzoic acid methyl ester (0.26 mmol as 3.0 mL solution in 2/1 THF-Et₂O), prepared as described in Bioorg. Med. Chem. letters, (2006), 641-644, and the mixture was stirred for 6 h. Saturated aqueous NH₄Cl solution (5 mL) was added, the mixture was warmed to RT, and then more NH₄Cl solution (5 mL) was added. The mixture was extracted with EtOAc (3 x 10 mL). The organic phase was washed with saturated aqueous NaCl (10 mL), dried over Na₂SO₄ and evaporated to give a colourless oil. A second batch of aldehyde (1.09 mmol) suspended in 10 mL THF was treated similarly, using 1.65 ml of the Grignard reagent (1.65 mmol) with stirring for 4 h. The crude products were combined and subjected to flash chromatography (silica, 97/3 CH₂Cl₂ – MeOH) to give the title alcohol (321.8 mg, 63% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.96 (m, 1H), 7.89 (m, 1H), 7.63 (m, 1H), 7.32 - 7.18 (m, 5H), 4.77 (m, 1H, CHOH), 3.93 (s, 3H), 3.35 (s, 3H), 2.86 (s, 3H), 2.75 (m, 2H, PhCH₂), 2.14 - 2.0 (m, 3H, CHOH and PhCH₂CH₂). LCMS [M+18]⁺=395

Step h



3-(Methanesulphonyl-methyl-amino)-5-[1-(2-methoxy-ethoxy)-3-phenyl-propyl]-benzoic acid (18h)

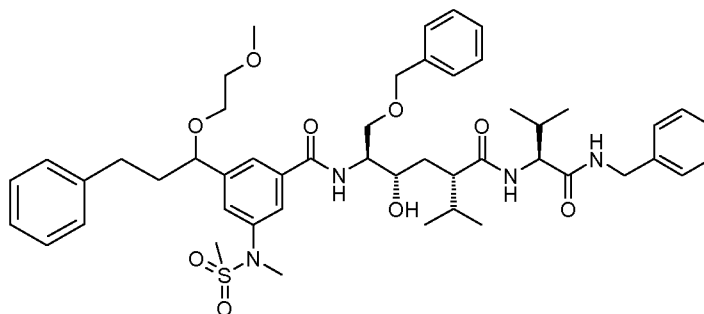
NaH (35.4 mg 60% dispersion in mineral oil, 2 eq) in DMF (4 mL) was added to a solution of alcohol 18g (167 mg, 0.442 mmol, 1 eq) in 2 mL DMF with cooling at -10 to -15 °C. After 30 min, 2-bromoethyl methyl ether (41.5 μ L, 1 eq) was added. The mixture was stirred in the cold bath for 3 h, then quenched with 1N HCl and MeOH, concentrated under vacuum, and partitioned between saturated aqueous NaCl and EtOAc. The organic phase was dried (Na_2SO_4) and evaporated. Flash column chromatography (silica, 95/5/0.5 CH_2Cl_2 -MeOH-HOAc) gave the carboxylic acid from hydrolysis (135.5 mg, 84%) but not the ether.

NaH (49 mg, 60 wt% dispersion, 6.8 eq) was added to the hydrolysis product above (65.1 mg, 0.18 mmol, 1 eq) followed by DMF (2 mL). The suspension was stirred for 20 min at RT, and then 2-bromoethyl methyl ether (115 μ L, 6.8eq) was added. After 4 h, the mixture was quenched with water – ice and acidified with 1N HCl. The mixture was extracted with EtOAc (4 x 10 mL). The organic phase was washed with saturated aqueous NaCl (10 mL), dried (Na_2SO_4), and evaporated. Flash chromatography (silica, 95/5/0.5 CH_2Cl_2 -MeOH-HOAc) gave the title compound (70.4 mg, 93% yield).

^1H NMR (400 MHz, CDCl_3) δ 7.98 – 7.94 (m, 2H), 7.66 (m, 1H), 7.3 – 7.14 (m, 5H), 4.32 (dd, 1H, $J = 8.6, 4.6$ Hz, CH_2OCH_2), 3.62 – 3.46 (m, 4H, $\text{OCH}_2\text{CH}_2\text{O}$), 3.39 (s, 3H), 3.36 (s, 3H), 2.87 (s, 3H), 2.84 – 2.66 (m, 2H, PhCH_2), 2.15 (m, 1H, PhCH_2CH_2), 1.95 (m, 1H, PhCH_2CH_2).

LCMS $[\text{M}+18]^+ = 439$

Step i



N-[4-(1-Benzylcarbamoyl-2-methyl-propylcarbamoyl)-1-benzyloxymethyl-2-hydroxy-5-methyl-hexyl]-3-(methanesulphonyl-methyl-amino)-5-[1-(2-methoxy-ethoxy)-3-phenyl-propyl]-benzamide (18i)

A solution of carboxylic acid 18h (0.038 mmol) and the amine (2S,4S,5S)-5-amino-6-benzyloxy-4-hydroxy-2-isopropylhexanoic acid (1S)-(1-benzylcarbamoyl-2-methylpropyl)amide (0.038 mmol) in CH_2Cl_2 was co-evaporated several times with toluene. HATU (16 mg, 0.042 mmol, 1.1 eq) was added, followed by DMF (0.50 mL) and then DIEA (20 μL , 0.0115 mmol, 3eq). After 2.5 h, the mixture was evaporated and then partitioned between 10% NaHCO_3 and CH_2Cl_2 . The organic phase was washed with saturated aqueous NaCl, dried (Na_2SO_4), and evaporated. Purification by prep HPLC-MS (gradient 30-65% MeCN – water, 0.1% TFA, in 4 min) gave the title compound as white solids (14.6 mg, 43% yield).

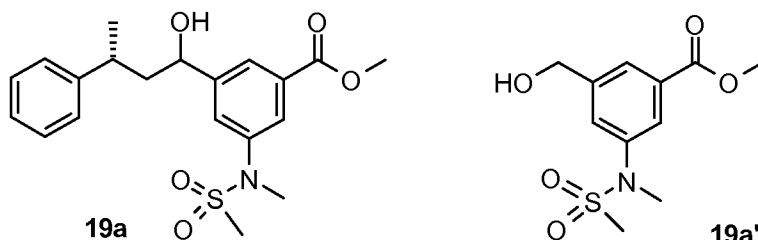
^1H NMR (500 MHz, CDCl_3) 2 diastereomers δ 7.76 (m, 1H), 7.65 (m, 1H), 7.53 (m, 1H), 7.35 – 7.15 (m, 15H), 7.03 (m, 1H, NH), 6.54 (m, 1H, NH), 6.38 (d, 1H, NH), 4.55 – 4.50 (m, 2H, OCH_2Ph), 4.41 (m, 2H, NHCH_2Ph), 4.30 – 4.24 (m, 2H), 4.16 (m, 1H), 3.93 – 3.76 (m, 1H, CHOH), 3.75 (m, 2H, $\text{CH}_2\text{OCH}_2\text{Ph}$), 3.60 (m, 1H), 3.49 – 3.45 (m, 3H), 3.35 and 3.34 (2s, 3H, OMe), 3.33 (s, 3H, NMe), 2.84 (s, 3H, SO_2Me), 2.80 and 2.72 (m, 1H each, PhCH_2CH_2), 2.25 – 2.07 (m, 3H), 1.93 (m, 1H), 1.85 – 1.65 (m, 3H), 0.94 (d, 3H), 0.92 (d, 3H), 0.87 (dd, 3H), 0.83 (dd, 3H).

LCMS 70 to 99 % B in 3 min, retention time = 0.99 min; $[\text{M}+18]^+ = 887$;

LCMS method : Flow 0.8 mL/min, ACE C8 3x50 mm, UV = 220 nm or 210 - 400 nm, API-ES positive and negative; Mobile phase A 10 mM NH_4Ac in 90% H_2O , B 10 mM NH_4Ac in 90% MeCN.

Example 19

Step a



3-(1-Hydroxy-3-phenyl-butyl)-5-(methanesulphonyl-methyl-amino)-benzoic acid methyl ester (19a)

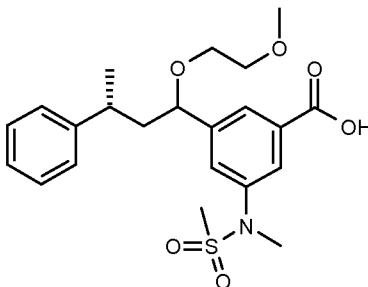
Excess Grignard reagent [(R)-2-phenyl-1-propylmagnesium bromide, prepared from (R)-1-bromo-2-phenylpropane (411 mg, 2.1 mmol), and 215 mg Mg in 5.5 mL THF] was added dropwise to a cooled solution (-78 °C) of the aldehyde 3-formyl-5-[methanesulphonyl(methyl)amino]benzoic acid methyl ester (147 mg, 0.54 mmol) (prepared as described in Bioorg. Med. Chem. letters, 2006, 641-644) in THF (3 mL) and stirred for 4h 15 min. The mixture was quenched with saturated aqueous NH_4Cl (10 mL), allowed to warm to RT, and then more NH_4Cl solution (5 mL) was added. The mixture was extracted with EtOAc (5 x 10 mL). The organic phase was washed with saturated aqueous NaCl (10 mL), dried over Na_2SO_4 and concentrated. The crude material was purified by flash chromatography (silica, 95/5 CH_2Cl_2

- acetone, then 90/10 CH₂Cl₂ – MeOH) which gave the desired alcohol 2a (62.5 mg, 30%) and also benzylic alcohol 2a' from reduction of the starting aldehyde.

LCMS [M+18] = 409.

2a': ¹H NMR (400 MHz, CDCl₃) δ7.95 (s, 1H), 7.89 (m, 1H), 7.63 (m, 1H), 4.75 (d, 2H, J = 6 Hz), 3.92 (s, 3H), 3.35 (s, 3H), 2.86 (s, 3H), 2.29 (t, 1H, J = 6 Hz). LCMS [M + 18]⁺ = 291

Step b

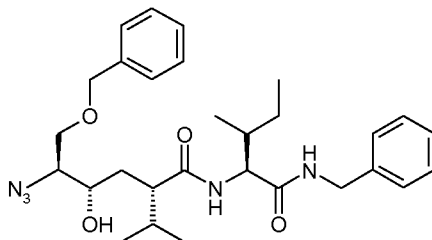


3-(Methanesulphonyl-methyl-amino)-5-[1-(2-methoxy-ethoxy)-3-phenyl-butyl]-benzoic acid (19b)

The methyl ester 19a (62.5 mg, 0.16 mmol) was hydrolyzed with 2N NaOH (0.25 mL, 0.5 mmol) in 2 mL 1/1 THF – MeOH by stirring at RT for 3h 15 min. The mixture was evaporated, diluted with 5 mL water, acidified with 1N HCl, and extracted with EtOAc (3 x 10 mL). The organic phase was washed with saturated NaCl (10 mL), dried (Na₂SO₄), and evaporated to give the carboxylic acid as white solids (56.4 mg, 93%).

NaH (28mg, 60 wt% dispersion, 12 eq) and DMF (1.5 mL) were added successively to the carboxylic acid above (0.057 mmol) and stirred at RT for 15 min. 2-Bromoethyl methyl ether (65 µL, 11.5 eq) was added. After 3.5 h, the mixture was quenched with water – ice, acidified with 1N HCl, and extracted with EtOAc (4 x 10 mL). The organic phase was washed with saturated aqueous NaCl (10 mL), dried (Na₂SO₄), and concentrated under vacuum. Flash chromatography (silica, 95/5/0.5 CH₂Cl₂ – MeOH – HOAc) gave the title compound as a white solid in quantitative yield. LCMS [M – H][–] = 434.

Step c

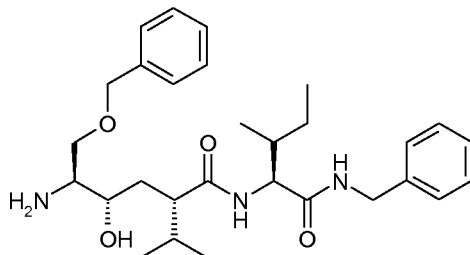


5-Azido-6-benzyloxy-4-hydroxy-2-isopropyl-hexanoic acid (1-benzylcarbamoyl-2-methyl-butyl)-amide (19c)

A mixture of the lactone (18h) (54 mg, 0.178 mmol), the amine (13a) (143 mg, 0.653 mmol), 2-hydroxypyridine (62 mg, 0.653 mmol) and EtNⁱPr₂ (100 µl, 0.575 mmol) was heated to 70 °C for

3 days. The reaction mixture was cooled to r.t. and taken into EtOAc/1 M HCl. The organic phase was washed with 1 M HCl, dried (Na₂SO₄) and evaporated which gave a yellow solid that was triturated into hot ^tBuOMe to give 65 mg (70%) of the title compound as a white solid. LC-MS: 524 (M+1).

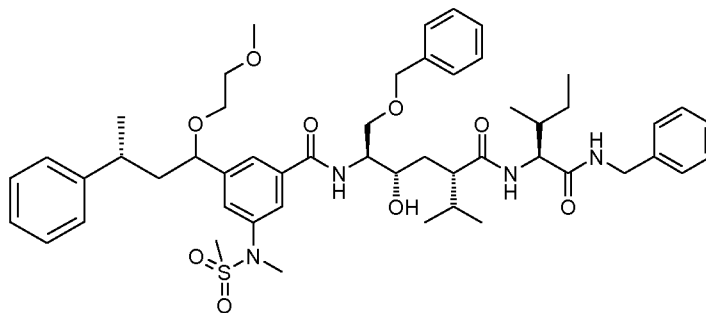
Step d



5-Amino-6-benzyloxy-4-hydroxy-2-isopropyl-hexanoic acid (1-benzylcarbamoyl-2-methyl-propyl)-amide (19d)

The azide (19c) in EtOAc:MeOH (50:1, 8 mL) was hydrogenated in the presence of Pd Lindlar. Filtration of the product and evaporation of the solvent afforded an oil that was purified by preparative HPLC (5% acetonitrile in H₂O with 0.1% TFA to 30% acetonitrile) to give 52 mg (38%) of the title compound as its TFA salt. LC-MS: 498 (M+1)

Step e



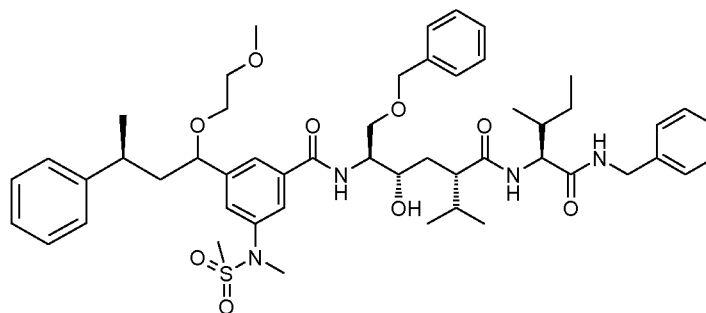
N-[4-(1-Benzylcarbamoyl-2-methyl-butylcarbamoyl)-1-benzyloxymethyl-2-hydroxy-5-methyl-hexyl]-3-(methanesulphonyl-methyl-amino)-5-[1-(2-methoxy-ethoxy)-3-phenyl-butyl]-benzamide (19e)

To the carboxylic acid 19b (0.057 mmol, previously co-evaporated with DMF)) were added in sequence 250 μ L DMF, HATU (28.8 mg, 0.0757 mmol), and DIEA (39.5 μ L, 0.226 mmol). After stirring for 10 min, the amine 2f (30.2 mg, 0.0605 mmol) and 200 μ L DMF were added. After 40 min, water (5 mL) was added and the mixture was extracted with CH₂Cl₂ (3 x 5 mL). The organic phase was washed successively with 5 mL each 10% NaHCO₃, 0.5 N HCl, and saturated aqueous NaCl. After drying (Na₂SO₄), the solvent was removed under vacuum. Flash chromatography (silica, 95/5 CH₂Cl₂ – MeOH) gave the final product example II as white solids (41.7 mg, 80%).

^1H NMR (500 MHz, CDCl_3) 2 diastereomers δ 7.76 and 7.70 (m, 1H), 7.62 and 7.52 (m, 1H), 7.46 and 7.44 (m, 1H), 7.34 - 7.16 (m, 15H), 7.01 - 6.95 (m, 1H, NH), 6.50 - 6.45 (m, 1H, NH), 6.29 - 6.26 (m, 1H, NH), 4.52 - 4.51 (m, 2H, OCH_2Ph), 4.45 - 4.36 (m, 2H, NHCH_2Ph), 4.34 - 4.31 (m, 1H), 4.25 and 3.95 - 3.90 (m, 2H, $\text{CHOCH}_2\text{CH}_2$) and CHOH), 4.15 (br, 1H), 3.78 - 3.72 (m, 3H), 3.57 - 3.24 (m, 4H, $\text{OCH}_2\text{CH}_2\text{O}$), the singlets 3.343, 3.331, 3.321, 3.318, 3.312, 3.306, and 3.303 (6H, OMe and NMe), 3.13 and 2.78 (m, 1H, PhCHMe), 2.85 and 2.83 (2s, 3H, SO_2Me), 2.23 - 2.16 and 2.04 (m, 2H), 1.94 (br, 1H), 1.86 - 1.64 (m, 4H), 1.51 and 1.12 (m, 2H), 1.26 - 1.24 (m, 3H, PhCHMe), 0.92 - 0.82 (m, 12H).

LCMS 70 to 99 % B in 3 min, retention time = 1.38 min; $[\text{M}+1]^+ = 915$

Example 20



N-[4-(1-Benzylcarbamoyl-2-methyl-butylcarbamoyl)-1-benzylloxymethyl-2-hydroxy-5-methyl-hexyl]-3-(methanesulphonyl-methyl-amino)-5-[1-(2-methoxy-ethoxy)-3-phenyl-butyl]-benzamide (20)

The procedure described in Example 19 was followed using the Grignard reagent [(S)-2-phenyl-1-propylmagnesium bromide (prepared from (S)-1-bromo-2-phenylpropane)] instead of and the same starting aldehyde. Upon addition of water in the HATU coupling step a white precipitate was formed which was subsequently filtered, washed with water, and freeze-dried from MeCN/water to give the title compound as white solids.

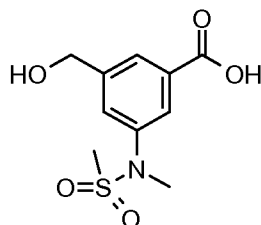
^1H NMR (500 MHz, CDCl_3) 2 diastereomers δ 7.75 and 7.70 (m, 1H), 7.61 and 7.52 (m, 1H), 7.46 and 7.44 (m, 1H), 7.34 - 7.16 (m, 15H), 6.98 (m, 1H, NH), 6.50 (m, 1H, NH), 6.30 (dd, 1H, NH), 4.53 - 4.52 (m, 2H, OCH_2Ph), 4.46 - 4.36 (m, 2H, NHCH_2Ph), 4.31 (m, 1H), 4.25 and 3.95 - 3.90 (m, 2H, $\text{CHOCH}_2\text{CH}_2$ and CHOH), 4.15 (br, 1H, NHCHCHOH), 3.78 - 3.72 (m, 3H), 3.58 - 3.24 (m, 4H, $\text{OCH}_2\text{CH}_2\text{O}$), the singlets 3.34, 3.32, and 3.30 (6H, OMe and NMe), 3.13 and 2.78 (m, 1H, PhCHMe), 2.85 and 2.83 (2s, 3H, SO_2Me), 2.30 - 2.17 and 2.04 (m, 2H), 1.94 (br, 1H), 1.85 - 1.63 (m, 4H), 1.51 and 1.12 (m, 2H), 1.26 and 1.24 (2s, 3H, PhCHMe), 0.92 and 0.91 (m, 3H, CH_2Me), 0.87 - 0.82 (m, 9H).

LCMS $[\text{M}+1]^+ = 915$

Example 21

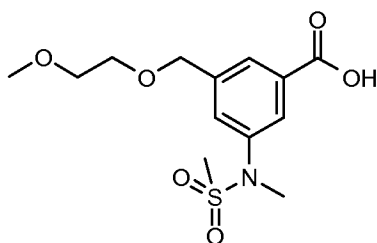
Step a

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The methyl ester of alcohol 19a' (80 mg, 0.29 mmol) was hydrolyzed by stirring with 0.45 mL 2N NaOH (0.9 mmol) in 3 mL 1/1 THF – MeOH for 3 h. The mixture was diluted with water (10 mL), acidified, and then extracted with EtOAc (4 x 15 mL). The organic phase was washed with saturated aqueous NaCl (10 mL), dried (Na₂SO₄), and evaporated to give the carboxylic acid as white solids in quantitative yield. Half of this material was used in the next step.

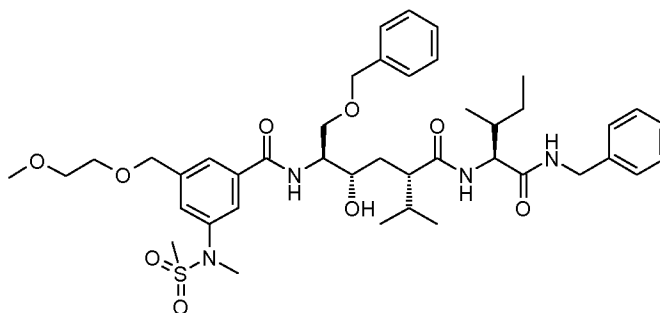
Step b



3-(Methanesulphonyl-methyl-amino)-5-(2-methoxy-ethoxymethyl)-benzoic acid (21b)

NaH (90mg, 60 wt% dispersion, 15 eq)) and DMF (2.0 mL) were added successively to the hydrolysis product 21a and stirred at RT for 15 min. 2-Bromoethyl methyl ether (15 eq) was added. After 2 h 15 min, the mixture was quenched with water – ice, acidified with 1N HCl, and extracted with EtOAc (4 x 15 mL). The organic phase was washed with saturated aqueous NaCl (15 mL), dried (Na₂SO₄), and concentrated under vacuum. Flash chromatography (silica, 95/5/0.5 CH₂Cl₂ – MeOH – HOAc) gave the title ether carboxylic acid as an oil (38 mg, 83%). LCMS [M-1]⁻ = 316.

Step c



N-[4-(1-Benzylcarbamoyl-2-methyl-butylcarbamoyl)-1-benzyloxymethyl-2-hydroxy-5-methyl-hexyl]-3-(methanesulphonyl-methyl-amino)-5-(2-methoxy-ethoxymethyl)-benzamide (21c)

The acid 21b (0.0544 mmol) was coupled to the amine 19d (29.1 mg, 0.0583 mmol) as described in Example 2 step d. Purification by chromatography (silica, 100/2 EtOAc – MeOH) gave the title compound as white solids (30.9 mg, 71%).

^1H NMR (400 MHz, CDCl_3) δ 7.75 (m, 1H), 7.64 (s, 1H), 7.54 (s, 1H), 7.32 – 7.20 (m, 10H), 6.98 (d, 1H), 6.61 (t, 1H), 6.40 (d, 1H), 4.58 (s, 2H), 4.50 (s, 2H), 4.43 – 4.29 (m, 3H), 4.15 (m, 1H), 3.92 (d, 1H), 3.80 (d, 1H), 3.73 (d, 2H), 3.66 – 3.63 (m, 2H), 3.57 – 3.55 (m, 2H), 3.36 (s, 3H), 3.30 (s, 3H), 2.82 (s, 3H), 2.18 (m, 1H), 1.92 (m, 1H), 1.84 – 1.63 (m, 3H), 1.50 (m, 1H), 1.11 (m, 1H), 0.91 – 0.80 (m, 12H).

LCMS 30-80% B in 3 min, retention time = 2.90 min, $[\text{M}+1]^+ = 797$.

Biological Examples

To evaluate the enzymatic inhibition of renin exhibited by the compounds of the invention, an assay using Fluorescence Resonance Energy Transfer (FRET) to generate a spectroscopic response to peptidase cleavage, was used. The activity was measured by a continuous detection of increased fluorescence intensity exhibited by the cleavage product (peptide-EVANS). The enzyme used in the assay was recombinant human renin (supplied by Proteos), the substrate consisted of a peptide which in one end is linked to a fluorophore, 5-(aminoethyl)aminonaphtalene sulphonate (EDANS), and in the other end to a non-fluorescent chromophore, 4'-dimethylaminoazobenzene (Dabcyl), typically Arg-Glu(EDANS)-Ile-His-Pro-Phe-His-Leu-Val-Ile-His-Thr-Lys(DABCYL)-Arg (Sigma-Aldrich). The cleavage site by human renin is the peptide bond between Leu and Val. The compounds were tested at a range of concentrations whereas the enzyme and substrate concentrations were fixed. The assay used employs the enzyme at a concentration of 6.25nM in an assay buffer consisting of 0.1 mM Tris-HCl, 0.05 M NaCl, 0.5 mM EDTA, 0.05% CHAPS at pH=7.4. The substrate was prepared at a 20 μM stock solution in DMSO. To each well of a 96-well polypropylene plate was added the enzyme containing assay buffer (90.0 μl) and inhibitor of different concentrations (1 μl). To control wells were added DMSO (1 μl) instead of inhibitor. The renin enzyme was preactivated by incubation at 37 °C for 20 min whereafter the reactions were started by addition of substrate, 10 μl /well, thus giving a total volume of 100 μl /well and a substrate concentration of 2 μM . The assay was performed during 20 min at 37 °C. The total concentration of DMSO was not above 1 %. Product fluorescence (emission filter 340 nm, excitation filter 500 nm) was monitored with a Thermo Labsystems Fluoroskan Ascent plate reader. The K_i was determined by Prism Software. Activity of the inhibitors was determined by measuring the fluorescence at λ_{ex} 340nm and λ_{em} 500nm. Percent inhibition is calculated as follows: % Inhibition is equal to the $(\text{Fluorescence}_{\text{plus inhibitor}} - \text{Fluorescence}_{\text{background}})$; divided by the $(\text{Fluorescence}_{\text{minus inhibitor}} - \text{Fluorescence}_{\text{background}})$;

For example, Table 1 shows enzymatic inhibition of renin for a representative selection of compounds according to the invention when tested in an renin enzyme assay such as the one described above. Category A indicates ≤ 50 nM inhibition, category B indicates 51 - 200 nM inhibition and category C indicates > 200 nM:

<u>Example No.</u>	<u>Ki</u>
1l	B
2e	A
3c	C
4c	C
5	C
6f	B
7c	C
8h	C
9e	A
10e	C
11f	C
12c	B
13d	A
14d	A
15d	A
16d	C
17	A
18h	A
19f	A
20	A
21c	B

To evaluate the enzymatic inhibition of BACE1 exhibited by the compounds of the invention, a TruPoint™ Beta-Secretase Assay Kit may be used. The assay is based on the close proximity of two labels, a fluorescent europium chelate and a quencher of europium fluorescence.

Fluorescence is strongly quenched when the labels are in close proximity of each other, and when the labels are separated, lanthanide fluorescence can be measured by time-resolved fluorometry (TRF).

The enzyme used in the assay is recombinant BACE1 (produced in house) and the substrate is a 10 amino acids long peptide with a fluorescent europium chelate coupled to one end and a quencher of europium fluorescence (QSY 7) coupled via lysine to the other end; EU-CEVNLDAEFK-QSY 7. The cleavage site by BACE1 is the peptide bond between L and D.

A spectroscopic response is generated by peptidase cleavage, and the activity was measured by a continuous detection of increased fluorescence intensity exhibited by the cleavage product. The compounds were tested at a range of concentrations whereas the enzyme and substrate concentrations were fixed. The assay used employs the enzyme at a concentration of 10 nM in a reaction buffer consisting of 50 mM sodium acetate, CHAPS, 0.05% Triton X-100 and EDTA at pH=4.5. The substrate was prepared at a 120 µM stock solution in distilled water. The stock

solution was diluted to 400 nM in an amount which was needed for the day. To each well of a 96-well half area polystyrene plate was added the enzyme containing reaction buffer (15 µl) and inhibitor of different concentrations in DMSO (1 µl). To control wells were added reaction buffer (15 µl) and DMSO (1 µl). The enzyme with inhibitor in DMSO was preincubated at room temperature (20-25 °C) for 30 min whereafter the reactions were started by addition of substrate, 15 µl/well, thus giving a total volume of 31 µl/well and a substrate concentration of 200 nM. Product TR-fluorescence was monitored during 90 min with a 1420 VICTOR and presented as Relative Fluorescence units (RFu). The IC₅₀ value was calculated with GraFit software. Activity of the inhibitors was determined by measuring the TR-fluorescence at λ_{ex} 330 nm and λ_{em} 615 nm. The inhibition is calculated as follows:

$$100 - \left(\frac{\text{RFu}_{\text{inhibitor}} - \text{RFu}_{\text{background}}}{\text{RFu}_{\text{enzyme control}} - \text{RFu}_{\text{background}}} \right) \times 100 = \% \text{ inhibition}$$

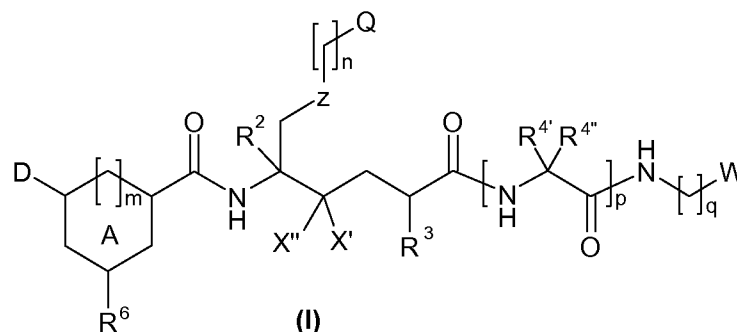
For example, Table 2 shows the enzymatic inhibition exhibited by a representative selection of compounds according to the invention when tested in a BACE enzyme assay such as the one described above. Category A indicates an IC₅₀ value of < 1 µM, category B indicates 1 - 5 µM and category C indicates > 5 µM.

TABLE 2

<u>Example No.</u>	<u>IC₅₀</u>		<u>Example No.</u>	
1l	A		12c	B
2e	A		13d	B
3c	C		14d	B
4c	B		15d	B
5	B		16d	A
6f	A		17	B
7c	A		18i	B
8h	C		19e	B
9e	A		20	B
10e	B		21c	C
11f	B			

Claims

1. A compound of the formula:



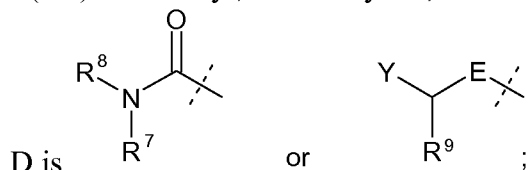
wherein

R^2 is H or C_1 - C_6 alkyl;

R^3 is C_1 - C_6 alkyl, C_1 - C_6 alkoxy C_1 - C_3 alkyl, C_1 - C_3 alkanediylaryl, C_1 - C_3 alkanediylheterocyclyl;

$R^{4'}$ is C_1 - C_6 alkyl and $R^{4''}$ is H; or $R^{4'}$ and $R^{4''}$ together with the carbon atom to which they are attached define C_3 - C_6 cycloalkyl;

R^6 is hydrogen, C_1 - C_6 alkyl, $N(Ra)S(=O)_rC_1$ - C_6 alkyl, $N(Ra)S(=O)_rNRaRb$, $S(=O)_rNRaRb$, $S(=O)_rC_1$ - C_6 alkyl, halo or cyano;



R^7 is C_1 - C_6 alkyl, C_1 - C_6 alkoxy C_1 - C_3 alkyl, hydroxy C_1 - C_3 alkyl, C_1 - C_3 alkanediylNRaRb, aryl, heterocyclyl, C_3 - C_6 cycloalkyl, C_1 - C_3 alkanediyl C_3 - C_6 cycloalkyl, C_1 - C_3 alkanediylaryl, C_1 - C_3 alkanediylheterocyclyl, C_1 - C_3 alkanediyl-O- C_0 - C_3 alkanediyl aryl or C_1 - C_3 alkanediyl-O- C_0 - C_3 alkanediyl heterocyclyl;

wherein the C_1 - C_3 alkanediyl moiety is optionally substituted with C_1 - C_6 alkyl;

R^8 is H, C_1 - C_6 alkyl; or

R^7 and R^8 together with the N atom to which they are attached define a heterocyclyl group;

R^9 is H, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 alkoxy C_1 - C_3 alkyl or C_1 - C_6 alkoxy C_1 - C_6 alkoxy C_0 - C_3 alkyl;

E is -CH(Rc)-CH(Rc)-, -NRd-CH(Rd)-, -CH(Rd)-NRd-, NRd-NRd-, -CH(Rd)-O-, -O-CH(Rd)-, -CH(Rc)-, -NRd-, or -O-;

Q is aryl or heterocyclyl;

W is H, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, aryl or heterocyclyl;

X' is H, F, OH, or NRaRb;

X'' is H or when X' is F, X'' can also be F;

Y is H, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 alkoxy C_1 - C_3 alkyl, C_1 - C_6 alkoxy- C_1 - C_6 alkoxy, C_0 - C_3 alkanediylaryl, C_0 - C_3 alkanediyl C_3 - C_6 cycloalkyl or C_0 - C_3 alkanediylheterocyclyl;

Z is O, S(=O)_r or NR_a;

ring A is a saturated, partially unsaturated or aromatic ring;

m is 0 or 1, whereby ring A defines a cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl or a phenyl ring;

n is 0, 1, 2 or 3;

p is 0 or 1;

q is 0, 1 or 2; thereby defining a bond, methylene or ethylene, or when q is 1, the methylene may alternatively be a 1,1-cyclopropyl group;

r is 0, 1 or 2;

R_a is H or C₁-C₆alkyl;

R_b is H or C₁-C₆alkyl; or R_a and R_b together with the nitrogen to which they are attached define a heterocyclyl group;

R_c is H, C₁-C₇alkyl, C₁-C₆alkoxy, C₁-C₆alkoxyC₁-C₃alkyl, C₁-C₆alkoxyC₁-C₆alkoxy, hydroxyC₀-C₃alkyl or C₀-C₃alkandiylnR_aR_b;

R_d is H, C₁-C₇alkyl, C₁-C₆alkoxyC₁-C₃alkyl, C₁-C₆alkoxyC₁-C₆alkoxyC₁-C₃alkyl, hydroxyC₁-C₃alkyl or C₁-C₃alkandiylnR_aR_b;

where aryl is independently phenyl, naphthyl, or phenyl fused to C₅-C₆cycloalkyl or C₅-C₆cycloalkenyl;

aryl is phenyl, naphthyl or phenyl fused to C₅-C₆cycloalkyl or C₅-C₆cycloalkenyl;

heterocyclyl is independently a 5 or 6 membered, saturated, partially unsaturated or heteroaryl ring containing 1 to 3 heteroatoms independently selected from S, O and N, the ring being optionally fused with a benzene ring;

and wherein each occurrence of C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₆cycloalkyl, aryl and heterocyclyl above (including those in composite expressions such as alkoxy or alkanediylaryl) is optionally substituted with 1 or 2, or where valence permits up to 3, substituents independently selected from C₁-C₄alkyl (optionally substituted with 1 or 2 substituents independently selected from C₀-C₃alkandiylyl*, amino, carbamoyl, amido or C₁-C₄alkoxyamido), C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₄cycloalkyl, C₁-C₄alkoxy, C₁-C₄alkoxyC₁-C₃alkyl, C₁-C₄alkoxyC₁-C₆alkoxyC₀-C₃alkyl, halo, haloC₁-C₄alkyl, polyhaloC₁-C₄alkyl, hydroxy, hydroxyC₁-C₄alkyl, amino, aminoC₁-C₄alkyl, carbamoyl, amido, cyano, azido, C₁-C₄alkylcarbonyl, a cyclic amine selected from pyrrolidinyl, piperidinyl, piperazinyl and morpholinyl, (any of which cyclic amines being optionally substituted with C₁-C₄alkyl or fluoro), C₀-C₃alkanediylC₃-C₆cycloalkyl, C₀-C₃alkanediylaryl*, C₀-C₃alkanediylheterocyclyl*, C₂-C₃alkenediylC₃-C₆cycloalkyl*, C₂-C₃alkenediylaryl*, C₂-C₃alkenediylheterocyclyl*, C₂-C₃alkynediylC₃-C₆cycloalkyl, C₂-C₃alkynediylaryl*, C₂-C₃alkynediylheterocyclyl*;

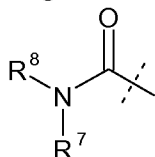
and wherein each occurrence of aryl* and heterocyclyl* above (including those in composite expressions such as alkanediylaryl* and alkanediylheterocyclyl*) is

independently optionally substituted with 1 or 2, or where valence permits up to 3, substituents independently selected from C₁-C₄alkyl, halo and haloC₁-C₄alkyl; or a pharmaceutically acceptable salt hydrate or N-oxide thereof.

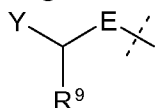
2. A compound according to claim 1, wherein ring A is phenyl.
3. A compound according to claim 1, wherein ring A is cyclopentyl.
4. A compound according to any preceding claim, wherein R⁶ is -N(C₀-C₂alkyl)S(=O)₂C₁-C₄alkyl, preferably -NHS(=O)₂CH₃.
5. A compound according to any preceding claim, wherein R² is H.
6. A compound according to any preceding claim, wherein n is 0 or 1.
7. A compound according to any of the preceding claims, wherein Q is a 5 or 6-membered aryl or heterocyclyl, preferably phenyl or pyridyl, which is optionally substituted with one, two or three substituents.
8. A compound according to claim 7, wherein the optional substituents are selected from C₁-C₄alkyl, C₃-C₆cycloalkyl, C₁-C₄alkoxy, C₁-C₄alkoxyC₁-C₆alkoxyC₀-C₃alkyl, halo and haloC₁-C₄alkyl.
9. A compound according to claim 7, wherein Q is phenyl, optionally substituted with one or two substituents independently selected from methyl, cyclopropyl, fluoro, chloro and 3-methoxy-propoxy.
10. A compound according to any preceding claim wherein Q is phenyl which is substituted in the meta position and/or in the para position.
11. A compound according to claim 10, wherein the substituent in the meta position is C₁-C₄alkoxyC₁-C₆alkoxy such as 3-methoxy-propoxy or 2-methoxy-ethoxy and the substituent in the para position is methyl, ethyl, cyclopropyl, fluoro, chloro or cyano
12. A compound according to claim 10, wherein Q is phenyl, substituted in the meta position with C₁-C₄alkoxyC₁-C₆alkoxy, such as 3-methoxy-propoxy or 2-methoxy-ethoxy and/or in the para position with optionally substituted phenyl or optionally substituted heteroaryl.

13. A compound according to claim 12, wherein the substituent in the para position is p-fluorophenyl, pyridyl, thienyl or furyl.
14. A compound according to any preceding claim, wherein X' is OH.
15. A compound according to any preceding claim, wherein R³ is C₁-C₄alkyl, preferably isopropyl or ethyl.
16. A compound according to any preceding claim, where p is 1 and R^{4'} is C₁-C₆alkyl, preferably sec. butyl or isopropyl.
17. A compound according to any preceding claim, wherein W is optionally substituted phenyl.
18. A compound according to claim 17, wherein the optional substituents are selected from fluoro, chloro, methyl and cyclopropyl.
19. A compound according to any preceding claim, wherein q is 0 or 1.

20. A compound according to any preceding claim, wherein D is

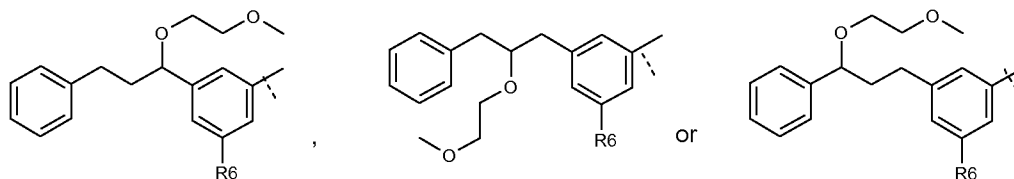


21. A compound according to claim 20, wherein R⁷ is C₁-C₃alkanediylaryl, such as benzyl or 1-phenylethyl.
22. A compound according to claim 20, wherein R⁸ is H or methyl.
23. A compound according to any preceding claim, wherein D is



24. A compound according to claim 23, wherein E is -CH(Rc)-CH(Rc)- and wherein one Rc is H and the other is H, C₁-C₆alkyl preferably pentyl or hexyl; or C₁-C₃alkoxyC₁-C₆alkoxy preferably 2-methoxyethoxy or 3-methoxypropoxy.
25. A compound according to claim 24, wherein R⁹ is phenyl and Y is hydrogen.

26. A compound according to claim 25, having any of the partial structures:



27. A pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of the preceding claims in association with a pharmaceutically acceptable adjuvant, diluent or carrier.
28. A compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims 1 to 26, for use in therapy.
29. Use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 26, in the manufacture of a medicament for use in the treatment or prevention of hypertension heart failure, glaucoma, cardiac infarction, kidney failure or restenosis.
30. Use according to claim 29, wherein the condition is hypertension.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2008/053765

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07C311/08 A61K31/18 A61P9/12 A61P9/04 A61P27/06
A61P13/12 C07C309/66 C07C311/07 C07C255/57

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07C C07D A61K A61P

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

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

EPO-Internal, BEILSTEIN Data, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	P. BÜHLMAYER, ET AL.: "Synthesis and biological activity of some transition-state inhibitors of human renin" JOURNAL OF MEDICINAL CHEMISTRY, vol. 31, no. 9, September 1988 (1988-09), pages 1839-1846, XP002463996 AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, US ISSN: 0022-2623 page 1839, left-hand column, lines 1-10; tables II-IV ----- -/--	1-30



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

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

Date of the actual completion of the international search

17 July 2008

Date of mailing of the international search report

24/07/2008

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2008/053765

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	J. RAHUEL, ET AL.: "Structure-based drug design: the discovery of novel nonpeptide orally active inhibitors of human renin" CHEMISTRY AND BIOLOGY, vol. 7, no. 7, 16 June 2000 (2000-06-16), pages 493-504, XP002254255 CURRENT BIOLOGY, LONDON, GB ISSN: 1074-5521 cited in the application table 1; compound 1 -----	1-30
A	N.E. MEALY, ET AL.: "Aliskiren fumarate" DRUGS OF THE FUTURE, vol. 26, no. 12, December 2001 (2001-12), pages 1139-1148, XP009017211 BARCELONA, ES ISSN: 0377-8282 cited in the application table I -----	1-30