PROTEASE INHIBITORS

FIELD OF THE INVENTION

This invention relates in general to C_{1-6}alkyl-4-amino-azepan-3-one protease inhibitors, particularly such inhibitors of cysteine and serine proteases, more particularly compounds which inhibit cysteine proteases, even more particularly compounds which inhibit cysteine proteases of the papain superfamily, yet more particularly compounds which inhibit cysteine proteases of the cathepsin family, most particularly compounds which inhibit cathepsin K. Such compounds are particularly useful for treating diseases in which cysteine proteases are implicated, especially diseases of excessive bone or cartilage loss, e.g., osteoporosis, periodontitis, and arthritis; and certain parasitic diseases, e.g., malaria.

BACKGROUND OF THE INVENTION

Cathepsins are a family of enzymes which are part of the papain superfamily of cysteine proteases. Cathepsins B, H, L, N and S have been described in the literature. Recently, cathepsin K polypeptide and the cDNA encoding such polypeptide were disclosed in U.S. Patent No. 5,501,969 (called cathepsin O therein). Cathepsin K has been recently expressed, purified, and characterized. Bossard, M. J., et al., (1996) *J. Biol. Chem.* **271**, 12517-12524; Drake, F.H., et al., (1996) *J. Biol. Chem.* **271**, 12511-12516; Bromme, D., et al., (1996) *J. Biol. Chem.* **271**, 2126-2132.

Cathepsin K has also been variously denoted as cathepsin O or cathepsin O2 in the literature. The designation cathepsin K is considered to be the most appropriate one.

Cathepsins function in the normal physiological process of protein degradation in animals, including humans, e.g., in the degradation of connective tissue. However, elevated levels of these enzymes in the body can result in pathological conditions leading to disease. Thus, cathepsins have been implicated as causative agents in various disease states, including but not limited to, infections by pneumocystis carinii, trypsanoma cruzi, trypsanoma brucei brucei, and Crithidia fusiculata; as well as in schistosomiasis, malaria, tumor metastasis, metachromatic leukodystrophy, muscular dystrophy, amytrophy, and the like. *See* International Publication Number WO 94/04172, published on March 3, 1994, and references cited therein. *See also* European Patent Application EP 0 603 873 A1, and references cited therein. Two bacterial cysteine proteases from P. gingivallis, called gingipains, have been implicated in the pathogenesis of gingivitis. Potempa, J., et al. (1994) *Perspectives in Drug Discovery and Design*, **2**, 445-458.

Cathepsin K is believed to play a causative role in diseases of excessive bone or cartilage loss. Bone is composed of a protein matrix in which spindle- or plate-shaped crystals of hydroxyapatite are incorporated. Type I collagen represents the major structural protein of bone comprising approximately 90% of the protein matrix. The remaining 10% of matrix is composed of a number of non-collagenous proteins, including osteocalcin, proteoglycans, osteopontin, osteonectin, thrombospondin, fibronectin, and bone sialoprotein. Skeletal bone undergoes remodelling at discrete foci throughout life. These foci, or remodelling units, undergo a cycle consisting of a bone resorption phase followed by a phase of bone replacement.

Bone resorption is carried out by osteoclasts, which are multinuclear cells of hematopoietic lineage. The osteoclasts adhere to the bone surface and form a tight sealing zone, followed by extensive membrane ruffling on their apical (i.e., resorbing) surface. This creates an enclosed extracellular compartment on the bone surface that is acidified by proton pumps in the ruffled membrane, and into which the osteoclast secretes proteolytic enzymes. The low pH of the compartment dissolves hydroxyapatite crystals at the bone surface, while the proteolytic enzymes digest the protein matrix. In this way, a resorption lacuna, or pit, is formed. At the end of this phase of the cycle, osteoblasts lay down a new protein matrix that is subsequently mineralized. In several disease states, such as osteoporosis and Paget's disease, the normal balance between bone resorption and formation is disrupted, and there is a net loss of bone at each cycle. Ultimately, this leads to weakening of the bone and may result in increased fracture risk with minimal trauma.

Several published studies have demonstrated that inhibitors of cysteine proteases are effective at inhibiting osteoclast-mediated bone resorption, and indicate an essential role for a cysteine proteases in bone resorption. For example, Delaisse, *et al.*, *Biochem. J.*, **1980**, *192*, 365, disclose a series of protease inhibitors in a mouse bone organ culture system and suggest that inhibitors of cysteine proteases (e.g., leupeptin, Z-Phe-Ala-CHN_2) prevent bone resorption, while serine protease inhibitors were ineffective. Delaisse, *et al.*, *Biochem. Biophys. Res. Commun.*, **1984**, *125*, 441, disclose that E-64 and leupeptin are also effective at preventing bone resorption *in vivo*, as measured by acute changes in serum calcium in rats on calcium deficient diets. Lerner, *et al.*, *J. Bone Min. Res.*, **1992**, *7*, 433, disclose that cystatin, an endogenous cysteine protease inhibitor, inhibits PTH stimulated bone resorption in mouse calvariae. Other studies, such as by Delaisse, *et al.*, *Bone*, **1987**, *8*, 305, Hill, *et al.*, *J. Cell. Biochem.*, **1994**, *56*, 118, and Everts, *et al.*, *J. Cell. Physiol.*, **1992**, *150*, 221, also report a correlation between inhibition of cysteine protease activity and bone resorption. Tezuka, *et al.*,

J. Biol. Chem., **1994**, *269*, 1106, Inaoka, *et al.*, *Biochem. Biophys. Res. Commun.*, **1995**, *206*, 89 and Shi, *et al.*, *FEBS Lett.*, **1995**, *357*, 129 disclose that under normal conditions cathepsin K, a cysteine protease, is abundantly expressed in osteoclasts and may be the major cysteine protease present in these cells.

The abundant selective expression of cathepsin K in osteoclasts strongly suggests that this enzyme is essential for bone resorption. Thus, selective inhibition of cathepsin K may provide an effective treatment for diseases of excessive bone loss, including, but not limited to, osteoporosis, gingival diseases such as gingivitis and periodontitis, Paget's disease, hypercalcemia of malignancy, and metabolic bone disease. Cathepsin K levels have also been demonstrated to be elevated in chondroclasts of osteoarthritic synovium. Thus, selective inhibition of cathepsin K may also be useful for treating diseases of excessive cartilage or matrix degradation, including, but not limited to, osteoarthritis and rheumatoid arthritis. Metastatic neoplastic cells also typically express high levels of proteolytic enzymes that degrade the surrounding matrix. Thus, selective inhibition of cathepsin K may also be useful for treating certain neoplastic diseases.

Several cysteine protease inhibitors are known. Palmer, (1995) *J. Med. Chem.*, *38*, 3193, disclose certain vinyl sulfones which irreversibly inhibit cysteine proteases, such as the cathepsins B, L, S, O2 and cruzain. Other classes of compounds, such as aldehydes, nitriles, α-ketocarbonyl compounds, halomethyl ketones, diazomethyl ketones, (acyloxy)methyl ketones, ketomethylsulfonium salts and epoxy succinyl compounds have also been reported to inhibit cysteine proteases. *See* Palmer, *id*, and references cited therein.

U.S. Patent No. 4,518,528 discloses peptidyl fluoromethyl ketones as irreversible inhibitors of cysteine protease. Published International Patent Application No. WO 94/04172, and European Patent Application Nos. EP 0 525 420 A1, EP 0 603 873 A1, and EP 0 611 756 A2 describe alkoxymethyl and mercaptomethyl ketones which inhibit the cysteine proteases cathepsins B, H and L. International Patent Application No. PCT/US94/08868 and and European Patent Application No. EP 0 623 592 A1 describe alkoxymethyl and mercaptomethyl ketones which inhibit the cysteine protease IL-1βconvertase. Alkoxymethyl and mercaptomethyl ketones have also been described as inhibitors of the serine protease kininogenase (International Patent Application No. PCT/GB91/01479).

Azapeptides which are designed to deliver the azaamino acid to the active site of serine proteases, and which possess a good leaving group, are disclosed by Elmore *et al.*, *Biochem. J.*, **1968**, *107*, 103, Garker *et al.*, *Biochem. J.*, **1974**, *139*, 555, Gray *et al.*, *Tetrahedron*, **1977**, *33*, 837, Gupton *et al.*, *J. Biol. Chem.*, **1984**, *259*, 4279, Powers *et al.*, *J. Biol. Chem.*, **1984**, *259*,

4288, and are known to inhibit serine proteases. In addition, *J. Med. Chem.*, **1992**, *35*, 4279, discloses certain azapeptide esters as cysteine protease inhibitors.

Antipain and leupeptin are described as reversible inhibitors of cysteine protease in McConnell et al., *J. Med. Chem.*, *33*, 86; and also have been disclosed as inhibitors of serine protease in Umezawa et al., 45 *Meth. Enzymol.* 678. E64 and its synthetic analogs are also well-known cysteine protease inhibitors (Barrett, *Biochem. J.*, *201*, 189, and Grinde, *Biochem. Biophys. Acta*, , *701*, 328).

1,3-diamido-propanones have been described as analgesic agents in U.S. Patent Nos.4,749,792 and 4,638,010.

Thus, a structurally diverse variety of protease inhibitors have been identified. However, these known inhibitors are not considered suitable for use as therapeutic agents in animals, especially humans, because they suffer from various shortcomings. These shortcomings include lack of selectivity, cytotoxicity, poor solubility, and overly rapid plasma clearance. A need therefore exists for methods of treating diseases caused by pathological levels of proteases, particularly cysteine proteases, more particularly cathepsins, most particularly cathepsin K, and for novel inhibitor compounds useful in such methods.

We have now discovered a novel class of C_{1-6}alkyl-4-amino-azepan-3-one compounds which are protease inhibitors, most particularly of cathepsin K.

SUMMARY OF THE INVENTION

An object of the present invention is to provide C_{1-6}alkyl-4-amino-azepan-3-one carbonyl protease inhibitors, particularly such inhibitors of cysteine and serine proteases, more particularly such compounds which inhibit cysteine proteases, even more particularly such compounds which inhibit cysteine proteases of the papain superfamily, yet more particularly such compounds which inhibit cysteine proteases of the cathepsin family, most particularly such compounds which inhibit cathepsin K, and which are useful for treating diseases which may be therapeutically modified by altering the activity of such proteases.

Accordingly, in the first aspect, this invention provides a compound according to Formula I.

In another aspect, this invention provides a pharmaceutical composition comprising a compound according to Formula I and a pharmaceutically acceptable carrier, diluent or excipient.

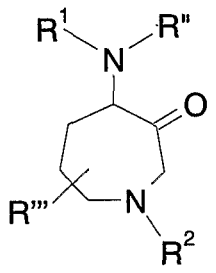
In yet another aspect, this invention provides intermediates useful in the preparation of the compounds of Formula I.

In still another aspect, this invention provides a method of treating diseases in which the disease pathology may be therapeutically modified by inhibiting proteases, particularly cysteine and serine proteases, more particularly cysteine proteases, even more particularly cysteine proteases of the papain superfamily, yet more particularly cysteine proteases of the cathepsin family, most particularly cathepsin K.

In a particular aspect, the compounds of this invention are especially useful for treating diseases characterized by bone loss, such as osteoporosis and gingival diseases, such as gingivitis and periodontitis, or by excessive cartilage or matrix degradation, such as osteoarthritis and rheumatoid arthritis; and for treating certain parasitic diseases, such as malaria.

DETAILED DESCRIPTION OF THE INVENTION

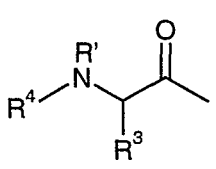
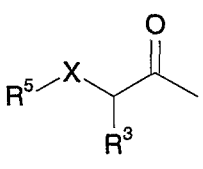
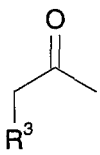
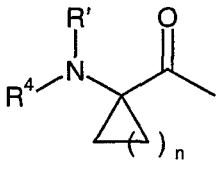
The present invention provides compounds of Formula I:



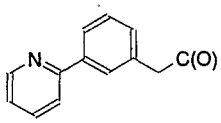
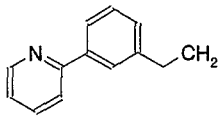
I

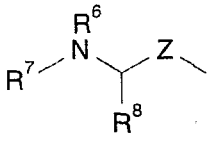
wherein:

R^1 is selected from the group consisting of:

 ;  ;  and  ;

R^2 is selected from the group consisting of: H, C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, $R^9C(O)$-, $R^9C(S)$-, R^9SO_2-, $R^9OC(O)$-,

$R^9R^{11}NC(O)$-, $R^9R^{11}NC(S)$-, $R^9(R^{11})NSO_2$-   and

 ;

R^3 is selected from the group consisting of: H, C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, HetC_{0-6}alkyl, ArC_{0-6}alkyl, Ar-ArC_{0-6}alkyl, Ar-HetC_{0-6}alkyl, Het-ArC_{0-6}alkyl, and Het-HetC_{0-6}alkyl;

R^3 and R' may be connected to form a pyrrolidine, piperidine or morpholine ring;

R^4 is selected from the group consisting of: H, C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, $R^5C(O)$-, $R^5C(S)$-, R^5SO_2-, $R^5OC(O)$-, $R^5R^{12}NC(O)$-, and $R^5R^{12}NC(S)$-;

R^5 is selected from the group consisting of: H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, C_{2-6}alkanonyl, Ar-C_{0-6}alkyl and Het-C_{0-6}alkyl;

R^6 is selected from the group consisting of: H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, and Het-C_{0-6}alkyl;

R^7 is selected from the group consisting of: H, C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, $R^{10}C(O)$-, $R^{10}C(S)$-, $R^{10}SO_2$-, $R^{10}OC(O)$-, $R^{10}R^{13}NC(O)$-, and $R^{10}R^{13}NC(S)$-;

R^8 is selected from the group consisting of: H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, HetC_{0-6}alkyl and ArC_{0-6}alkyl;

R^9 is selected from the group consisting of: C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl and Het-C_{0-6}alkyl;

R^{10} is selected from the group consisting of: C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl and Het-C_{0-6}alkyl;

R^{11} is selected from the group consisting of: H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, and Het-C_{0-6}alkyl;

R^{12} is selected from the group consisting of: H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, and Het-C_{0-6}alkyl;

R^{13} is selected from the group consisting of: H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, and Het-C_{0-6}alkyl;

R' is selected from the group consisting of: H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, and Het-C_{0-6}alkyl;

R" is selected from the group consisting of: H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl;

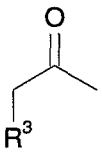
R"' is C_{1-6}alkyl;

X is selected from the group consisting of: CH_2, S, and O;

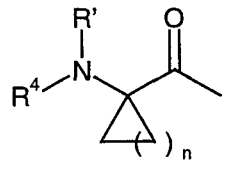
Z is selected from the group consisting of: C(O) and CH_2;

n is an integer from 1 to 5;

and pharmaceutically acceptable salts, hydrates and solvates thereof.

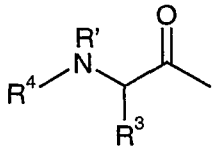


In compounds of Formula I, when R^1 is , R^3 is selected from the group consisting of: H, C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, Het-C_{0-6}alkyl, Ar-C_{0-6}alkyl, Ar-ArC_{0-6}alkyl, Ar-HetC_{0-6}alkyl, Het-ArC_{0-6}alkyl, and Het-HetC_{0-6}alkyl. Preferably, R^3 is Ar-ArC_{0-6}alkyl, more preferably 3-isobutyl biphenyl.



In compounds of Formula I, when R^1 is , n is preferably 4, to provide 1-amino-1-acyl cyclohexane compounds. The cycloalkyl ring may be unsubstituted or substituted with one or more of C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, HetC_{0-6}alkyl, ArC_{0-6}alkyl, or halogen.

The cycloalkyl ring is more preferably unsubstituted.



In compounds of Formula I, when R^1 is :

R^3 is selected from the group consisting of: H, C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, Het-C_{0-6}alkyl, Ar-C_{0-6}alkyl, Ar-ArC_{0-6}alkyl, Ar-HetC_{0-6}alkyl, Het-ArC_{0-6}alkyl, and Het-HetC_{0-6}alkyl;

R^3 is preferably selected from the group consisting of: H, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, and C_{1-6}alkyl;

R^3 is more preferably selected from the group consisting of:

H, methyl, ethyl, n-propyl, prop-2-yl, n-butyl, isobutyl, but-2-yl, cyclopropylmethyl, cyclohexylmethyl, 2-methanesulfinyl-ethyl, 1-hydroxyethyl, toluyl, naphthalen-2-ylmethyl, benzyloxymethyl, and hydroxymethyl.

R^3 is even more preferably selected from the group consisting of: toluyl, isobutyl and cyclohexylmethyl.

R^3 is most preferably isobutyl.

R^4 is selected from the group consisting of: H, C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, $R^5C(O)$-, $R^5C(S)$-, R^5SO_2-, $R^5OC(O)$-, $R^5R^{12}NC(O)$-, and $R^5R^{12}NC(S)$-.

R^4 is preferably selected from the group consisting of: $R^5OC(O)$-, $R^5C(O)$- and R^5SO_2-.

R^4 is most preferably $R^5C(O)$-.

In some embodiments, R^4 is preferably methanesulfonyl.

R^5 is selected from the group consisting of: H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, C_{2-6}alkanonyl, Ar-C_{0-6}alkyl or Het-C_{0-6}alkyl.

Preferably R^5 is selected from the group consisting of: C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, C_{2-6}alkanonyl, Ar-C_{0-6}alkyl and Het-C_{0-6}alkyl.

More preferably, and especially when R^4 is $R^5C(O)$-, R^5 is selected from the group consisting of:

methyl, especially halogenated methyl, more especially trifluoromethyl , especially C_{1-6}alkoxy and aryloxy substituted methyl, more especially phenoxy-methyl , 4-fluoro-phenoxy-methyl , especially heterocycle substituted methyl, more especially 2-thiophenyl-methyl ;

butyl, especially aryl substituted butyl, more especially 4-(4-methoxy)phenyl-butyl;

isopentyl;

cyclohexyl;

pentanonyl, especially 4-pentanonyl;

butenyl, especially aryl substituted butenyl, more especially 4,4-bis(4-methoxyphenyl)-but-3-enyl;

phenyl, especially phenyl substituted with one or more halogens, more especially 3,4-dichlorophenyl and 4-fluorophenyl, especially phenyl substituted with one or more C_{1-6}

alkoxy or aryloxy groups, more especially 3,4-dimethoxy-phenyl, 3-benzyloxy-4-methoxy-phenyl, especially phenyl substituted with one or more sulfonyl groups, more especially 4-methanesulfonyl-phenyl;

benzyl;

naphthalenyl, especially naphthylen-2-yl;

benzo[1,3]dioxolyl, especially benzo[1,3]dioxol-5-yl,

furanyl, especially furan-2-yl, especially substituted furanyl, such as 5-nitro-furan-2-yl, 5-(4-nitrophenyl)-furan-2-yl, 5-(3-trifluoromethyl-phenyl)-furan-2-yl, more especially halogen substituted furanyl, even more especially 5-bromo-furan-2-yl, more especially aryl substituted furanyl, even more especially 5-(4-chloro-phenyl)-furan-2-yl;

tetrahydrofuranyl, especially tetrahydrofuran-2-yl;

benzofuranyl, especially benzofuran-2-yl, and especially C_{1-6}alkoxy substituted benzofuranyl,, more especially 5-(2-piperazin-4-carboxylic acid *tert*-butyl ester- ethoxy) benzofuran-2-yl, 5-(2-morpholino-4-yl-ethoxy)-benzofuran-2-yl, 5-(2-piperazin-1-yl-ethoxy)benzofuran-2-yl, 5-(2-cyclohexyl-ethoxy)-benzofuran-2-yl; 7-methoxy-benzofuran-2-yl, 5-methoxy-benzofura-2-yl, 5,6-dimethoxy-benzofuran-2-yl, especially halogen substituted benzofuranyl, more especially 5-fluoro-benzofuran-2-yl, 5,6-difluoro-benzofuran-2-yl, especially C_{1-6}alkyl substituted benzofuranyl, most especially 3-methyl-benzofuran-2-yl;

benzo[*b*]thiophenyl, especially benzo[*b*]thiophen-2-yl; especially C_{1-6}alkoxy substituted benzo[*b*]thiophenyl, more especially 5,6-dimethoxy- benzo[*b*]thiophen-2-yl ;

quinolinyl, especially quinolin-2-yl, quinolin-3-yl, quinolin-4-yl, quinolin-6-yl, and quinolin-8-yl;

quinoxalinyl, especially quinoxalin-2-yl;

1,8 naphthyridinyl, especially 1,8 naphthyridin-2-yl;

indolyl, especially indol-2-yl, especially indol-6-yl, indol-5-yl, especially C_{1-6}alkyl substituted indolyl, more especially N-methyl-indol-2-yl;

pyridinyl, especially pyridin-2-yl , pyridin-5-yl, especially 1-oxy-pyridin-2-yl, especially C_{1-6}alkyl substituted pyridinyl, more especially 2-methyl-pyridin-5-yl;

furo[3,2-b]pyridinyl, especially furo[3,2-b]pyridin-2-yl, and C_{1-6}alkyl substituted furo[3,2-b]pyridinyl, especially 3-methyl-furo[3,2-b]pyridin-2-yl;

thiophenyl, especially thiophen-3-yl, especially C_{1-6}alkyl substituted thiophenyl, more especially 5-methyl-thiophen-2-yl, especially halogen substituted thiophenyl, more especially 4,5-dibromo-thiophen-2-yl;

thieno[3,2-*b*]thiophene, especially thieno[3,2-*b*]thiophene-2-yl, more especially C_{1-6}alkyl substituted thieno[3,2-*b*]thiophene-2-yl, more especially 5-*tert*-butyl-3-methyl-thieno[3,2-*b*]thiophene-2-yl;

isoxazolyl, especially isoxazol-4-yl, especially C_{1-6}alkyl substituted isoxazolyl, more especially 3,5-dimethyl- isoxazol-4-yl; and

oxazolyl, especially oxazol-4-yl, more especially 5-methyl-2-phenyl oxazol-4-yl, 2-phenyl-5-trifluoromethyl-oxazol-4-yl;

When R^4 is R^5SO_2, R^5 is preferably pyridin-2-yl or 1-oxo-pyridin-2-yl.

R' is selected from the group consisting of: H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, and Het-C_{0-6}alkyl.

Preferably R' selected from the group consisting of: H and naphthalen-2-yl-methyl.

Most preferably R' is H.

R" selected from the group consisting of: H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, and Het-C_{0-6}alkyl.

Most preferably R" is H.

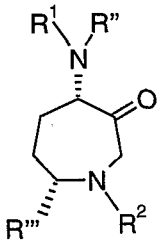
R'" is:

C_{1-6}alkyl, especially selected from the group consisting of: methyl, ethyl, propyl, butyl, pentyl and hexyl, more especially methyl;

preferably 5-, 6- or 7- C_{1-6}alkyl, especially selected from the group consisting of: 5-, 6- or 7-methyl, -ethyl, -propyl, -butyl, -pentyl and -hexyl, more especially 5-, 6- or 7-methyl;

more preferably 6- or 7- C_{1-6}alkyl, especially selected from the group consisting of: 6- or 7-methyl, -ethyl, -propyl, -butyl, -pentyl and -hexyl, more especially 6- or 7-methyl;

yet more preferably *cis*-7- C_{1-6}alkyl as shown in Formula Ia:

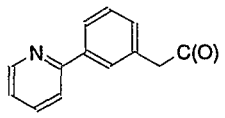


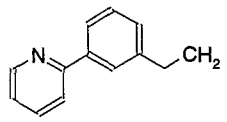
Ia

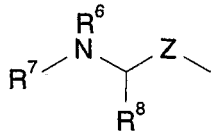
wherein R''' is C_{1-6}alkyl, especially selected from the group consisting of: methyl, ethyl, propyl, butyl, pentyl and hexyl;

most preferably *cis*-7- methyl, as shown in Formula Ia wherein R''' is methyl.

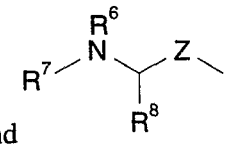
In compounds of Formula I, R^2 is selected from the group consisting of: H, C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, $R^9C(O)$-, $R^9C(S)$-, R^9SO_2-, $R^9OC(O)$-, $R^9R^{11}NC(O)$-, $R^9R^{11}NC(S)$-, $R^9R^{11}NSO_2$-,





, and 

.

Preferably R^2 is selected from the group consisting of: Ar-C_{0-6}alkyl, $R^9C(O)$-, R^9SO_2, $R^9R^{11}NC(O)$-, and 

.

More preferably, R^2 is selected from the group consisting of: Ar-C_{0-6}alkyl, $R^9C(O)$-, and R^9SO_2.

Most preferably R^2 is R^9SO_2.

In such embodiments:

R^6 is selected from the group consisting of: H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl, preferably H.

R^7 is selected from the group consisting of: H, C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, $R^{10}C(O)$-, $R^{10}C(S)$-, $R^{10}SO_2$-, $R^{10}OC(O)$-, $R^{10}R^{13}NC(O)$-, $R^{10}R^{13}NC(S)$-, R^7 is preferably $R^{10}OC(O)$.

R^8 is selected from the group consisting of: H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, HetC_{0-6}alkyl and ArC_{0-6}alkyl; preferably C_{1-6}alkyl, more preferably isobutyl.

R^9 is selected from the group consisting of: C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, and Het-C_{0-6}alkyl.

More preferably, R^9 is selected from the group consisting of:

methyl;

ethyl, especially C_{1-6}alkyl-substituted ethyl, more especially 2-cyclohexyl-ethyl;

butyl, especially C_{1-6}butyl, more especially 3-methylbutyl;

tert-butyl, particularly when R^2 is $R^9OC(O)$;

isopentyl;

phenyl, especially halogen substituted phenyl, more especially 3,4-dichlorophenyl , 4-bromophenyl, 2-fluorophenyl, 4-fluorophenyl, 3-chlorophenyl, 4-chlorophenyl, especially C_{1-6}alkoxy phenyl, more especially 3-methoxyphenyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl, especially cyanophenyl, more especially 2-cyanophenyl;

toluyl, especially Het-substituted toluyl, more especially 3-(pyridin-2-yl)toluyl;

naphthylenyl, especially naphthylen-2-yl;

benzoyl, especially 2-benzoyl;

benzo[1,3]dioxolyl, especially benzo[1,3]dioxol-5-yl;

benzo[1,2,5]oxadiazolyl, especially benzo[1,2,5]oxadiazol-4-yl;

pyridinyl, especially pyridin-2-yl, pyridin-3-yl, especially 1-oxy-pyridinyl, more especially 1-oxy-pyridin-2-yl, 1-oxy-pyridin-3-yl; especially C_{1-6}alkylpyridinyl, more especially 3-methyl-pyridin-2-yl, 6-methyl-pyridin-2-yl,

thiophene, especially thiophene-2-yl;

thiazolyl, especially thiazol-2-yl;

1H-imidazolyl, especially 1H-imidazol-2-yl, 1H-imidazol-4-yl, more especially C_{1-6}alkyl substituted imidazolyl, even more especially 1-methyl-1H-imidazol-2-yl, 1-methyl-1H-imidazol-4-yl;

1H-[1,2,4]triazolyl, especially 1H-[1,2,4]triazol-3-yl, more especially C_{1-6}alkyl substituted 1H-[1,2,4]triazolyl, even more especially 5-methyl-1H-[1,2,4]triazol-3-yl; and

quinolinyl.

When R^2 is R^9SO_2, R^9 is most preferably selected from the group consisting of: pyridin-2-yl and 1-oxy-pyridin-2-yl.

R^{10} is selected from the group consisting of: C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl or Het-C_{0-6}alkyl; preferably C_{1-6}alkyl, Ar-C_{0-6}alkyl and Het-C_{0-6}alkyl.

Z is selected from the group consisting of: C(O) and CH_2.

R^2 is also preferably:

H;

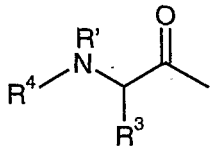
toluyl;

aryl substituted ethyl, especially 2-phenyl ethyl, 2-[3-(pyridin-2-yl) phenyl] ethyl.

Compounds of Formula I where R" is H and and R"' is methyl are preferred.

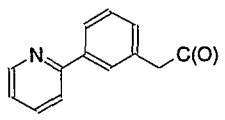
More preferred are compounds of Formula I wherein:

R^1 is

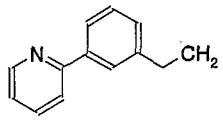


;

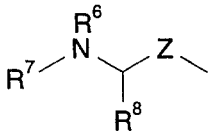
R^2 is selected from the group consisting of: H, C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, $R^9C(O)$-, $R^9C(S)$-, R^9SO_2-, $R^9OC(O)$-, $R^9R^{11}NC(O)$-, $R^9R^{11}NC(S)$-, $R^9(R^{11})NSO_2$-,



,



and



;

R^3 is selected from the group consisting of: H, C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, and Ar-C_{0-6}alkyl;

R^4 is selected from the group consisting of: $R^5C(O)$-, R^5SO_2-, and$R^5OC(O)$-;

R^5 is selected from the group consisting of: C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, C_{2-6}alkanonyl, Ar-C_{0-6}alkyl and Het-C_{0-6}alkyl;

R^6 is selected from the group consisting of: H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, and Het-C_{0-6}alkyl;

R^7 is selected from the group consisting of: H, C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, $R^{10}C(O)$-, $R^{10}C(S)$-, $R^{10}SO_2$-, $R^{10}OC(O)$-, $R^{10}R^{13}NC(O)$-, and $R^{10}R^{13}NC(S)$-;

R^8 is selected from the group consisting of: H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, HetC_{0-6}alkyl and ArC_{0-6}alkyl;

R^9 is selected from the group consisting of: C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl and Het-C_{0-6}alkyl;

R^{10} is selected from the group consisting of: C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl and Het-C_{0-6}alkyl;

R^{11} is selected from the group consisting of: H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, and Het-C_{0-6}alkyl;

R^{12} is selected from the group consisting of: H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, and Het-C_{0-6}alkyl;

R^{13} is selected from the group consisting of: H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, and Het-C_{0-6}alkyl;

R' is H;

R" is H;

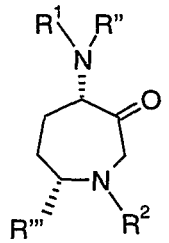
R"' is selected from the group consisting of:

C_{1-6}alkyl, especially selected from the group consisting of: methyl, ethyl, propyl, butyl, pentyl and hexyl, more especially methyl;

preferably 5-, 6- or 7- C_{1-6}alkyl, especially selected from the group consisting of: 5-, 6- or 7-methyl, -ethyl, -propyl, -butyl, -pentyl and -hexyl, more especially 5-, 6- or 7-methyl;

more preferably 6- or 7- C_{1-6}alkyl, especially selected from the group consisting of: 6- or 7-methyl, -ethyl, -propyl, -butyl, -pentyl and -hexyl, more especially 6- or 7-methyl;

yet more preferably *cis*-7- C_{1-6}alkyl as shown in Formula Ia:



Ia

wherein R"' is C_{1-6}alkyl, especially selected from the group consisting of: methyl, ethyl, propyl, butyl, pentyl and hexyl;

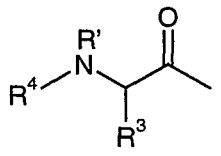
most preferably *cis*-7- methyl, as shown in Formula Ia wherein R"' is methyl; and

Z is selected from the group consisting of: C(O) and CH_2.

Particularly preferred are such compounds wherein R^3 is isobutyl.

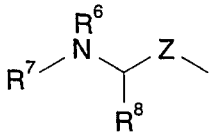
Still more preferred are compounds of Formula I wherein:

R^1 is



;

R^2 is selected from the group consisting of: Ar-C_{0-6}alkyl, $R^9C(O)$-, R^9SO_2,



$R^9R^{11}NC(O)$-, and ;

R^3 is selected from the group consisting of: H, C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, and Ar-C_{0-6}alkyl;

R^4 is selected from the group consisting of: $R^5OC(O)$-, $R^5C(O)$- and R^5SO_2-;

$R^5$is selected from the group consisting of: C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, C_{2-6}alkanonyl, Ar-C_{0-6}alkyl and Het-C_{0-6}alkyl;

R^6 is H;

R^7 is $R^{10}OC(O)$;

R^8 is C_{1-6}alkyl;

R^9 is selected from the group consisting of: C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl and Het-C_{0-6}alkyl;

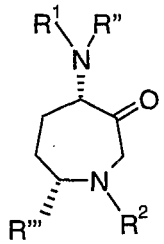
R^{10} is selected from the group consisting of: C_{1-6}alkyl, Ar-C_{0-6}alkyl and Het-C_{0-6}alkyl;

R^{11} is selected from the group consisting of: C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl and Het-C_{0-6}alkyl;

R'is H;

R"is H;

R"' is methyl, preferably 5-, 6- or 7-methyl, more preferably 6- or 7-methyl, most preferably *cis*-7- methyl, as shown in Formula Ia:



Ia

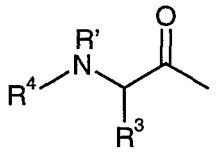
wherein R"' is methyl; and

Z is selected from the group consisting of: C(O) and CH_2.

Even more preferred are such compounds of Formula I wherein R^2 is selected from the group consisting of: Ar-C_{0-6}alkyl, $R^9C(O)$-, R^9SO_2.

Yet more preferred are compounds of Formula I wherein:

R^1 is



;

R^2 is selected from the group consisting of: Ar-C_{0-6}alkyl, $R^9C(O)$- and R^9SO_2;

R^3 is selected from the group consisting of: H, methyl, ethyl, n-propyl, prop-2-yl, n-butyl, isobutyl, but-2-yl, cyclopropylmethyl, cyclohexylmethyl, 2-methanesulfinyl-ethyl, 1-hydroxyethyl, toluyl, naphthalen-2-ylmethyl, benzyloxymethyl, and hydroxymethyl;

R^4 is $R^5C(O)$-;

R^5 is selected from the group consisting of: methyl, especially halogenated methyl, more especially trifluoromethyl, especially C_{1-6}alkoxy and aryloxy substituted methyl, more especially phenoxy-methyl, 4-fluoro-phenoxy-methyl, especially heterocycle substituted methyl, more especially 2-thiophenyl-methyl;

butyl, especially aryl substituted butyl, more especially 4-(4-methoxy)phenyl-butyl;

isopentyl;

cyclohexyl;

pentanonyl, especially 4-pentanonyl;

butenyl, especially aryl substituted butenyl, more especially 4,4-bis(4-methoxyphenyl)-but-3-enyl;

phenyl, especially phenyl substituted with one or more halogens, more especially 3,4-dichlorophenyl and 4-fluorophenyl, especially phenyl substituted with one or more C_{1-6}alkoxy or aryloxy groups, more especially 3,4-dimethoxy-phenyl, 3-benzyloxy-4-methoxy-phenyl, especially phenyl substituted with one or more sulfonyl groups, more especially 4-methanesulfonyl-phenyl;

benzyl;

naphthylen-2-yl;

benzo[1,3]dioxolyl, especially benzo[1,3]dioxol-5-yl,

furanyl, especially furan-2-yl, especially substituted furanyl, such as 5-nitro-furan-2-yl, 5-(4-nitrophenyl)-furan-2-yl, 5-(3-trifluoromethyl-phenyl)-furan-2-yl, more especially halogen substituted furanyl, even more especially 5-bromo-furan-2-yl, more especially aryl substituted furanyl, even more especially 5-(4-chloro-phenyl)-furan-2-yl;

tetrahydrofuran-2-yl;

benzofuranyl, especially benzofuran-2-yl, and especially C_{1-6}alkoxy substituted benzofuranyl, more especially 5-(2-piperazin-4-carboxylic acid *tert*-butyl ester- ethoxy) benzofuran-2-yl, 5-(2-morpholino-4-yl-ethoxy)-benzofuran-2-yl, 5-(2-piperazin-1-yl-ethoxy)benzofuran-2-yl, 5-(2-cyclohexyl-ethoxy)-benzofuran-2-yl, 7-methoxy-benzofuran-2-yl, 5-methoxy-benzofuran-2-yl, 5,6-dimethoxy-benzofuran-2-yl, especially halogen substituted benzofuranyl, more especially 5-fluoro-benzofuran-2-yl, 5,6-difluoro-benzofuran-2-yl, especially C_{1-6}alkyl substituted benzofuranyl, most especially 3-methyl-benzofuran-2-yl;

benzo[*b*]thiophenyl, especially benzo[*b*]thiophen-2-yl; especially C_{1-6}alkoxy substituted benzo[*b*]thiophenyl, more especially 5,6-dimethoxy- benzo[*b*]thiophen-2-yl;

quinolinyl, especially quinolin-2-yl, quinolin-3-yl, quinolin-4-yl, quinolin-6-yl, and quinolin-8-yl;

quinoxalinyl, especially quinoxalin-2-yl;

1,8 naphthyridinyl, especially 1,8 naphthyridin-2-yl;

indolyl, especially indol-2-yl, especially indol-6-yl, indol-5-yl, especially C_{1-6}alkyl substituted indolyl, more especially N-methyl-indol-2-yl ;

pyridinyl, especially pyridin-2-yl , pyridin-5-yl, especially 1-oxy-pyridin-2-yl, especially C_{1-6}alkyl substituted pyridinyl, more especially 2-methyl-pyridin-5-yl;

furo[3,2-b]pyridinyl, especially furo[3,2-b]pyridin-2-yl, and C_{1-6}alkyl substituted furo[3,2-b]pyridinyl, especially 3-methyl-furo[3,2-b]pyridin-2-yl;

thiophenyl, especially thiophen-3-yl, especially C_{1-6}alkyl substituted thiophenyl, more especially 5-methyl-thiophen-2-yl, especially halogen substituted thiophenyl, more especially 4,5-dibromo-thiophen-2-yl;

thieno[3,2-*b*]thiophene, especially thieno[3,2-*b*]thiophene-2-yl, more especially C_{1-6}alkyl substituted thieno[3,2-*b*]thiophene-2-yl, more especially 5-*tert*-butyl-3-methyl-thieno[3,2-*b*]thiophene-2-yl;

isoxazolyl, especially isoxazol-4-yl, especially C_{1-6}alkyl substituted isoxazolyl, more especially 3,5-dimethyl- isoxazol-4-yl; and

oxazolyl, especially oxazol-4-yl, more especially 5-methyl-2-phenyl oxazol-4-yl , 2-phenyl-5-trifluoromethyl-oxazol-4-yl;

R^9 is selected from the group consisting of:

methyl;

ethyl, especially C_{1-6}alkyl-substituted ethyl, more especially 2-cyclohexyl-ethyl;

butyl, especially C_{1-6}butyl, more especially 3-methylbutyl;

tert-butyl, particularly when R^2 is $R^9OC(O)$;

isopentyl;

phenyl, especially halogen substituted phenyl, more especially 3,4-dichlorophenyl , 4-bromophenyl, 2-fluorophenyl, 4-fluorophenyl , 3-chlorophenyl, 4-chlorophenyl, especially C_{1-6}alkoxy phenyl, more especially 3-methoxyphenyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl, especially cyanophenyl, more especially 2-cyanophenyl ;

toluyl, especially Het-substituted toluyl, more especially 3-(pyridin-2-yl)toluyl;

naphthylene, especially naphthyl-2-ene;

benzoyl, especially 2-benzoyl;

benzo[1,3]dioxolyl, especially benzo[1,3]dioxol-5-yl;

benzo[1,2,5]oxadiazolyl, especially benzo[1,2,5]oxadiazol-4-yl;

pyridinyl, especially pyridin-2-yl, pyridin-3-yl, especially 1-oxy-pyridinyl, more especially 1-oxy-pyridin-2-yl, 1-oxy-pyridin-3-yl; especially C_{1-6}alkylpyridinyl, more especially 3-methyl-pyridin-2-yl, 6-methyl-pyridin-2-yl,

thiophenyl, especially thiophene-2-yl;

thiazolyl, especially thiazol-2-yl;

1H-imidazolyl, especially 1H-imidazol-2-yl(74), 1H-imidazol-4-yl, more especially C_{1-6}alkyl substituted imidazolyl, even more especially 1-methyl-1H-imidazol-2-yl, 1-methyl-1H-imidazol-4-yl; and

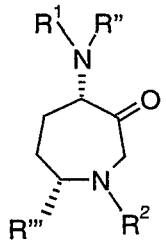
1H-[1,2,4]triazolyl, especially 1H-[1,2,4]triazol-3-yl, more especially C_{1-6}alkyl substituted 1H-[1,2,4]triazolyl, even more especially 5-methyl-1H-[1,2,4]triazol-3-yl; and

quinolinyl;

R' is H;

R" is H; and

R"' is methyl, preferably 5-, 6- or 7-methyl, more preferably 6- or 7-methyl, most preferably *cis*-7- methyl, as shown in Formula Ia:

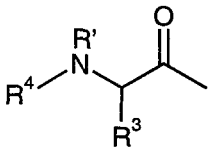


Ia

wherein R'" is methyl.

Even yet more preferred are compounds of Formula I wherein:

R^1 is



;

R^2 is R^9SO_2;

R^3 is C_{1-6}alkyl;

R^4 is $R^5C(O)$;

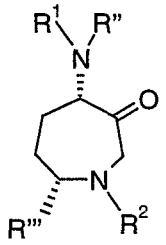
R^5 is Het-C_{0-6}alkyl;

R^9 is Het-C_{0-6}alkyl;

R' is H;

R" is H; and

R'" is selected from the group consisting of: 5-, 6- or 7-methyl, preferably 6- or 7-methyl, most preferably *cis*-7-methyl, as shown in Formula Ia:

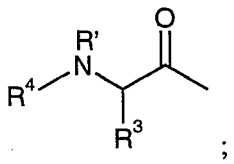


Ia

wherein R'" is methyl.

Still yet more preferred are compounds of Formula I wherein:

R^1 is



;

R^2 is R^9SO_2;

R^3 is isobutyl;

R^4 is $R^5C(O)$;

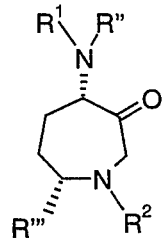
R^5 is selected from the group consisting of: 5-methoxybenzofuran-2-yl, benzo[*b*]thiophen-2-yl, 3-methyl-benzofuran-2-yl, thieno[3,2-b]thiophen-2-yl, benzofuran-2-yl, furo[3,2-b]pyridin-2-yl, and 3-methyl-furo[3,2-b]pyridin-2-yl; preferably benzofuran-2-yl, furo[3,2-b]pyridin-2-yl, and 3-methyl-furo[3,2-b]pyridin-2-yl; most preferably benzofuran-2-yl.

R^9 is selected from the group consisting of: pyridin-2-yl and 1-oxy-pyridin-2-yl, preferably pyridin-2-yl.

R' is H;

R" is H; and

R"' is selected from the group consisting of: 5-, 6- or 7-methyl, preferably 6- or 7-methyl, most preferably *cis*-7-methyl, as shown in Formula Ia:

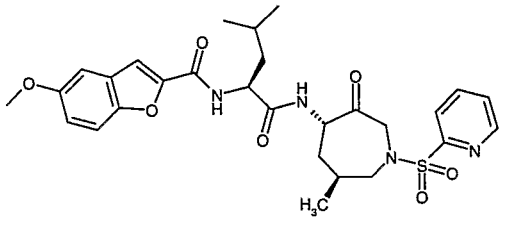


Ia

wherein R"' is methyl.

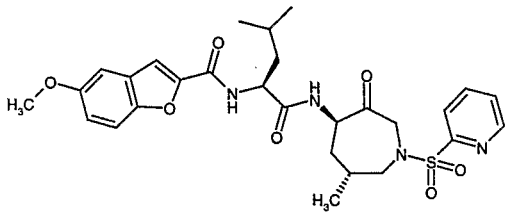
Compounds of Formula I selected from the following group are particularly preferred embodiments of the present invention:

5-methoxy-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(4S,6S)-6-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide:



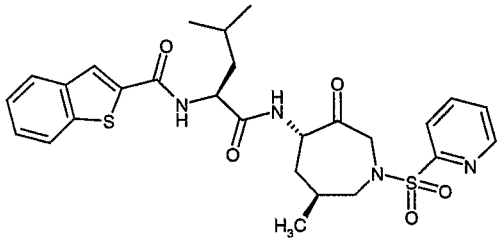
;

5-methoxy-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(4R,6R)-6-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide:



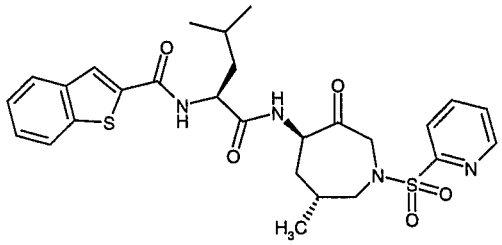
;

benzo[b]thiophene-2-carboxylic acid {(S)- 1-[(4S,6S)-6-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide:



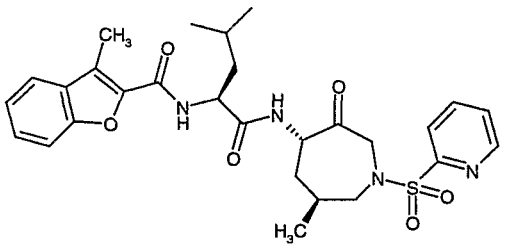
;

benzo[b]thiophene-2-carboxylic acid {(S)- 1-[(4R,6R)-6-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide:



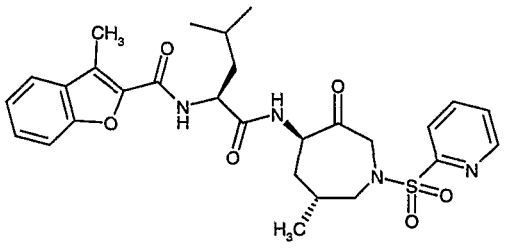
;

3-methyl-benzofuran-2-carboxylic acid {(S)- 1-[(4S,6S)-6-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide:



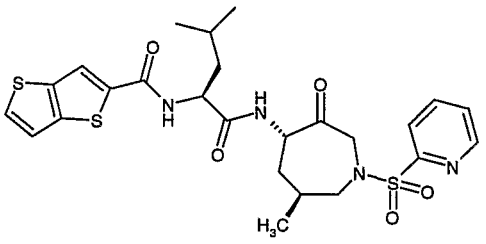
;

3-methyl-benzofuran-2-carboxylic acid {(S)- 1-[(4R,6R)-6-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide:



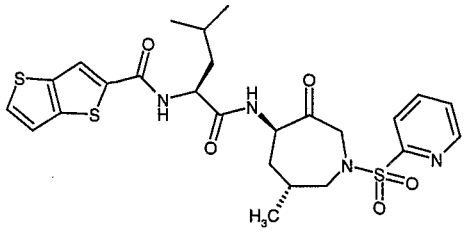
;

thieno[3,2-b]thiophene-2-carboxylic acid {(S)- 1-[(4S,6S)-6-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide:



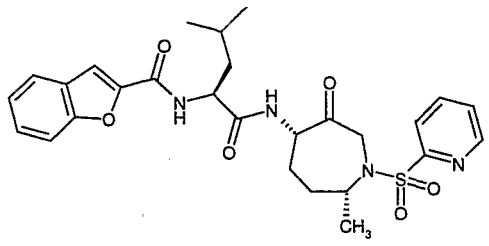
;

thieno[3,2-b] thiophene -2-carboxylic acid {(S)- 1-[(4R,6R)-6-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide:



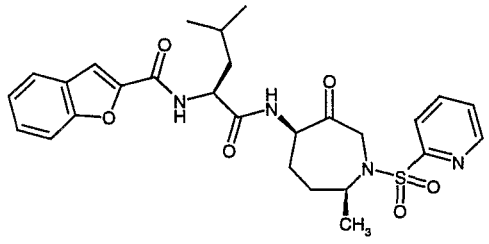
;

benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide:



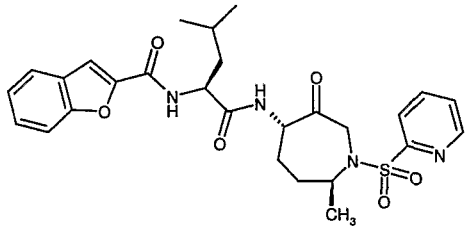
;

benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(4R,7S)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide:



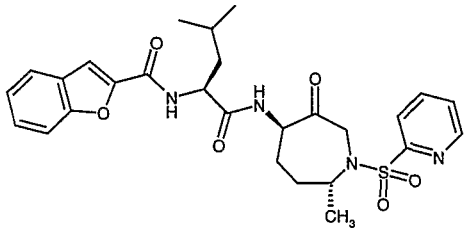
;

benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(4S,7S)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide:



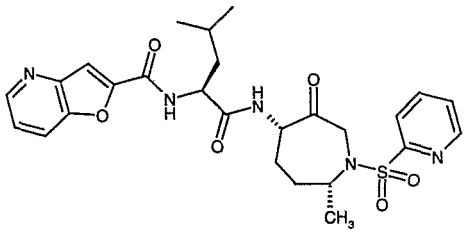
;

benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(4R,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide:



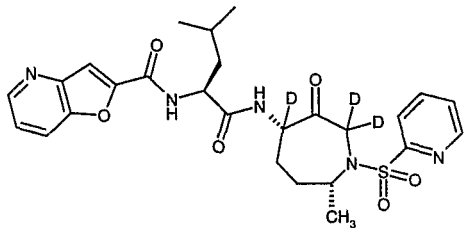
;

furo[3,2-b]pyridine-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide:



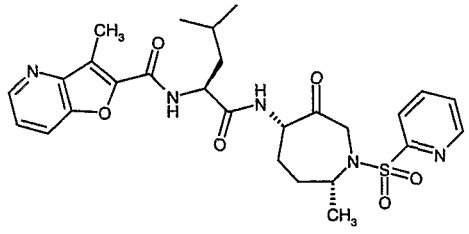
;

2,2,4-trideutero-furo[3,2-b]pyridine-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide:



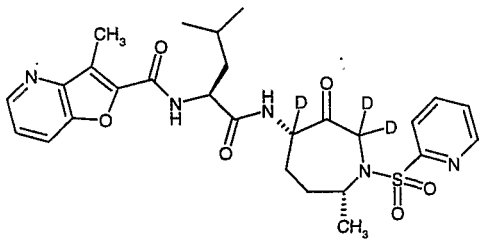
;

3-methyl-furo[3,2-b]pyridine-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide:



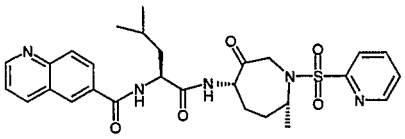
;

2,2,4-trideutero-3-methyl-furo[3,2-b]pyridine-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide:



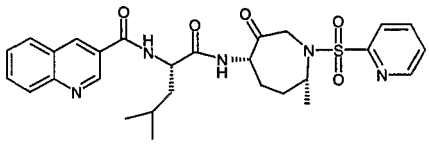
;

quinoline-6-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide:



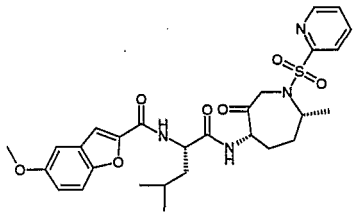
;

quinoline-3-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide



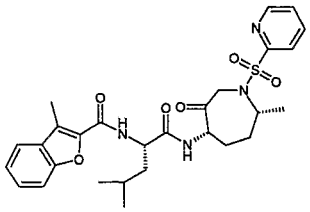
;

5-methoxy-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide



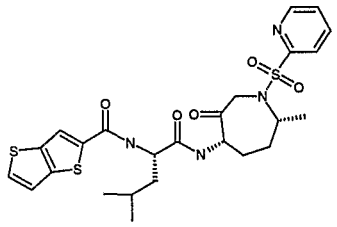
;

3-methyl-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide



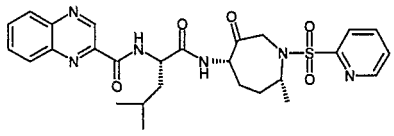
;

thieno[3,2-b]thiophene-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide



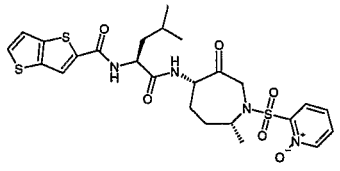
;

quinoxaline-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide



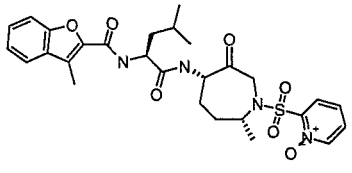
;

thieno[3,2-b] thiophene-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide



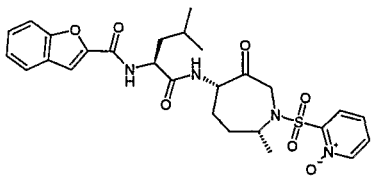
;

3-methyl-benzofuran-2-carboxylicacid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide

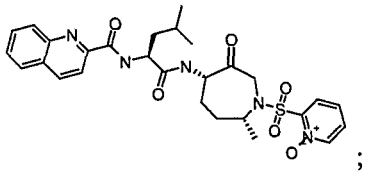


;

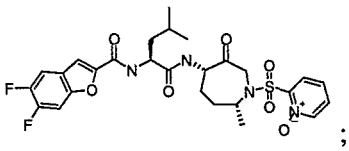
benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide


;

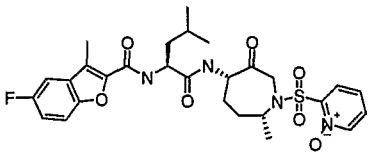
quinoline-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide


;

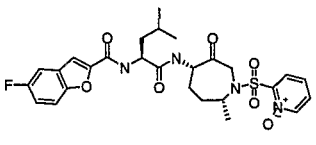
5,6-difluoro-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide


;

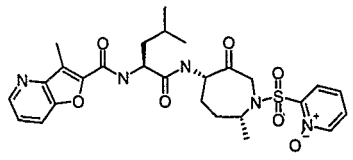
5-fluoro-3-methyl-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide


;

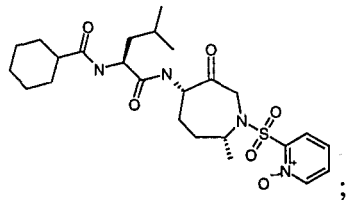
5-fluoro-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide


;

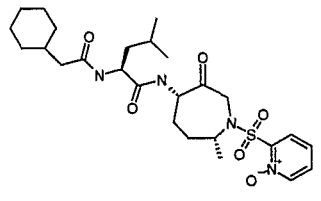
3-methyl-furo[3,2-b]]pyridine-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide


;

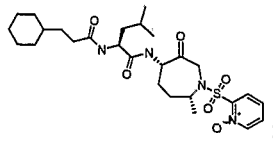
cyclohexanecarboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide


;

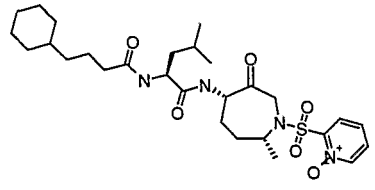
(S)-2-(2-cyclohexyl-ethanoylamino)-4-methyl-pentanoic acid [(4S,7R)-7-methyl-3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-yl]-amide


;

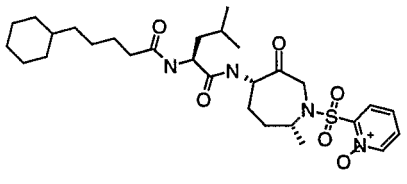
(S)-2-(3-cyclohexyl-propanoylamino)-4-methyl-pentanoic acid [(4S,7R)-7-methyl-3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-yl]-amide


;

(S)-2-(4-cyclohexyl-butanoylamino)-4-methyl-pentanoic acid [(4S,7R)-7-methyl-3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-yl]-amide

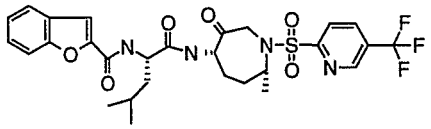

;

(S)-2-(5-cyclohexyl-pentanoylamino)-4-methyl-pentanoic acid [(4S,7R)-7-methyl-3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-yl]-amide



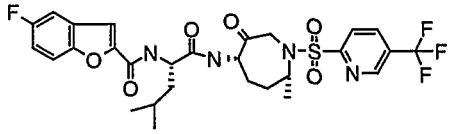
;

benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(5-trifluoromethyl-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide



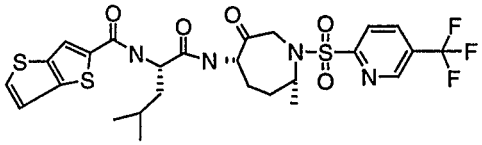
;

5-fluoro-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(5-trifluoromethyl-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide



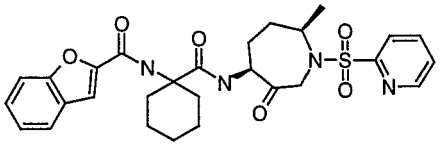
;

thieno[3,2-b] thiophene-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(5-trifluoromethyl-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide



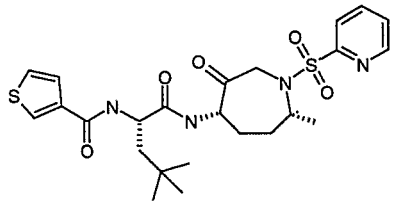
;

benzofuran-2-carboxylic acid {1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-cyclohexyl}-amide



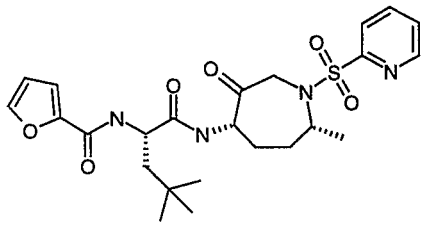
;

thiophene-3-carboxylic acid {(S)-3,3-dimethyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide



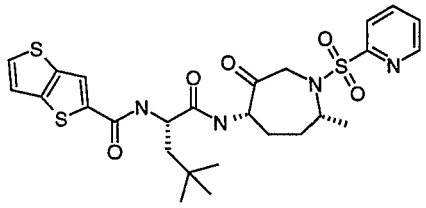
;

furan-2-carboxylic acid {(S)-3,3-dimethyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide



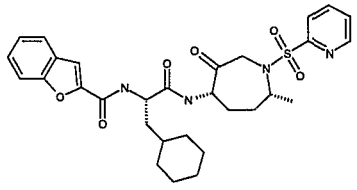
;

thieno[3,2-b] thiophene-2-carboxylic acid {(S)-3,3-dimethyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide



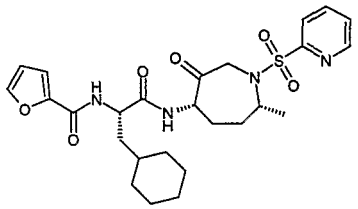
;

benzofuran-2-carboxylic acid {(S)-2-cyclohexyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide



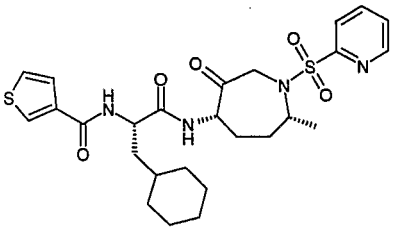
;

furan-2-carboxylic acid {(S)-2-cyclohexyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide



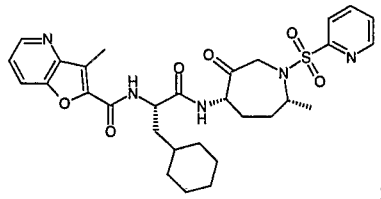
;

thiophene-3-carboxylic acid {(S)-2-cyclohexyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide



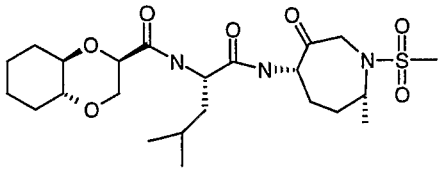
;

3-methyl-furo[3,2-b]- pyridine-2-carboxylic acid {(S)-2-cyclohexyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide



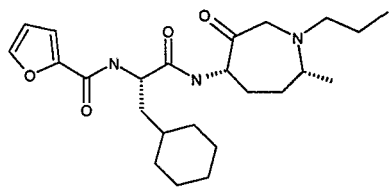
;

(2R,4aR,8aR)-octahydro-benzo[1,4]dioxine-2-carboxylic acid [(S)-1-((4S,7R)-1-methanesulfonyl-7-methy l-3-oxo-azepan-4-ylcarbamoyl)-3-methyl-butyl]-amide



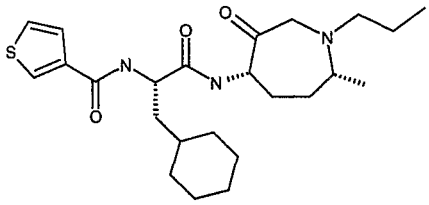
;

furan-2-carboxylic acid [(S)-2-cyclohexyl-1-((4S,7R)-7-methyl-3-oxo-1-propyl-azepan-4-ylcarbamoyl)-ethyl]-amide



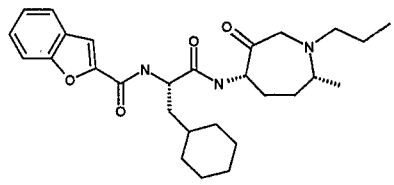
;

thiophene-3-carboxylic acid [(S)-2-cyclohexyl-1-((4S,7R)-7-methyl-3-oxo-1-propyl-azepan-4-ylcarbamoyl)-ethyl]-amide



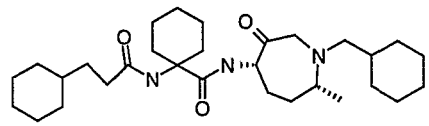
;

benzofuran-2-carboxylic acid [(S)-2-cyclohexyl-1-((4S,7R)-7-methyl-3-oxo-1-propyl-azepan-4-ylcarbamoyl)-ethyl]-amide



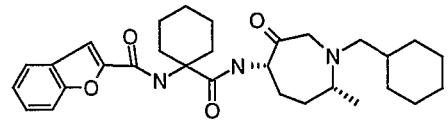
;

1-(3-cyclohexyl-propanoylamino)-cyclohexanecarboxylic acid ((4S,7R)-1-cyclohexylmethyl-7-methyl-3-oxo-azepan-4-yl)-amide



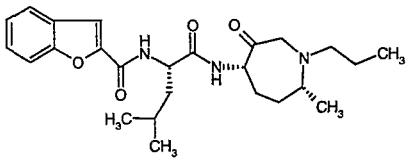
;

benzofuran-2-carboxylic acid [1-((4S,7R)-1-cyclohexylmethyl-7-methyl-3-oxo-azepan-4-ylcarbamoyl)-cyclohexyl]-amide



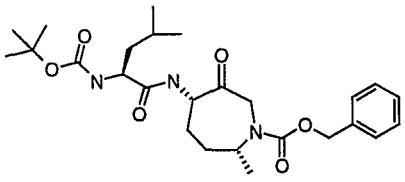
;

benzofuran-2-carboxylic acid [(S)-3-methyl-1-((4S,7R)-7-methyl-3-oxo-1-propyl-azepan-4-ylcarbamoyl)- butyl]-amide



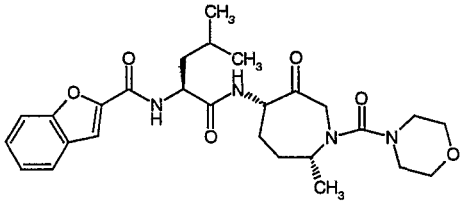
;

(2R,5S)-5-((S)-2-tert-butoxycarbonylamino-4-methyl-pentanoylamino)-2-methyl-6-oxo-azepane-1-carboxylic acid benzyl ester



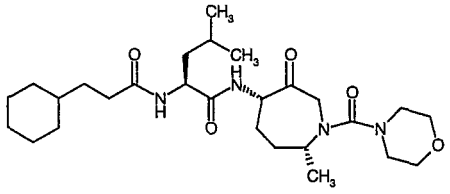
;

benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-1-(1-morpholin-4-yl-methanoyl)-3-oxo- azepan-4-ylcarbamoyl]-butyl}-amide



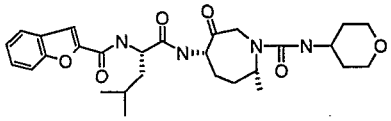
;

(S)-2-(3-cyclohexyl-propanoylamino)-4-methyl-pentanoic acid [(4S,7R)-7-methyl-1-(1-morpholin-4-yl-me thanoyl)-3-oxo-azepan-4-yl]-amide

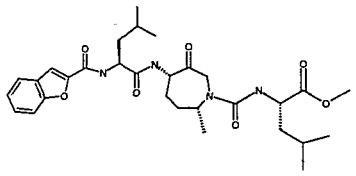


;

(2R,5S)-5-{(S)-2-[(1-benzofuran-2-yl-methanoyl)-amino]-4-methyl-pentanoylamino}-2-methyl-6-oxo-azepane-1-carboxylic acid (tetrahydro-pyran-4-yl)-amide

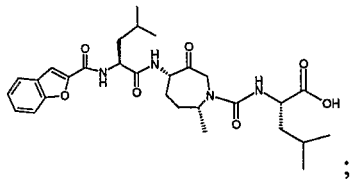


(S)-2-{[1-((2R,5S)-5-{(S)-2-[(1-benzofuran-2-yl-methanoyl)-amino]-4-methyl-pentanoylamino}-2-methyl-6-oxo-azepan-1-yl)-methanoyl]-amino}-4-methyl-pentanoic acid methyl ester



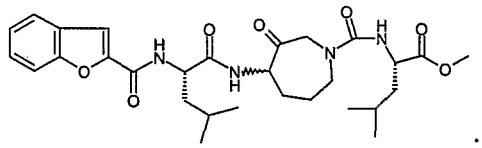
;

(S)-2-{[1-((2R,5S)-5-{(S)-2-[(1-benzofuran-2-yl-methanoyl)-amino]-4-methyl-pentanoylamino}-2-methyl-6-oxo-azepan-1-yl)-methanoyl]-amino}-4-methyl-pentanoic acid



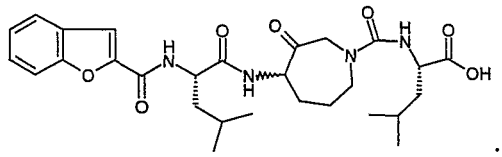
;

(S)-2-{[1-(4-{(S)-2-[(1-benzofuran-2-yl-methanoyl)-amino]-4-methyl-pentanoylamino}-3-oxo-azepan-1-yl)-methanoyl]-amino}-4-methyl-pentanoica cid methyl ester



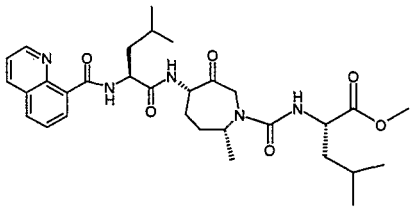
;

(S)-2-{[1-(4-{(S)-2-[(1-benzofuran-2-yl-methanoyl)-amino]-4-methyl-pentanoylamino}-3-oxo-azepan-1-yl)-methanoyl]-amino}-4-methyl-pentanoic acid



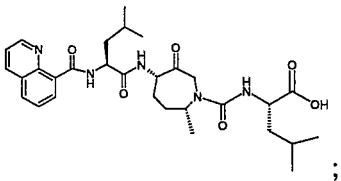
;

(S)-4-methyl-2-{[1-((2R,5S)-2-methyl-5-{(S)-4-methyl-2-[(1-quinolin-8-yl-methanoyl)-amino]-pentanoylamino}-6-oxo-azepan-1-yl)-methanoyl]-amino}-pentanoic acid methyl ester



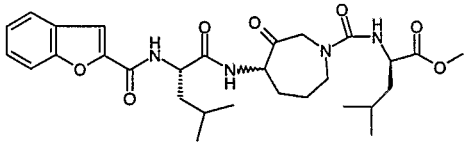
;

(S)-4-methyl-2-{[1-((2R,5S)-2-methyl-5-{(S)-4-methyl-2-[(1-quinolin-8-yl-methanoyl)-amino]-pentanoylamino}-6-oxo-azepan-1-yl)-methanoyl]-amino}-pentanoic acid



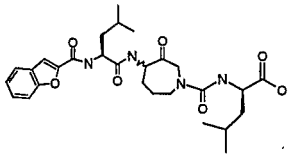
;

(R)-2-{[1-(4-{(S)-2-[(1-benzofuran-2-yl-methanoyl)-amino]-4-methyl-pentanoylamino}-3-oxo-azepan-1-yl)-methanoyl]-amino}-4-methyl-pentanoic acid methyl ester



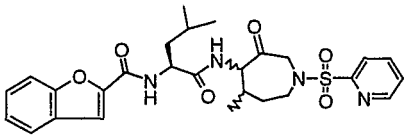
;

(R)-2-{[1-(4-{(S)-2-[(1-benzofuran-2-yl-methanoyl)-amino]-4-methyl-pentanoylamino}-3-oxo-azepan-1-yl)-methanoyl]-amino}-4-methyl-pentanoic acid



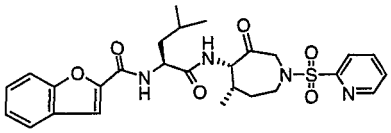
;

4,5 (R,S)-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[5-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide:



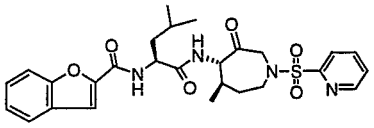
;

4S, 5S-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[5-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide:



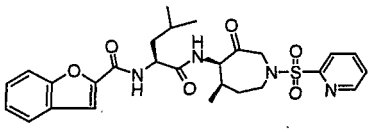
;

4S, 5R-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[5-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide



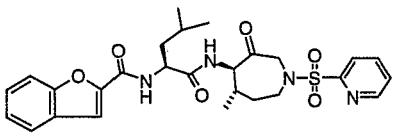
;

4R, 5R-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[5-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide



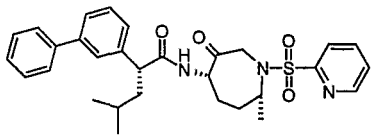
;

4R, 5S-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[5-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide:



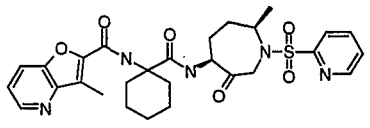
;

(R)-2-biphenyl-3-yl-4-methyl-pentanoic acid [(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-yl]-amide:



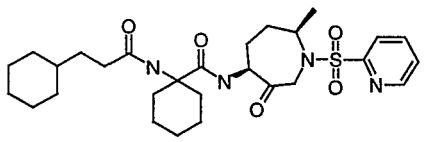
;

3-Methyl-furo[3,2-b]-pyridine-2-carboxylic acid {1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-cyclohexyl}-amide:

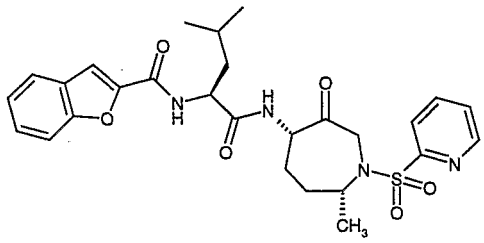


; and

1-(3-cyclohexyl-propanoylamino)-cyclohexanecarboxylic acid [(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-yl]-amide:



A most particularly preferred embodiment of the present invention is benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide:



Specific representative compounds of the present invention are set forth in Examples 1-64.

Compared to the corresponding 5- and 6- membered ring compounds, the 7- membered ring compounds of the present invention are configurationally more stable at the carbon center alpha to the ketone.

The present invention includes deuterated analogs of the inventive compounds. Representative examples of such a deuterated compounds are set forth in Examples 7, 9 and 11. A representative synthetic route for the deuterated compounds of the present invention is set forth in Scheme 4, below. The deuterated compounds of the present invention exhibit superior chiral stability compared to the protonated isomer.

Definitions

The present invention includes all hydrates, solvates, complexes and prodrugs of the compounds of this invention. Prodrugs are any covalently bonded compounds which release the active parent drug according to Formula I *in vivo*. If a chiral center or another form of an isomeric center is present in a compound of the present invention, all forms of such isomer or isomers, including enantiomers and diastereomers, are intended to be covered herein. Inventive compounds containing a chiral center may be used as a racemic mixture, an enantiomerically enriched mixture, or the racemic mixture may be separated using well-known techniques and an individual enantiomer may be used alone. In cases in which compounds have unsaturated carbon-carbon double bonds, both the cis (Z) and trans (E) isomers are within the scope of this invention. In cases wherein compounds may exist in tautomeric forms, such as keto-enol tautomers, each tautomeric form is contemplated as being included within this invention whether existing in equilibrium or predominantly in one form.

The meaning of any substituent at any one occurrence in Formula I or any subformula thereof is independent of its meaning, or any other substituent's meaning, at any other occurrence, unless specified otherwise.

Abbreviations and symbols commonly used in the peptide and chemical arts are used herein to describe the compounds of the present invention. In general, the amino acid abbreviations follow the IUPAC-IUB Joint Commission on Biochemical Nomenclature as described in *Eur. J. Biochem.*, 158, 9 (1984).

"Proteases" are enzymes that catalyze the cleavage of amide bonds of peptides and proteins by nucleophilic substitution at the amide bond, ultimately resulting in hydrolysis. Such proteases include: cysteine proteases, serine proteases, aspartic proteases, and

metalloproteases. The compounds of the present invention are capable of binding more strongly to the enzyme than the substrate and in general are not subject to cleavage after enzyme catalyzed attack by the nucleophile. They therefore competitively prevent proteases from recognizing and hydrolyzing natural substrates and thereby act as inhibitors.

The term "amino acid" as used herein refers to the D- or L- isomers of alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine and valine.

"Hydrogen" or "H" includes all of its possible isotopes, including "deuterium" or "D" or "^{2}H"; and "tritium" or "T" or "^{3}H".

"C_{1-6}alkyl" as applied herein is meant to include substituted and unsubstituted methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl and t-butyl, pentyl, n-pentyl, isopentyl, neopentyl and hexyl and the simple aliphatic isomers thereof. C_{1-6}alkyl may be optionally substituted by a moiety selected from the group consisting of: OR^{14}, $C(O)R^{14}$, SR^{14}, $S(O)R^{14}$, $NR^{14}{}_2$, $R^{14}NC(O)OR^5$, CO_2R^{14}, $CO_2NR^{14}{}_2$, $N(C{=}NH)NH_2$, Het, C_{3-6}cycloalkyl, and Ar; where R^5 is selected from the group consisting of: H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl and Het-C_{0-6}alkyl; and R^{14} is selected from the group consisting of: H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, and Het-C_{0-6}alkyl;

"C_{3-6}cycloalkyl" as applied herein is meant to include substituted and unsubstituted cyclopropane, cyclobutane, cyclopentane and cyclohexane.

"C_{2-6} alkenyl" as applied herein means an alkyl group of 2 to 6 carbons wherein a carbon-carbon single bond is replaced by a carbon-carbon double bond. C_{2-6}alkenyl includes ethylene, 1-propene, 2-propene, 1-butene, 2-butene, isobutene and the several isomeric pentenes and hexenes. Both cis and trans isomers are included.

"C_{2-6}alkanonyl" as applied herein is meant to include unsubstituted and substituted acetyl, propanonyl, butanonyl, pentanonyl, and hexanonyl.

"C_{2-6}alkynyl" means an alkyl group of 2 to 6 carbons wherein one carbon-carbon single bond is replaced by a carbon-carbon triple bond. C_{2-6} alkynyl includes acetylene, 1-propyne, 2-propyne, 1-butyne, 2-butyne, 3-butyne and the simple isomers of pentyne and hexyne.

"Halogen" means F, Cl, Br, and I.

"Ar" or "aryl" means phenyl or naphthyl, optionally substituted by one or more of Ph-C_{0-6}alkyl; Het-C_{0-6}alkyl; C_{1-6}alkoxy; Ph-C_{0-6}alkoxy; Het-C_{0-6}alkoxy; OH, $(CH_2)_{1-6}NR^{15}R^{16}$; $O(CH_2)_{1-6}NR^{15}R^{16}$; C_{1-6}alkyl, OR^{17}, $N(R^{17})_2$, SR^{17}, CF_3, NO_2, CN,

CO_2R^{17}, $CON(R^{17})$, F, Cl, Br or I; where R^{15} and R^{16} are H, C_{1-6}alkyl, Ph-C_{0-6}alkyl, naphthyl-C_{0-6}alkyl or Het-C_{0-6}alkyl; and R^{17} is phenyl, naphthyl, or C_{1-6}alkyl.

"Ar-Ar" means aryl covalently linked to a second aryl. Examples of "Ar-Ar" include biphenyl or naphythyl-phenyl or phenyl-naphthyl.

As used herein "Het" or "heterocyclic" represents a stable 5- to 7-membered monocyclic, a stable 7- to 10-membered bicyclic, or a stable 11- to 18-membered tricyclic heterocyclic ring which is either saturated or unsaturated, and which consists of carbon atoms and from one to three heteroatoms selected from the group consisting of N, O and S, and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure, and may optionally be substituted with one or two moieties selected from C_{0-6}Ar, C_{1-6}alkyl, OR^{17}, $N(R^{17})_2$, SR^{17}, CF_3, NO_2, CN, CO_2R^{17}, $CON(R^{17})$, F, Cl, Br and I, where R^{17} is phenyl, naphthyl, or C_{1-6}alkyl. Examples of such heterocycles include piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, imidazolyl, pyridinyl, 1-oxo-pyridinyl, pyrazinyl, oxazolidinyl, oxazolinyl, oxazolyl, isoxazolyl, morpholinyl, thiazolidinyl, thiazolinyl, thiazolyl, quinuclidinyl, indolyl, quinolinyl, quinoxalinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, benzoxazolyl, furanyl, benzofuranyl, thiophenyl, benzo[b]thiophenyl, thieno[3,2-b]thiophenyl, benzo[1,3]dioxolyl, 1,8 naphthyridinyl, pyranyl, tetrahydrofuranyl, tetrahydropyranyl, thienyl, benzoxazolyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, and oxadiazolyl, as well as triazolyl, thiadiazolyl, oxadiazolyl, isothiazolyl, imidazolyl, pyridazinyl, pyrimidinyl, triazinyl and tetrazinyl which are available by routine chemical synthesis and are stable. The term heteroatom as applied herein refers to oxygen, nitrogen and sulfur.

"Ar-Het" means an aryl group covalently linked to a heterocycle. Examples of "Ar-Het" include phenyl-piperidine, phenyl-piperazine, phenyl-2-oxopiperazine, naphthyl-piperidine, naphthyl-piperazine, and naphthyl-2-oxopiperazine.

"Het-Ar" means a heterocycle covalently linked to a aryl group. Examples of such "Het-Ar" include piperidinyl-phenyl, piperazinyl-phenyl, 2-oxopiperazinyl-phenyl, piperidinyl-naphthyl, piperazinyl-naphthyl, and 2-oxopiperazinyl-naphthyl.

"Het-Het" means a heterocycle covalently linked to a second heterocycle. Examples of such "Het-Het" include bipyridine, pyridinyl-piperidine, pyridinyl-piperazine, pyridinyl-2-oxopiperazine, thiophenyl-piperidine, thiophenyl-piperazine, and thiophenyl-2-oxopiperazine.

Here and throughout this application the term C_0 denotes the absence of the substituent group immediately following; for instance, in the moiety ArC_{0-6}alkyl, when C is 0, the substituent is Ar, e.g., phenyl. Conversely, when the moiety ArC_{0-6}alkyl is identified as a specific aromatic group, e.g., phenyl, it is understood that the value of C is 0.

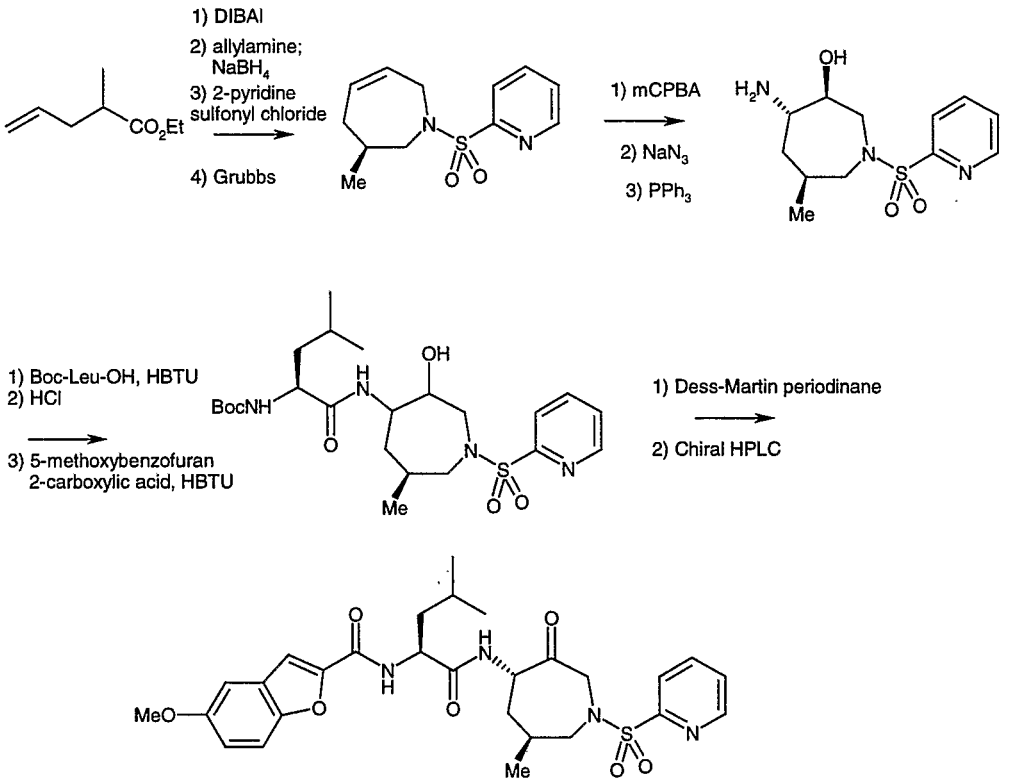
Certain radical groups are abbreviated herein. t-Bu refers to the tertiary butyl radical, Boc refers to the t-butyloxycarbonyl radical, Fmoc refers to the fluorenylmethoxycarbonyl radical, Ph refers to the phenyl radical, Cbz refers to the benzyloxycarbonyl radical.

Certain reagents are abbreviated herein. m-CPBA refers to 3-chloroperoxybenzoic acid, EDC refers to N-ethyl-N'(dimethylaminopropyl)-carbodiimide, DMF refers to dimethyl formamide, DMSO refers to dimethyl sulfoxide, TEA refers to triethylamine, TFA refers to trifluoroacetic acid, and THF refers to tetrahydrofuran.

Methods of Preparation

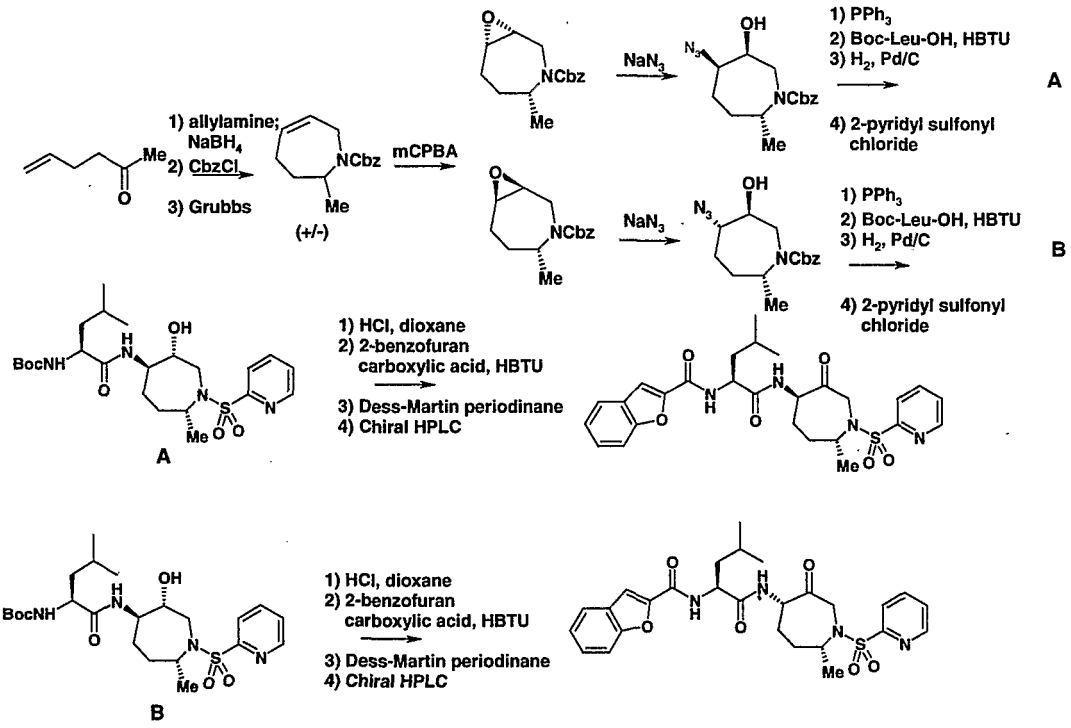
Compounds of the general formula I may be prepared in a fashion analogous to that outlined in Schemes 1 to 8.

Scheme 1



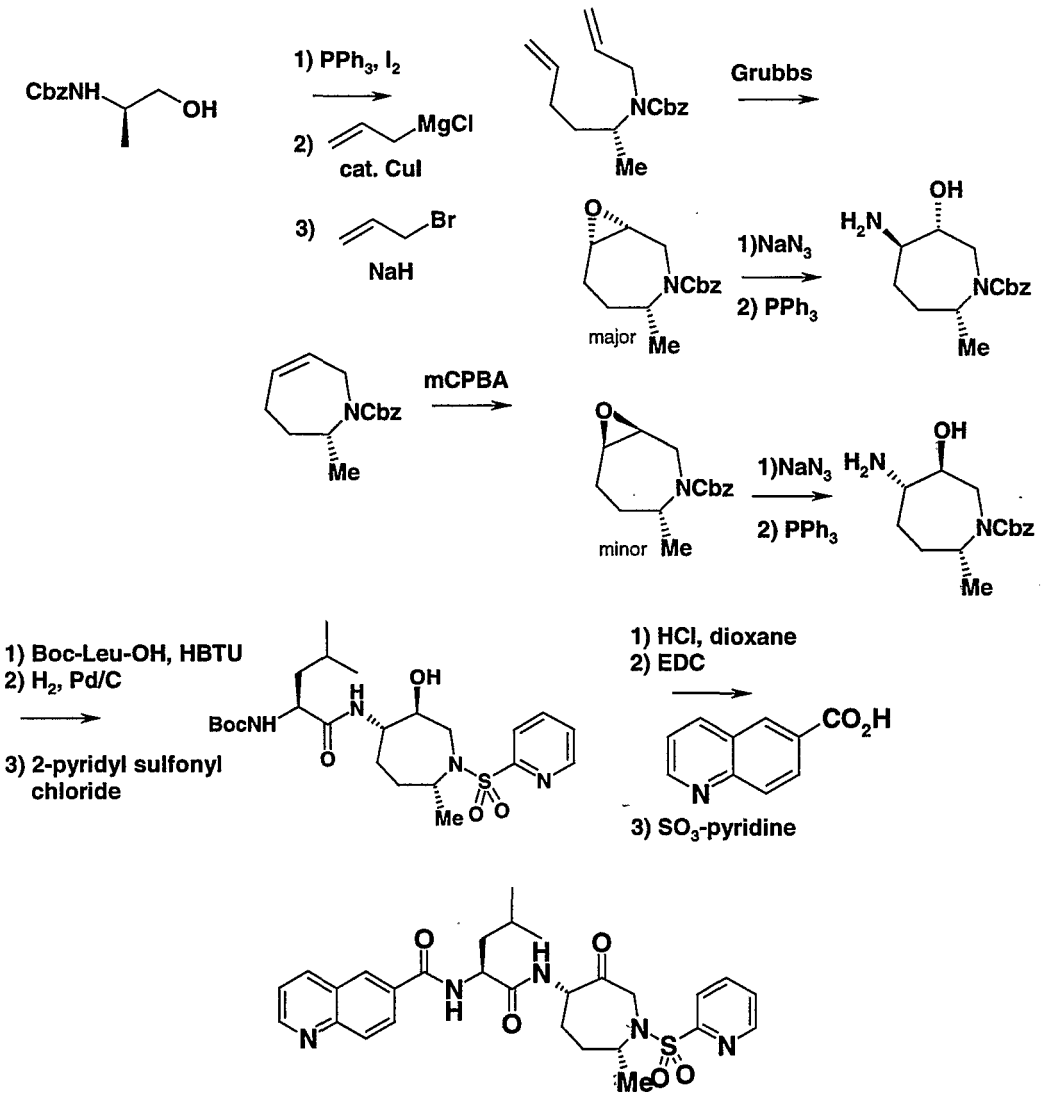
2-Methyl-pent-4-enoic acid ethyl ester is converted to a N-2-pyridinesulfonyl-azapine by reduction to the aldehyde, reductive amination with allylamine, sulfonylation with 2-pyridyl sulfonyl chloride, and olefin metathesis with Grubbs' catalyst. Epoxidation with mCPBA affords a mixture of epoxides that are separable by column chromatography. The syn epoxide is converted into an amino alcohol by opening with sodium azide followed by reduction with triphenylphosphine. Acylation of the free amine with Boc-leucine and a coupling reagent such as HBTU or EDC, followed by deprotection of the Boc group with HCl, and acylation with a variety of aromatic carboxylic acids and coupling reagents such as HBTU or EDC gives the intermediate alcohols. Final oxidation with Dess-Martin periodinane and HPLC affords the desired ketones.

Scheme 2



5-Hexen-2-one is converted to a N-carbobenzyloxy-azapine by reductive amination with allylamine, protection with carbobenzyloxychloride, and olefin metathesis with Grubbs' catalyst. Epoxidation with mCPBA affords a mixture of epoxides that are separable by column chromatography. Each epoxide is converted into an amino alcohol by opening with sodium azide followed by reduction with triphenylphosphine. Acylation of the free amine with Boc-leucine and a coupling reagent such as HBTU or EDC, followed by deprotection of the Cbz group by hydrogenolysis provides the secondary amines which are in turn sulfonylated with 2-pyridine sulfonylchloride. Deprotection of the Boc groups with HCl and acylation with a variety of aromatic carboxylic acids and coupling reagents such as HBTU or EDC gives the intermediate alcohols. Final oxidation with Dess-Martin periodinane and HPLC affords the desired ketones.

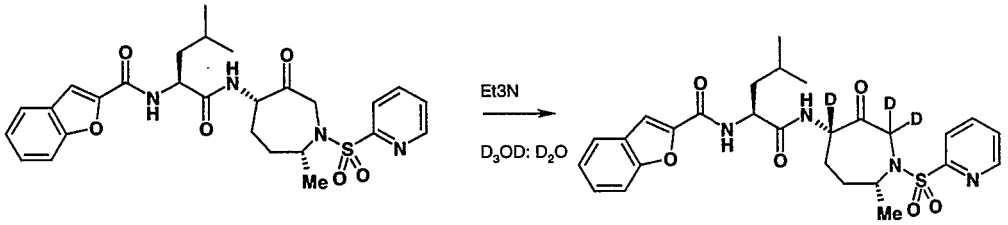
Scheme 3



Carbobenyzloxy-D-alaninol (Cbz-D-alaninol)is first converted to an iodide, then is reacted with allyl Grignard with a copper (I) catalyst or a similar allyl organometallic reagent. The amine is then alkylated with allyl iodide. Grubbs' catalyst is then used to form the azapine ring by ring closing metathesis. Epoxidation of the alkene followed by separation of the diastereomers followed by opening of the epoxide of the minor component with sodium azide provides the intermediate azido alcohol. Reduction of the azide followed by acylation of the amine with a protected amino acid such as Boc-leucine, followed by deprotection of the Cbz gives the intermediate secondary amine, which is then sulfonylated with a sulfonyl chloride such as pyridine sulfonyl chloride. Deprotection of the Boc group followed by acylation with an acylating agent such as quinoline-6-carboxylic

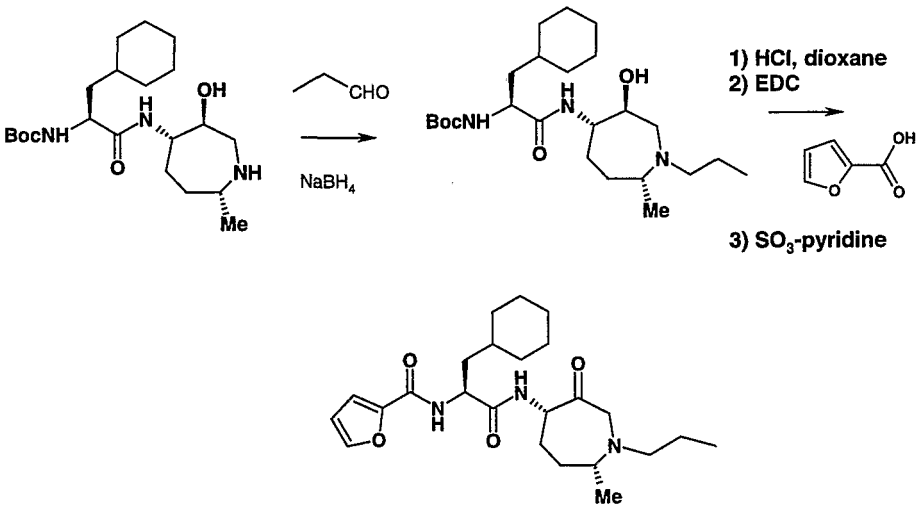
acid, HBTU, NMM, and final oxidation of the secondary alcohol to the ketone with an oxidant such as sulfur trioxide-pyridine or Dess-Martin periodinane provides the desired products.

Scheme 4



Deuterated inhibitors can be prepared from the parent inhibitors such as benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide by treating with a base such as triethyl amine and stirring for several days in a deteurated protic solvent such as CD_3OD: D_2O.

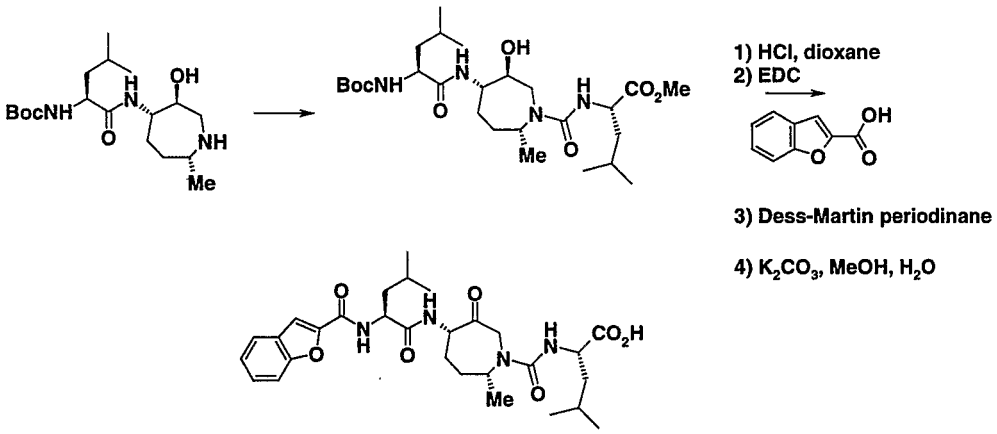
Scheme 5



Intermediate (S)-3-Cyclohexyl-N-((3S,4S,7R)-3-hydroxy-7-methyl-azepan-4-yl)-2-methyl-propionamide, as described in Scheme 3 (using Boc-cyclohexylalanine instead of Boc-L-leucine), is reductively aminated with an aldehyde or a ketone such as propionaldehyde, then treated with a reducing agent such as sodium borohydride. Deprotection of the Boc group followed by acylation with an acylating agent such as 2-furan carboxylic acid,

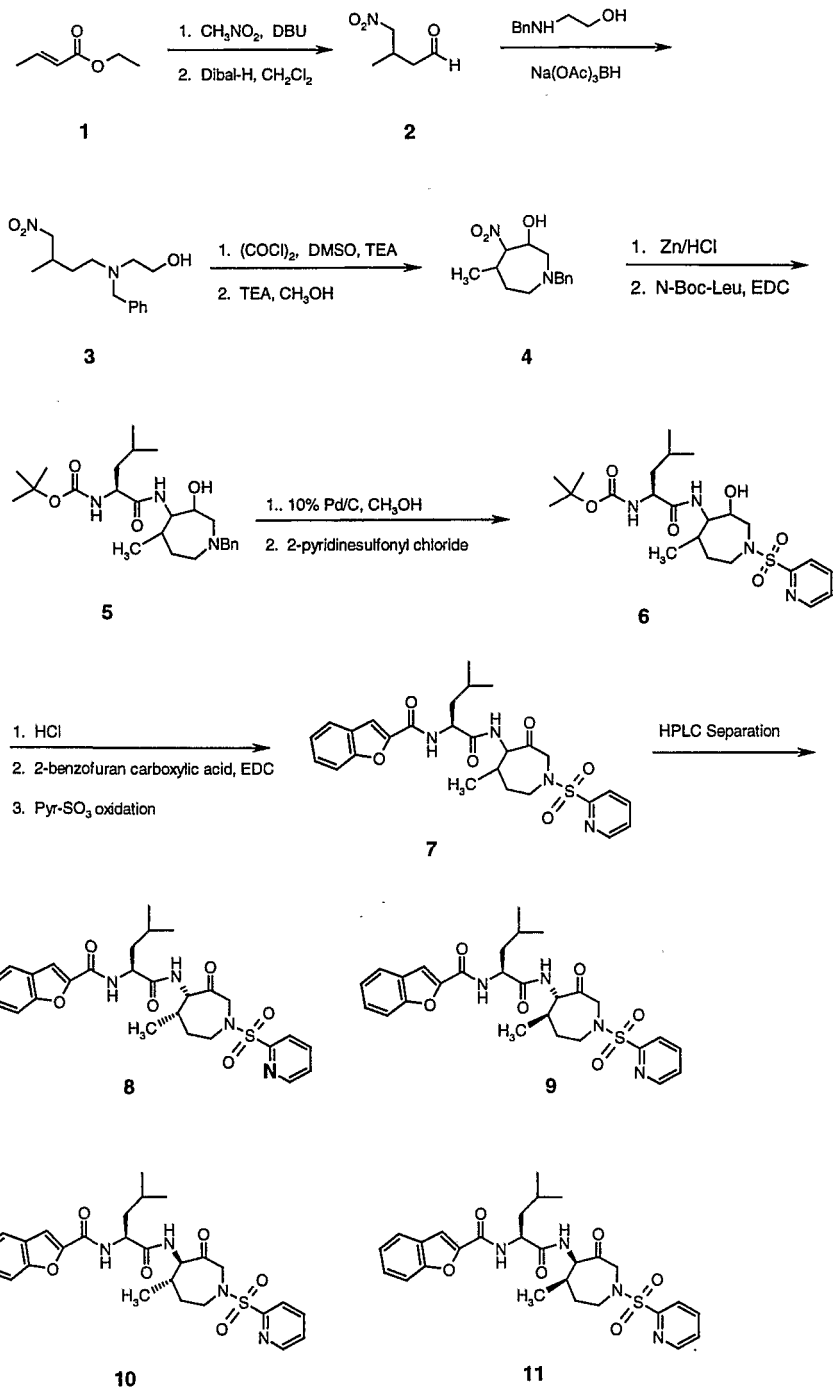
HBTU, NMM, and final oxidation of the secondary alcohol to the ketone with an oxidant such as sulfur trioxide-pyridine provides the desired products.

Scheme 6



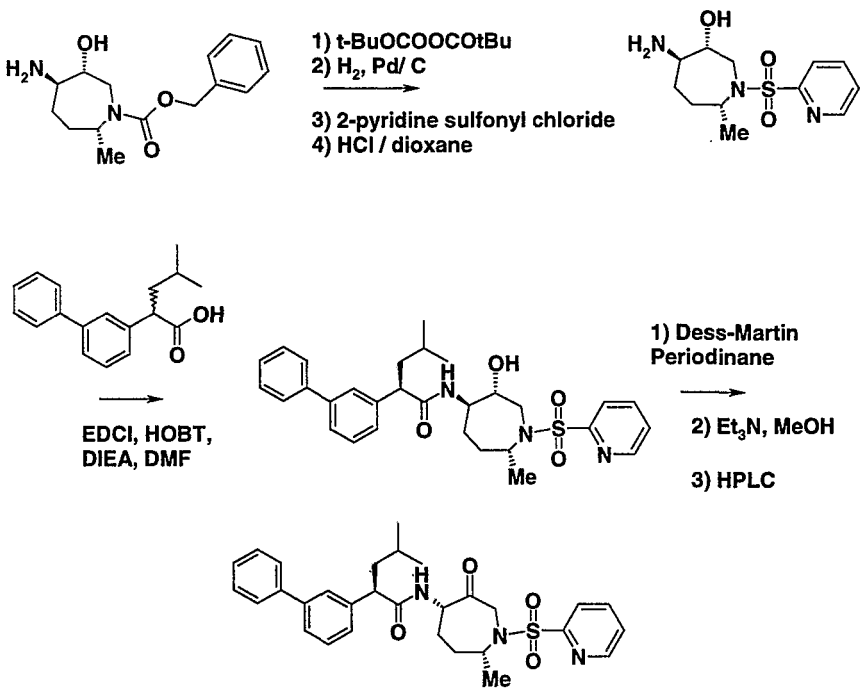
Intermediate [(S)-1-((S)-3-Hydroxy-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid tert-butyl ester, as described in Scheme 3, is acylated with an isocyanate such as (S)-(-)-2-isocyanato-4-methylvaleric acid methyl ester. Deprotection of the Boc group followed by acylation with an acylating agent such as benzofuran-2-carboxylic acid, HBTU, NMM, and final oxidation of the secondary alcohol to the ketone with an oxidant such as Dess-Martin periodinane or sulfur trioxide-pyridine provides the desired products.

Scheme 7


1. CH_3NO_2, DBU
2. Dibal-H, CH_2Cl_2
BnNH OH
$Na(OAc)_3BH$
1
2
3
1. $(COCl)_2$, DMSO, TEA
2. TEA, CH_3OH
4
1. Zn/HCl
2. N-Boc-Leu, EDC
5
1.. 10% Pd/C, CH_3OH
2. 2-pyridinesulfonyl chloride
6
1. HCl
2. 2-benzofuran carboxylic acid, EDC
3. Pyr-SO_3 oxidation
7
HPLC Separation
8
9
10
11

The synthesis of the C-5 methyl azepinone, 4,5 (R,S)-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[5-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide, (Example 61) is outlined above in Scheme 7. Michael addition of nitromethane to ethyl crotonate **7-1** followed by reduction of the intermediate ester with a reducing agent such as diisobutyl aluminum hydride (Dibal-H) provides the aldehyde **7-2**. Reductive amination of **7-2** with N-benzyl ethanolamine in the presence of a reducing agent such as sodium triacetoxyborohydride provides the nitro-alcohol **7-3**. Oxidation of **7-3** using an oxidant common to the art such as DMSO and oxalyl chloride followed by treatment of the crude intermediate aldehyde with a base such as triethylamine effects the nitro-aldol reaction to give the azepanol **7-4**. Reduction of the nitro group with zinc in the presence of hydrochloric acid followed by coupling of the resulting amine with N-Boc-leucine in the presence of a coupling agent common to the art such as EDC provides intermediate **7-5**. Reductive removal of the N-benzyl moiety with hydrogen gas in the presence of a catalyst such as 10% Pd on carbon followed by sulfonylation with a sulfonyl chloride in the presence of a base such as N-methylmorpholine or triethyl amine provides the sulfonamide intermediate **7-6**. Removal of the N-Boc protecting group under acidic conditions followed by coupling of the resulting amine salt with benzofuran-2-carboxylic acid and oxidation of the alcohol with an oxidant common to the art such as pyridine sulfur trioxide complex or Dess-Martin periodinane provides the ketone **7**. The individual diastereomers of **7-7** may be separated by HPLC methods to provide diastereomers **7-8**, **7-9**, **7-10** and **7-11**.

Scheme 8



Intermediate (2R,5R,6R)-5-Amino-6-hydroxy-2-methyl-azepane-1-carboxylic acid benzyl ester (derived from the major epoxide of Scheme 3) is protected with Boc anhydride. Then, the Cbz group is removed by hydrogenolysis. Sulfonylation is then accomplished with 2-pyridine sulfonyl chloride, and the Boc group is removed with hydrochloric acid in dioxane. The primary amine is then coupled with 2-biphenyl-3-yl-4-methyl-pentanoic acid (as described in. *J. Am. Chem. Soc.* **1997**, *120*, 9114), then the secondary alcohol to the ketone with an oxidant such as Dess-Martin periodinane or sulfur trioxide-pyridine. The azepanone is then epimerized using triethylamine in MeOH to provide a mixture of diastereomers. The desired compound is obtained by separation of the diastereomers using chiral HPLC.

The starting materials used herein are commercially available amino acids or are prepared by routine methods well known to those of ordinary skill in the art and can be found in standard reference books, such as the COMPENDIUM OF ORGANIC SYNTHETIC METHODS, Vol. I-VI (published by Wiley-Interscience).

Coupling methods to form amide bonds herein are generally well known to the art. The methods of peptide synthesis generally set forth by Bodansky *et al.*, THE PRACTICE OF PEPTIDE SYNTHESIS, Springer-Verlag, Berlin, 1984; E. Gross and J. Meienhofer, THE PEPTIDES, Vol. 1, 1-284 (1979); and J.M. Stewart and J.D. Young, SOLID PHASE

PEPTIDE SYNTHESIS, 2d Ed., Pierce Chemical Co., Rockford, Ill., 1984. are generally illustrative of the technique and are incorporated herein by reference.

Synthetic methods to prepare the compounds of this invention frequently employ protective groups to mask a reactive functionality or minimize unwanted side reactions. Such protective groups are described generally in Green, T.W, PROTECTIVE GROUPS IN ORGANIC SYNTHESIS, John Wiley & Sons, New York (1981). The term "amino protecting groups" generally refers to the Boc, acetyl, benzoyl, Fmoc and Cbz groups and derivatives thereof as known to the art. Methods for protection and deprotection, and replacement of an amino protecting group with another moiety are well known.

Acid addition salts of the compounds of Formula I are prepared in a standard manner in a suitable solvent from the parent compound and an excess of an acid, such as hydrochloric, hydrobromic, hydrofluoric, sulfuric, phosphoric, acetic, trifluoroacetic, maleic, succinic or methanesulfonic. Certain of the compounds form inner salts or zwitterions which may be acceptable. Cationic salts are prepared by treating the parent compound with an excess of an alkaline reagent, such as a hydroxide, carbonate or alkoxide, containing the appropriate cation; or with an appropriate organic amine. Cations such as Li^+, Na^+, K^+, Ca^{++}, Mg^{++} and NH_4^+ are specific examples of cations present in pharmaceutically acceptable salts. Halides, sulfate, phosphate, alkanoates (such as acetate and trifluoroacetate), benzoates, and sulfonates (such as mesylate) are examples of anions present in pharmaceutically acceptable salts.

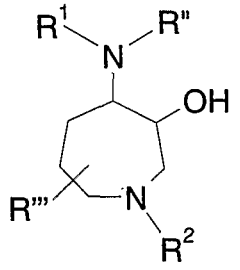
This invention also provides a pharmaceutical composition which comprises a compound according to Formula I and a pharmaceutically acceptable carrier, diluent or excipient. Accordingly, the compounds of Formula I may be used in the manufacture of a medicament. Pharmaceutical compositions of the compounds of Formula I prepared as hereinbefore described may be formulated as solutions or lyophilized powders for parenteral administration. Powders may be reconstituted by addition of a suitable diluent or other pharmaceutically acceptable carrier prior to use. The liquid formulation may be a buffered, isotonic, aqueous solution. Examples of suitable diluents are normal isotonic saline solution, standard 5% dextrose in water or buffered sodium or ammonium acetate solution. Such formulation is especially suitable for parenteral administration, but may also be used for oral administration or contained in a metered dose inhaler or nebulizer for insufflation. It may be desirable to add excipients such as polyvinylpyrrolidone, gelatin, hydroxy cellulose, acacia, polyethylene glycol, mannitol, sodium chloride or sodium citrate.

Alternately, these compounds may be encapsulated, tableted or prepared in an emulsion or syrup for oral administration. Pharmaceutically acceptable solid or liquid carriers may be added to enhance or stabilize the composition, or to facilitate preparation of the composition. Solid carriers include starch, lactose, calcium sulfate dihydrate, terra alba, magnesium stearate or stearic acid, talc, pectin, acacia, agar or gelatin. Liquid carriers include syrup, peanut oil, olive oil, saline and water. The carrier may also include a sustained release material such as glyceryl monostearate or glyceryl distearate, alone or with a wax. The amount of solid carrier varies but, preferably, will be between about 20 mg to about 1 g per dosage unit. The pharmaceutical preparations are made following the conventional techniques of pharmacy involving milling, mixing, granulating, and compressing, when necessary, for tablet forms; or milling, mixing and filling for hard gelatin capsule forms. When a liquid carrier is used, the preparation will be in the form of a syrup, elixir, emulsion or an aqueous or non-aqueous suspension. Such a liquid formulation may be administered directly p.o. or filled into a soft gelatin capsule.

For rectal administration, the compounds of this invention may also be combined with excipients such as cocoa butter, glycerin, gelatin or polyethylene glycols and molded into a suppository.

Novel Intermediates

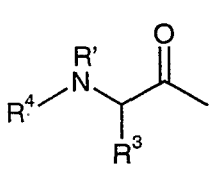
Referring to the methods of preparing the compounds of Formula I set forth in Schemes 1-8 above, the skilled artisan will appreciate that the present invention includes all novel intermediates required to make the compounds of Formula I. In particular, the present invention provides the compounds of Formula II:



II

wherein:

R^1 is selected from the group consisting of: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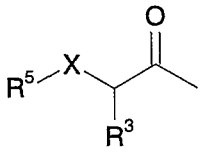
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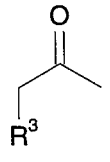
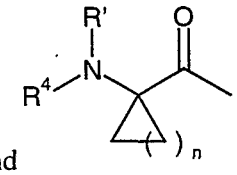
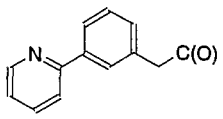

;and

;

R^2 is selected from the group consisting of: H, C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, $R^9C(O)$-, $R^9C(S)$-, R^9SO_2-, $R^9OC(O)$-, $R^9R^{11}NC(O)$-, $R^9R^{11}NC(S)$-, $R^9(R^{11})NSO_2$-

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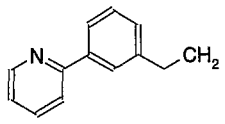
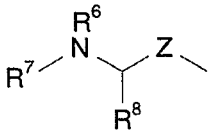

and

;

R^3 is selected from the group consisting of: H, C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, HetC_{0-6}alkyl, ArC_{0-6}alkyl, Ar-ArC_{0-6}alkyl, Ar-HetC_{0-6}alkyl, Het-ArC_{0-6}alkyl, and Het-HetC_{0-6}alkyl;

;

R^3 and R' may be connected to form a pyrrolidine, piperidine or morpholine ring;

R^4 is selected from the group consisting of: H, C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, $R^5C(O)$-, $R^5C(S)$-, R^5SO_2-, $R^5OC(O)$-, $R^5R^{12}NC(O)$-, and $R^5R^{12}NC(S)$-;

R^5 is selected from the group consisting of: H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl and Het-C_{0-6}alkyl;

R^6 is selected from the group consisting of: H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl;

R^7 is selected from the group consisting of: H, C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, $R^{10}C(O)$-, $R^{10}C(S)$-, $R^{10}SO_2$-, $R^{10}OC(O)$-, $R^{10}R^{13}NC(O)$-, and $R^{10}R^{13}NC(S)$-;

R^8 is selected from the group consisting of: H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, HetC_{0-6}alkyl and ArC_{0-6}alkyl;

R^9 is selected from the group consisting of: C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl and Het-C_{0-6}alkyl;

R^{10} is independently selected from the group consisting of: C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl and Het-C_{0-6}alkyl;

R^{11} is selected from the group consisting of: H, C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, and Het-C_{0-6}alkyl;

R^{12} is selected from the group consisting of: H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, and Het-C_{0-6}alkyl;

R^{13} is selected from the group consisting of: H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, and Het-C_{0-6}alkyl;

R' is selected from the group consisting of: H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, and Het-C_{0-6}alkyl;

R" is selected from the group consisting of: H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl;

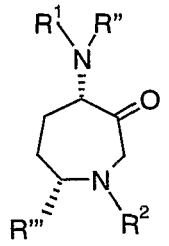
R"' is selected from the group consisting of:

C_{1-6}alkyl, especially selected from the group consisting of: methyl, ethyl, propyl, butyl, pentyl and hexyl, more especially methyl;

preferably 5-, 6- or 7- C_{1-6}alkyl, especially selected from the group consisting of: 5-, 6- or 7-methyl, -ethyl, -propyl, -butyl, -pentyl and -hexyl, more especially 5-, 6- or 7-methyl;

more preferably 6- or 7- C_{1-6}alkyl, especially selected from the group consisting of: 6- or 7-methyl, -ethyl, -propyl, -butyl, -pentyl and -hexyl, more especially 6- or 7-methyl;

yet more preferably *cis*-7- C_{1-6}alkyl as shown in Formula Ia:



Ia

wherein R"' is C_{1-6}alkyl, especially selected from the group consisting of: methyl, ethyl, propyl, butyl, pentyl and hexyl;

most preferably *cis*-7- methyl, as shown in Formula Ia wherein R"' is methyl;

X is selected from the group consisting of: CH_2, S, and O;

Z is selected from the group consisting of: C(O) and CH_2;

n is an integer from 1 to 5;

and pharmaceutically acceptable salts, hydrates and solvates thereof.

The following compounds are preferred novel intermediates:

3-methyl-1-(pyridine-2-sulfonyl)-2,3,4,7-tetrahydro-1H-azepine;

5-methyl-3-(pyridine-2-sulfonyl)-8-oxa-3-aza-bicyclo[5.1.0]octane;

4-azido-5-methyl-1-(pyridine-2-sulfonyl)-azepan-3-ol;

4-amino-6-methyl-1-(pyridine-2-sulfonyl)-azepan-3-ol;

{(S)-1-[3-hydroxy-6-methyl-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-3-methyl-butyl}-carbamic acid tert-butyl ester;

5-methoxy-benzofuran-2-carboxylic acid {(S)-1-[3-hydroxy-6-methyl-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide;

allyl-(1-methyl-pent-4-enyl)-carbamic acid benzyl ester;

2-methyl-2,3,4,7-tetrahydro-azepine-1-carboxylic acid benzyl ester;

4-methyl-8-oxa-3-aza-bicyclo[5.1.0]octane-3-carboxylic acid benzyl ester;

5-azido-6-hydroxy-2-methyl-azepane-1-carboxylic acid benzyl ester;

5-amino-6-hydroxy-2-methyl-azepane-1-carboxylic acid benzyl ester;

(2R,5S,6S)-5-((S)-2- tert -butoxycarbonylamino-4-methyl-pentanoylamino)-6-hydroxy-2-methyl-azepane-1 -carboxylic acid benzyl ester;

(2S,5R,6R)-5-((S)-2- tert -butoxycarbonylamino-4-methyl-pentanoylamino)-6-hydroxy-2-methyl-azepane-1 -carboxylic acid benzyl ester;

[(S)-1-((3S,4S,7R)-3-hydroxy-7-methyl-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid tert -butyl ester;

[(S)-1-((3R,4R,7S)-3-hydroxy-7-methyl-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid tert -butyl ester;

[(S)-1-((3S,4S,7R)-1-benzenesulfonyl-3-hydroxy-7-methyl-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid tert -butyl ester;

[(S)-1-((3R,4R,7S)-1-benzenesulfonyl-3-hydroxy-7-methyl-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid tert -butyl ester;

(S)-2-amino-4-methyl-pentanoic acid ((3S,4S,7R)-1-(2-pyridine)-sulfonyl-3-hydroxy-7-methyl-azepan-4-yl)-amide;

(S)-2-amino-4-methyl-pentanoic acid ((3R,4R,7S)-1-(2-pyridine)-sulfonyl-3-hydroxy-7-methyl-azepan-4-yl)-amide;

benzofuran-2-carboxylic acid {(S)-1-[(3S,4S,7R)-3-hydroxy-7-methyl-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide;

benzofuran-2-carboxylic acid {(S)-1-[(3R,4R,7S)-3-hydroxy-7-methyl-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide;

((R)-1-methyl-pent-4-enyl)-carbamic acid benzyl ester;

allyl-((R)-1-methyl-pent-4-enyl)-carbamic acid benzyl ester;

2-methyl-2,3,4,7-tetrahydro-azepine-1-carboxylic acid benzyl ester;

(1S,4R,7R)-4-methyl-8-oxa-3-aza-bicyclo[5.1.0]octane-3-carboxylic acid benzyl ester;

(2R,5S,6S)-5-azido-6-hydroxy-2-methyl-azepane-1-carboxylic acid benzyl ester;

(2R,5S,6S)-5-amino-6-hydroxy-2-methyl-azepane-1-carboxylic acid benzyl ester;

(2R,5S,6S)-5-((S)-2- tert -butoxycarbonylamino-4-methyl-pentanoylamino)-6-hydroxy-2-methyl-azepane-1 -carboxylic acid benzyl ester;

[(S)-1-((3S,4S,7R)-3-hydroxy-7-methyl-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid tert -butyl ester;

[(S)-1-((3S,4S,7R)-2-pyridinesulfonyl-3-hydroxy-7-methyl-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid tert -butyl ester;

(S)-2-amino-4-methyl-pentanoic acid ((3S,4S,7R)-1-(2-pyridine)-sulfonyl-3-hydroxy-7-methyl-azepan-4-yl)-amide;

5-methoxy-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(3R,4R,6R)-6-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

benzo[b]thiophene-2-carboxylic acid {(S)- 1-[(3S,4S,6S)-6-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide;

benzo[b]thiophene-2-carboxylic acid {(S)- 1-[(3R,4R,6R)-6-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide;

3•methyl-benzofuran-2-carboxylic acid {(S)- 1-[(3S,4S,6S)-6-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide;

3-methyl-benzofuran-2-carboxylic acid {(S)- 1-[(3R,4R,6R)-6-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide;

thieno[3,2-b]thiophene-2-carboxylic acid {(S)- 1-[(3S,4S,6S)-6-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide;

thieno[3,2-b]thiophene-2-carboxylic acid {(S)- 1-[(3S,4R,6R)-6-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide;

benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(3S,4S,7R)-7-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(3S,4S,7S)-7-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(3R,4R,7S)-7-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(3R,4R,7R)-7-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

((R)-2-iodo-1-methyl-ethyl)-carbamic acid benzyl ester

((R)-1-methyl-pent-4-enyl)-carbamic acid benzyl ester;

allyl-((R)-1-methyl-pent-4-enyl)-carbamic acid benzyl ester;

2-methyl-2,3,4,7-tetrahydro-azepine-1-carboxylic acid benzyl ester;

(1S,4R,7R)-4-methyl-8-oxa-3-aza-bicyclo[5.1.0]octane-3-carboxylic acid benzyl ester;

(2R,5S,6S)-5-azido-6-hydroxy-2-methyl-azepane-1-carboxylic acid benzyl ester;

(2R,5S,6S)-5-amino-6-hydroxy-2-methyl-azepane-1-carboxylic acid benzyl ester;

(2R,5S,6S)-5-((S)-2- tert -butoxycarbonylamino-4-methyl-pentanoylamino)-6-hydroxy-2-methyl-azepane-1 -carboxylic acid benzyl ester;

[(S)-1-((3S,4S,7R)-3-hydroxy-7-methyl-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid tert -butyl ester;

[(S)-1-((3S,4S,7R)-2-pyridinesulfonyl-3-hydroxy-7-methyl-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid tert -butyl ester;

(S)-2-amino-4-methyl-pentanoic acid ((3S,4S,7R)-1-(2-pyridine)-sulfonyl-3-hydroxy-7-methyl-azepan-4-yl)-amide;

furo[3,2-b]pyridine-2-carboxylic acid {(S)-1-[(3S,4S,7R)-3-hydroxy-7-methyl-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide;

furo[3,2-b]pyridine-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

3-methyl-furo[3,2-b]pyridine-2-carboxylic acid {(S)-1-[(3S,4S,7R)-3-hydroxy-7-methyl-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide;

3-methyl-furo[3,2-b]pyridine-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

quinoline-6-carboxylic acid {(S)-3-methyl-1-[(3S,4S,7R)-7-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

quinoline-3-carboxylic acid {(S)-3-methyl-1-[(3S,4S,7R)-7-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

5-methoxy-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(3S,4S,7R)-7-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

3-methyl-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(3S,4S,7R)-7-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

thieno[3,2-b]thiophene-2-carboxylic acid {(S)-3-methyl-1-[(3S,4S,7R)-7-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

quinoxaline-2-carboxylic acid {(S)-3-methyl-1-[(3S,4S,7R)-7-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

thieno[3,2-b] thiophene-2-carboxylic acid {(S)-3-methyl-1-[(3S,4S,7R)-7-methyl-3-hydroxy-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

3-methyl-benzofuran-2-carboxylicacid {(S)-3-methyl-1-[(3S,4S,7R)-7-methyl-3-hydroxy-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(3S,4S,7R)-7-methyl-3-hydroxy-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

quinoline-2-carboxylic acid {(S)-3-methyl-1-[(3S,4S,7R)-7-methyl-3-hydroxy-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

5,6-difluoro-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(3S,4S,7R)-7-methyl-3-hydroxy-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

5-fluoro-3-methyl-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(3S,4S,7R)-7-methyl-3-hydroxy-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

5-fluoro-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(3S,4S,7R)-7-methyl-3-hydroxy-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

3-methyl-furo[3,2-b]]pyridine-2-carboxylic acid {(S)-3-methyl-1-[(3S,4S,7R)-7-methyl-3-hydroxy-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

cyclohexanecarboxylic acid {(S)-3-methyl-1-[(3S,4S,7R)-7-methyl-3-hydroxy-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

(S)-2-(2-cyclohexyl-ethanoylamino)-4-methyl-pentanoic acid [(3S,4S,7R)-7-methyl-3-hydroxy-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-yl]-amide;

(S)-2-(3-cyclohexyl-propanoylamino)-4-methyl-pentanoic acid [(3S,4S,7R)-7-methyl-3-hydroxy-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-yl]-amide;

(S)-2-(4-cyclohexyl-butanoylamino)-4-methyl-pentanoic acid [(3S,4S,7R)-7-methyl-3-hydroxy-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-yl]-amide;

(S)-2-(5-cyclohexyl-pentanoylamino)-4-methyl-pentanoic acid [(3S,4S,7R)-7-methyl-3-hydroxy-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-yl]-amide;

benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(3S,4S,7R)-7-methyl-3-hydroxy-1-(5-trifluoromethyl-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

5-fluoro-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(3S,4S,7R)-7-methyl-3-hydroxy-1-(5-trifluoromethyl-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

thieno[3,2-b] thiophene-2-carboxylic acid {(S)-3-methyl-1-[(3S,4S,7R)-7-methyl-3-hydroxy-1-(5-trifluoromethyl-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

benzofuran-2-carboxylic acid {1-[(3S,4S,7R)-7-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-cyclohexyl}-amide;

thiophene-3-carboxylic acid {(S)-3,3-dimethyl-1-[(3S,4S,7R)-7-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

furan-2-carboxylic acid {(S)-3,3-dimethyl-1-[(3S,4S,7R)-7-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

thieno[3,2-b] thiophene-2-carboxylic acid {(S)-3,3-dimethyl-1-[(3S,4S,7R)-7-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

benzofuran-2-carboxylic acid {(S)-2-cyclohexyl-1-[(3S,4S,7R)-7-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide;

furan-2-carboxylic acid {(S)-2-cyclohexyl-1-[(3S,4S,7R)-7-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide;

thiophene-3-carboxylic acid {(S)-2-cyclohexyl-1-[(3S,4S,7R)-7-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide;

3-methyl-furo[3,2-b]- pyridine-2-carboxylic acid {(S)-2-cyclohexyl-1-[(3S,4S,7R)-7-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide;

(2R,4aR,8aR)-octahydro-benzo[1,4]dioxine-2-carboxylic acid [(S)-1-((3S,4S,7R)-1-methanesulfonyl-7-methy l-3-hydroxy-azepan-4-ylcarbamoyl)-3-methyl-butyl]-amide;

furan-2-carboxylic acid [(S)-2-cyclohexyl-1-((3S,4S,7R)-7-methyl-3-hydroxy-1-propyl-azepan-4-ylcarbamoyl)-ethyl]-amide;

thiophene-3-carboxylic acid [(S)-2-cyclohexyl-1-((3S,4S,7R)-7-methyl-3-hydroxy-1-propyl-azepan-4-ylcarbamoyl)-ethyl]-amide;

benzofuran-2-carboxylic acid [(S)-2-cyclohexyl-1-((3S,4S,7R)-7-methyl-3-hydroxy-1-propyl-azepan-4-ylcarbamoyl)-ethyl]-amide;

1-(3-cyclohexyl-propanoylamino)-cyclohexanecarboxylic acid ((3S,4S,7R)-1-cyclohexylmethyl-7-methyl-3-hydroxy-azepan-4-yl)-amide;

benzofuran-2-carboxylic acid [1-((3S,4S,7R)-1-cyclohexylmethyl-7-methyl-3-hydroxy-azepan-4-ylcarbamoyl)-cyclohexyl]-amide;

benzofuran-2-carboxylic acid [(S)-3-methyl-1-((3S,4S,7R)-7-methyl-3-hydroxy-1-propyl-azepan-4-ylcarbamoyl)- butyl]-amide;

(2R,5S)-5-((S)-2-tert-butoxycarbonylamino-4-methyl-pentanoylamino)-2-methyl-6-hydroxy-azepane-1-carboxylic acid benzyl ester;

benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(3S,4S,7R)-7-methyl-1-(1-morpholin-4-yl-methanoyl)-3-hydroxy- azepan-4-ylcarbamoyl]-butyl}-amide;

(S)-2-(3-cyclohexyl-propanoylamino)-4-methyl-pentanoic acid [(3S,4S,7R)-7-methyl-1-(1-morpholin-4-yl-me thanoyl)-3-hydroxy-azepan-4-yl]-amide;

(2R,5S,6S)-5-{(S)-2-[(1-benzofuran-2-yl-methanoyl)-amino]-4-methyl-pentanoylamino}-2-methyl-6-hydroxy-azepane-1-carboxylic acid (tetrahydro-pyran-4-yl)-amide;

(S)-2-{[1-((2R,5S,6S)-5-{(S)-2-[(1-benzofuran-2-yl-methanoyl)-amino]-4-methyl-pentanoylamino}-2-methyl-6-hydroxy-azepan-1-yl)-methanoyl]-amino}-4-methyl-pentanoic acid methyl ester;

(S)-2-{[1-(4-{(S)-2-[(1-benzofuran-2-yl-methanoyl)-amino]-4-methyl-pentanoylamino}-3-hydroxy-azepan-1-yl)-methanoyl]-amino}-4-methyl-pentanoica cid methyl ester;

(S)-4-methyl-2-{[1-((2R,5S,6S)-2-methyl-5-{(S)-4-methyl-2-[(1-quinolin-8-yl-methanoyl)-amino]-pentanoylamino}-6-hydroxy-azepan-1-yl)-methanoyl]-amino}-pentanoic acid methyl ester;

(R)-2-{[1-(4-{(S)-2-[(1-benzofuran-2-yl-methanoyl)-amino]-4-methyl-pentanoylamino}-3-hydroxy-azepan-1-yl)-methanoyl]-amino}-4-methyl-pentanoic acid methyl ester;

2-biphenyl-3-yl-4-methyl-pentanoic acid [(3R, 4R,7R)-7-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-yl]-amide;

3-methyl-furo[3,2-b]-pyridine-2-carboxylic acid {1-[(4S,7R)-7-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-cyclohexyl}-amide; and

1-(3-cyclohexyl-propanoylamino)-cyclohexanecarboxylic acid [(4S,7R)-7-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-yl]-amide.

Process for Synthesis of Inventive Compounds

Referring to Schemes 1-8 herein above, the present invention provides a process for the synthesis of compounds of Formula (I) comprising the step of oxidizing the appropriate compound of Formula (II) with an oxidant to provide the compound of Formula (I) as a mixture of diastereomers. Preferably the oxidant is sulfur trioxide-pyridine complex.

Referring to Scheme 4, the present invention also provides a process for the synthesis of deuterated compounds of Formula (I). Specifically, when a deuterated isomer is desired, an additional step, following the oxidation step, of deuterating the protonated isomer with a deuterating agent to provide the deuterated compound of Formula (I) as a mixture of diastereomers is added to the synthesis. Preferably, the deuterating agent is CD_3OD:D_2O (10:1) in triethylamine.

The process further comprises the step of separating the diasteromers of Formula (I) by separating means, preferably by high presssure liquid chromatography (HPLC).

Utility of the Present Invention

The compounds of Formula I are useful as protease inhibitors, particularly as inhibitors of cysteine and serine proteases, more particularly as inhibitors of cysteine proteases, even more particularly as inhibitors of cysteine proteases of the papain superfamily, yet more particularly as inhibitors of cysteine proteases of the cathepsin family, most particularly as inhibitors of cathepsin K. The present invention also provides useful compositions and formulations of said compounds, including pharmaceutical compositions and formulations of said compounds.

The present compounds are useful for treating diseases in which cysteine proteases are implicated, including infections by pneumocystis carinii, trypsanoma cruzi, trypsanoma brucei, and Crithidia fusiculata; as well as in schistosomiasis, malaria, tumor metastasis, metachromatic leukodystrophy, muscular dystrophy, amytrophy; and especially diseases in which cathepsin K is implicated, most particularly diseases of excessive bone or cartilage loss, including osteoporosis, gingival disease including gingivitis and periodontitis, arthritis, more specifically, osteoarthritis and rheumatoid arthritis, Paget's disease; hypercalcemia of malignancy, and metabolic bone disease.

Parasites known to utilize cysteine proteases in their life cycle (and the diseases caused by these parasites) include *Trypanosoma cruzi*, *Trypanosoma Brucei* [trypanosomiasis (African sleeping sickness, Chagas disease)], *Leishmania mexicana*, *Leishmania pifanoi*, *Leishmania major* (leishmaniasis), *Schistosoma mansoni* (schistosomiasis), *Onchocerca volvulus* [onchocerciasis (river blindness)] *Brugia pahangi*,

Entamoeba histolytica, *Giardia lambia*, the helminths, *Haemonchus contortus* and *Fasciola hepatica*, as well as helminths of the genera *Spirometra*, *Trichinella*, *Necator* and *Ascaris*, and protozoa of the genera *Cryptosporidium*, *Eimeria*, *Toxoplasma* and *Naegleria*. The compounds of the present invention are suitable for treating diseases caused by these parasites which may be therapeutically modified by altering the activity of cysteine proteases. In particular, the present compounds are useful for treating malaria by inhibiting falcipain.

Metastatic neoplastic cells also typically express high levels of proteolytic enzymes that degrade the surrounding matrix, and certain tumors and metastatic neoplasias may be effectively treated with the compounds of this invention.

The present invention also provides methods of treatment of diseases caused by pathological levels of proteases, particularly cysteine and serine proteases, more particularly cysteine proteases, even more particularly cysteine proteases of the papain superfamily, yet more particularly cysteine proteases of the cathepsin family, which methods comprise administering to an animal, particularly a mammal, most particularly a human in need thereof a compound of the present invention. The present invention especially provides methods of treatment of diseases caused by pathological levels of cathepsin K, which methods comprise administering to an animal, particularly a mammal, most particularly a human in need thereof an inhibitor of cathepsin K, including a compound of the present invention. The present invention particularly provides methods for treating diseases in which cysteine proteases are implicated, including infections by pneumocystis carinii, trypsanoma cruzi, trypsanoma brucei, and Crithidia fusiculata; as well as in schistosomiasis, malaria, tumor metastasis, metachromatic leukodystrophy, muscular dystrophy, amytrophy, and especially diseases in which cathepsin K is implicated, most particularly diseases of excessive bone or cartilage loss, including osteoporosis, gingival disease including gingivitis and periodontitis, arthritis, more specifically, osteoarthritis and rheumatoid arthritis, Paget's disease, hypercalcemia of malignancy, and metabolic bone disease.

The present method provides treatment of diseases (in parentheses) caused by infection by *Trypanosoma cruzi*, *Trypanosoma Brucei* [trypanosomiasis (African sleeping sickness, Chagas disease)], *Leishmania mexicana*, *Leishmania pifanoi*, *Leishmania major* (leishmaniasis), *Schistosoma mansoni* (schistosomiasis), *Onchocerca volvulus* [onchocerciasis (river blindness)] *Brugia pahangi*, *Entamoeba histolytica*, *Giardia lambia*, the helminths, *Haemonchus contortus* and *Fasciola hepatica*, as well as helminths of the

genera *Spirometra*, *Trichinella*, *Necator* and *Ascaris*, and protozoa of the genera *Cryptosporidium*, *Eimeria*, *Toxoplasma* and *Naegleria* by inhibiting cysteine proteases of the papain superfamily by administering to a patient in need thereof, particularly an animal, more particularly a mammal, most particularly a human being, one or more of the above-listed compounds.

Most particularly, the present invention provides a method of treating malaria, caused by infection with *Plasmodium falciparum,* by the inhibition of falcipain by administering to a patient in need thereof, particularly an animal, more particularly a mammal, most particularly a human being, one or more of the above-listed compounds.

The present method may be practiced by administering the above-listed compounds alone or in combination, with each other, or with other therapeutically effective compounds.

This invention further provides a method for treating osteoporosis or inhibiting bone loss which comprises internal administration to a patient of an effective amount of a compound of Formula I, alone or in combination with other inhibitors of bone resorption, such as bisphosphonates (i.e., allendronate), hormone replacement therapy, anti-estrogens, or calcitonin. In addition, treatment with a compound of this invention and an anabolic agent, such as bone morphogenic protein, iproflavone, may be used to prevent bone loss or to increase bone mass.

For acute therapy, parenteral administration of a compound of Formula I is preferred. An intravenous infusion of the compound in 5% dextrose in water or normal saline, or a similar formulation with suitable excipients, is most effective, although an intramuscular bolus injection is also useful. Typically, the parenteral dose will be about 0.01 to about 100 mg/kg; preferably between 0.1 and 20 mg/kg, in a manner to maintain the concentration of drug in the plasma at a concentration effective to inhibit cathepsin K. The compounds are administered one to four times daily at a level to achieve a total daily dose of about 0.4 to about 400 mg/kg/day. The precise amount of an inventive compound which is therapeutically effective, and the route by which such compound is best administered, is readily determined by one of ordinary skill in the art by comparing the blood level of the agent to the concentration required to have a therapeutic effect.

The compounds of this invention may also be administered orally to the patient, in a manner such that the concentration of drug is sufficient to inhibit bone resorption or to achieve any other therapeutic indication as disclosed herein. Typically, a pharmaceutical

composition containing the compound is administered at an oral dose of between about 0.1 to about 50 mg/kg in a manner consistent with the condition of the patient. Preferably the oral dose would be about 0.5 to about 20 mg/kg.

No unacceptable toxicological effects are expected when compounds of the present invention are administered in accordance with the present invention.

Biological Assays

The compounds of this invention may be tested in one of several biological assays to determine the concentration of compound which is required to have a given pharmacological effect.

Determination of cathepsin K proteolytic catalytic activity

All assays for cathepsin K were carried out with human recombinant enzyme. Standard assay conditions for the determination of kinetic constants used a fluorogenic peptide substrate, typically Cbz-Phe-Arg-AMC, and were determined in 100 mM Na acetate at pH 5.5 containing 20 mM cysteine and 5 mM EDTA. Stock substrate solutions were prepared at concentrations of 10 or 20 mM in DMSO with 20 uM final substrate concentration in the assays. All assays contained 10% DMSO. Independent experiments found that this level of DMSO had no effect on enzyme activity or kinetic constants. All assays were conducted at ambient temperature. Product fluorescence (excitation at 360 nM; emission at 460 nM) was monitored with a Perceptive Biosystems Cytofluor II fluorescent plate reader. Product progress curves were generated over 20 to 30 minutes following formation of AMC product.

Inhibition studies

Potential inhibitors were evaluated using the progress curve method. Assays were carried out in the presence of variable concentrations of test compound. Reactions were initiated by addition of enzyme to buffered solutions of inhibitor and substrate. Data analysis was conducted according to one of two procedures depending on the appearance of the progress curves in the presence of inhibitors. For those compounds whose progress curves were linear, apparent inhibition constants ($K_{i,app}$) were calculated according to equation 1 (Brandt *et al.*, *Biochemitsry,* **1989**, *28*, 140):

$$v = V_m A / [K_a(1 + I/K_{i,\,app}) + A] \qquad (1)$$

where v is the velocity of the reaction with maximal velocity V_m, A is the concentration of substrate with Michaelis constant of K_a, and I is the concentration of inhibitor.

For those compounds whose progress curves showed downward curvature characteristic of time-dependent inhibition, the data from individual sets was analyzed to give k_{obs} according to equation 2:

$$[AMC] = v_{ss}\, t + (v_0 - v_{ss})\,[1 - exp\,(-k_{obs}t)] / k_{obs} \qquad (2)$$

where [AMC] is the concentration of product formed over time t, v_0 is the initial reaction velocity and v_{ss} is the final steady state rate. Values for k_{obs} were then analyzed as a linear function of inhibitor concentration to generate an apparent second order rate constant (k_{obs} / inhibitor concentration or k_{obs} / [I]) describing the time-dependent inhibition. A complete discussion of this kinetic treatment has been fully described (Morrison *et al.*, *Adv. Enzymol. Relat. Areas Mol. Biol.*, **1988**, *61*, 201).

Human Osteoclast Resorption Assay

Aliquots of osteoclastoma-derived cell suspensions were removed from liquid nitrogen storage, warmed rapidly at 37°C and washed x1 in RPMI-1640 medium by centrifugation (1000 rpm, 5 min at 4°C). The medium was aspirated and replaced with murine anti-HLA-DR antibody, diluted 1:3 in RPMI-1640 medium, and incubated for 30 min on ice The cell suspension was mixed frequently.

The cells were washed x2 with cold RPMI-1640 by centrifugation (1000 rpm, 5 min at 4°C) and then transferred to a sterile 15 mL centrifuge tube. The number of mononuclear cells were enumerated in an improved Neubauer counting chamber.

Sufficient magnetic beads (5 / mononuclear cell), coated with goat anti-mouse IgG, were removed from their stock bottle and placed into 5 mL of fresh medium (this washes away the toxic azide preservative). The medium was removed by immobilizing the beads on a magnet and is replaced with fresh medium.

The beads were mixed with the cells and the suspension was incubated for 30 min on ice. The suspension was mixed frequently. The bead-coated cells were immobilized on a magnet and the remaining cells (osteoclast-rich fraction) were decanted into a sterile 50 mL centrifuge tube. Fresh medium was added to the bead-coated cells to dislodge any

trapped osteoclasts. This wash process was repeated x10. The bead-coated cells were discarded.

The osteoclasts were enumerated in a counting chamber, using a large-bore disposable plastic pasteur pipette to charge the chamber with the sample. The cells were pelleted by centrifugation and the density of osteoclasts adjusted to $1.5x10^4$/mL in EMEM medium, supplemented with 10% fetal calf serum and 1.7g/litre of sodium bicarbonate. 3 mL aliquots of the cell suspension (per treatment) were decanted into 15 mL centrifuge tubes. These cells were pelleted by centrifugation. To each tube 3 mL of the appropriate treatment was added (diluted to 50 uM in the EMEM medium). Also included were appropriate vehicle controls, a positive control (87MEM1 diluted to 100 ug/mL) and an isotype control (IgG2a diluted to 100 ug/mL). The tubes were incubate at 37°C for 30 min.

0.5 mL aliquots of the cells were seeded onto sterile dentine slices in a 48-well plate and incubated at 37°C for 2 h. Each treatment was screened in quadruplicate. The slices were washed in six changes of warm PBS (10 mL / well in a 6-well plate) and then placed into fresh treatment or control and incubated at 37°C for 48 h. The slices were then washed in phosphate buffered saline and fixed in 2% glutaraldehyde (in 0.2M sodium cacodylate) for 5 min., following which they were washed in water and incubated in buffer for 5 min at 37°C. The slices were then washed in cold water and incubated in cold acetate buffer / fast red garnet for 5 min at 4°C. Excess buffer was aspirated, and the slices were air dried following a wash in water.

The TRAP positive osteoclasts were enumerated by bright-field microscopy and were then removed from the surface of the dentine by sonication. Pit volumes were determined using the Nikon/Lasertec ILM21W confocal microscope.

General

Nuclear magnetic resonance spectra were recorded at either 250 or 400 MHz using, respectively, a Bruker AM 250 or Bruker AC 400 spectrometer. $CDCl_3$ is deuteriochloroform, DMSO-d_6 is hexadeuteriodimethylsulfoxide, and CD_3OD is tetradeuteriomethanol. Chemical shifts are reported in parts per million (d) downfield from the internal standard tetramethylsilane. Abbreviations for NMR data are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, app = apparent, br = broad. J indicates the NMR coupling constant measured in Hertz. Continuous wave infrared (IR) spectra were recorded on a Perkin-Elmer 683 infrared spectrometer, and Fourier transform infrared (FTIR) spectra were

recorded on a Nicolet Impact 400 D infrared spectrometer. IR and FTIR spectra were recorded in transmission mode, and band positions are reported in inverse wavenumbers (cm^{-1}). Mass spectra were taken on either VG 70 FE, PE Syx API III, or VG ZAB HF instruments, using fast atom bombardment (FAB) or electrospray (ES) ionization techniques. Elemental analyses were obtained using a Perkin-Elmer 240C elemental analyzer. Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. All temperatures are reported in degrees Celsius.

Analtech Silica Gel GF and E. Merck Silica Gel 60 F-254 thin layer plates were used for thin layer chromatography. Both flash and gravity chromatography were carried out on E. Merck Kieselgel 60 (230-400 mesh) silica gel.

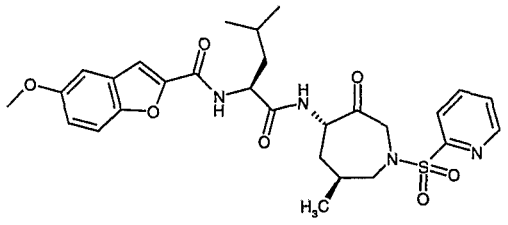
Where indicated, certain of the materials were purchased from the Aldrich Chemical Co., Milwaukee, Wisconsin, Chemical Dynamics Corp., South Plainfield, New Jersey, and Advanced Chemtech, Louisville, Kentucky.

Examples

In the following synthetic examples, temperature is in degrees Centigrade (°C). Unless otherwise indicated, all of the starting materials were obtained from commercial sources. Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. These Examples are given to illustrate the invention, not to limit its scope. Reference is made to the claims for what is reserved to the inventors hereunder.

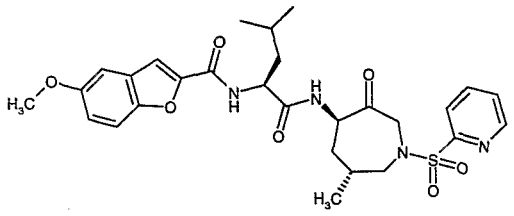
Example 1

5-Methoxy-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(4S,6S)-6-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide



; and

5-Methoxy-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(4R,6R)-6-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide



a. Allyl-(2-methyl-pent-4-enyl)-amine

To a solution of 2-methyl-pent-4-enoic acid ethyl ester (7.1 g, 50 mmol) was added dropwise a solution of DIBAL (1.0 M in hexanes, 75 ml) at –78 C over 1.0 h. After the addition, the reaction mixture was stirred at –78C for another hour. The reaction was quenched with saturated NH4Cl (10ml) and 4% HCl, then was extracted with EtOAc (3 x 100 ml). The combined organic extracts were dried with $MgSO_4$, filtered, concentrated by rotary evaporation and the crude reaction product was used in the next reaction without further purification. 2-Methyl-4-pentenal (3.3 g, 33.7 mmol) was dissolved in CH_2Cl_2 (100 ml). To this solution allylamine (2.9g, 50.5 mmol) was added. Molecular sieves (5 g) were used to absorb water generated during the reaction. The mixture was stirred at room temperature over night. The reaction mixture was concentrated by rotary evaporation and the crude product was used in the next reaction without further purification. Allyl-(2-methyl-pent-4-enylidene)-amine (3.2 g, 23.4 mmol) was diluted in 50 ml MeOH. To the solution $NaBH_4$ (1.0 g, 26.3 mmol) was added at 0°C. After addition the mixture was stirred at RT for 5h. The reaction mixture was concentrated and the residue was partitioned between EtOAc/ 20% aq. NaOH. The organic layer was dried over Na_2SO_4, fitered and concentrated by rotary evaporation to give allyl-(2-methyl-pent-4-enyl)-amine (1.5 g 48% yield): 1H-NMR (400Hz, CDCl3): d= 5.93-5.68 (m, 2H), 5.18-4.92(m, 4H), 3.21(d, 2H), 2.60-2.40(m, 2H), 1.97-1.65(m, 2H), 0.92(d, 3H)

b. Pyridine-2-sulfonic acid allyl-(2-methyl-pent-4-enyl)-amide

Allyl-(2-methyl-pent-4-enyl)-amine (1.0 g, 7.2 mmol) and NMM (1.7 g, 17.2 mmol) were mixed in 30 ml CH_2Cl_2. 2-pyridinesulphonyl chloride (1.53 g, 8.6 mmol) was added slowly to the solution while it was cooled in an ice-water bath. After addition, the reaction mixture was stirred at RT overnight. The reaction mixture was washed with 10% $NaHCO_3$ and the brine, then was purified by column chromatography to give the title compound as a colorless oil (1.2g ,60% yield): MS (M+H+) 281.2; 1H-NMR (400Hz, CDCl3): d= 8.70(d,

1H), 8.0-7.75(m, 2H), 7.5 (m, 1H) 5.80-5.60(m, 2H), 5.15-4.92(m, 4H), 4.00-3.90(m, 2H), 3.20-3.06(m, 2H), 2.15(m, 1H), 1.85(m, 2H), 0.89(d, 3H)

c. 3-methyl-1-(pyridine-2-sulfonyl)-2,3,4,7-tetrahydro-1H-azepine

Pyridine-2-sulfonic acid allyl-(2-methyl-pent-4-enyl)-amide (1.2 g, 4.3 mmol) was diluted in CH_2Cl_2 (100ml). After carefully degass by Ar, Grubbs catalyst (0.35 g, 0.43 mmol) was added under Ar protection. The mixture was then refluxed for 2h before the reaction mixture was concentrated by rotary evaporation. The product was purified by column chromatography (5%-20% EtOAc/hexanes) to give the title compound (0.9 g, 83 % yield): MS (M+H+):253.2; 1H-NMR (400Hz, CDCl3): d= 8.70(d, 1H), 8.0-7.75(m, 2H), 7.5 (m, 1H) 5.79-5.60(m, 2H), 4.00(d, 2H), 3.65(dd, 1H), 3.22(dd, 1H), 2.30-2.05(m, 3H), 0.96(d, 3H)

d. 5-methyl-3-(pyridine-2-sulfonyl)-8-oxa-3-aza-bicyclo[5.1.0]octane

To the solution of 3-methyl-1-(pyridine-2-sulfonyl)-2,3,4,7-tetrahydro-1H-azepine (1.3g, 5.16 mmol) in CH_2Cl_2 (50 ml) was added $NaHCO_3$ (1.3 g, 15.5 mmol) and then mCPBA (2.67 g, 15.5 mmol) in portions. Stirred at RT for 4h before worked up by washing with 15% NaOH, saturated K_2CO_3 and brine. Dried over Na_2SO_4. The reaction mixture was concentrated by rotary evaporation and two insomers were seperated on column chromatography (30%-40% EtoAc/ Hexane). The first elution (trans- isomer, 230mg) was used in next steps, the second elution (cis- insomer 200mg) was saved.: MS (M+H+): 269.0; 1H-NMR (400Hz, CDCl3): d= 8.70(d, 1H), 8.0-7.75(m, 2H), 7.50 (m, 1H) 4.39(m, 1H), 3.92(m, 1H), 3.34-2.00(m, 6H), 1.40(m, 1H), 0.88(d, 3H)

e. 4-Azido-5-methyl-1-(pyridine-2-sulfonyl)-azepan-3-ol

5-methyl-3-(pyridine-2-sulfonyl)-8-oxa-3-aza-bicyclo[5.1.0]octane (230mg, 0.86mmol) was dissolved in the mixture of 8 ml MeOH and 2 ml H_2O. NaN_3 (170 mg, 2.6 mmol) and NH_4Cl (140 mg, 2.6 mmol) were added to the solution. The resulting mixture was refluxed overnight. After the removal of MeOH, the residue was diluted in EtOAc and washed with 10% $NaHCO_3$ and brine. Purified on column chromatography gave the title compound (170 mg, yield 64 %). MS (M+H+) 312.2; 1H-NMR (400Hz, CDCl3): d= 8.69(d, 1H), 8.04-7.94(m, 2H), 7.54 (m, 1H) 4.00-2.95 (m, 7H), 2.20(m, 1H), 1.90-1.74(m, 2H), 0.98(d, 3H)

f. 4-Amino-6-methyl-1-(pyridine-2-sulfonyl)-azepan-3-ol

4-Azido-6-methyl-1-(pyridine-2-sulfonyl)-azepan-3-ol (0.33 g, 1.06 mmol) was dissolved in THF(50ml) and H_2O(0.2 ml). PPh_3 (0.42 g, 1.59 mmol) was added to this solution. The reaction mixture was stirred at 45°C over night. TLC showed no starting material left. THF was evaperated, azeotroped by toluene (2 x 100 ml). The resulting thick oil was dissolved in MeOH, treated with HCl in ether to adjust pH to acidic. More ether was added and the solution turned cloudy to give the title compound as a white precipitate (0.21 g, 71 % yield) MS (M+H+) 286.0; 1H-NMR (400Hz, CD3OD): d (ppm): 8.72(d, 1H), 8.14-7.99(m, 2H), 7.68(m, 1H), 3.85-3.69(m, 2H), 3.38-3.22(m, 3H), 3.10-3.04(m, 2H), 2.04(m, 1H), 1.82-1.66(m, 2H), 1.02(d, 3H)

g. {(S)-1-[3-Hydroxy-6-methyl-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-3-methyl-butyl}-carbamic acid tert-butyl ester

4-Amino-6-methyl-1-(pyridine-2-sulfonyl)-azepan-3-ol HCl salt (0.21 g, 0.59 mmol) was dissolved in 5 ml DMF. To this solution, was added Boc-Leu-OH (0.22 g, 0.88 mmol)and HBTU (0.34 g, 0.90 mmol) and then NMM (0.24 g, 2.4 mmol). The mixture was stirred at RT overnight. DMF was removed under high vacuum. The residue was diluted in EtOAc and washed with H_2O, 10% $NaHCO_3$ and brine. Purification by column chromatography gave the title compound (0.2 g, 68 % yield). MS (M+H+): 499.1; 1H-NMR (400Hz, CDCl3): 8.75(d, 1H), 8.0-7.75(m, 2H), 7.5 5(m, 1H) 5.10(m, 1H), 4.15-2.90(m, 10H), 2.10-1.48(m, 14H), 1.00(m, 9H)

h. 5-Methoxy-benzofuran-2-carboxylic acid {(S)-1-[3-hydroxy-6-methyl-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide

To {(S)-1-[3-hydroxy-6-methyl-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-3-methyl-butyl}-carbamic acid tert-butyl ester (0.13 g, 0.28 mmol) was added HCl/dioxane (4M, 2.8ml, 11.2 mmol). The mixture was stirred at RT for 2h before solvents and excess amount of HCl was removed on rotavapor. The result white solid was dissolved in 5 ml DMF. To the solution was added 5-methoxy-benzofuran-2-carboxylic acid (63.4mg, 0.33 mmol), HBTU (125 g, 0.33 mmol) and NMM (0.14 g, 1.34 mmol). The mixture was stirred at RT overnight. DMF was then removed and the residue was re-dissolved in EtOAc (50ml), washed with 10% $NaHCO_3$ (50 ml x2) and brine (50 ml). The combined organics were concentrated by rotary evaporation. Purification by column chromatograghy gave the title compound (110mg in 69 % yield, 2 steps): MS (M+H+):573.4; 1H-NMR (400Hz,

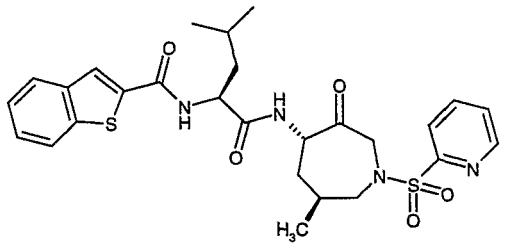
CDCl3): d= 8.74-8.66(dd, 1H), 7.96-6.97(m, 9H), 4.72(m, 1H), 4.18-3.21(m, 7H), 2.81(m, 1H), 2.04-1.74(m, 6H), 1.25(m, 2H), 0.99-0.87(m, 9H)

i. 5-Methoxy-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(4S,6S)-6-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide and 5-methoxy-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(4R,6R)-6-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide

To a solution of 5-methoxy-benzofuran-2-carboxylic acid {(S)-1-[3-hydroxy-6-methyl-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide (110mg, 0.19mmol) in 5ml CH_2Cl_2, was added Dess-Martin reagent (122 mg, 0.29 mmol) at RT. The solution was stirred for 2 h when 50 ml CH_2Cl_2 was added and then washed with 10% $NaHCO_3$ and brine. Purification by column chromatograghy (50% ethyl acetate in hexane) gave the title compound (90 mg, 82% yield). 1H-NMR (400Hz, CDCl3): d (ppm): 8.69(d, 1H), 7.94(m, 2H), 7.39-7.24(m, 3H), 7.02(m, 4H), 5.26(m, 1H), 4.69(m, 2H), 3.84(m, 4H), 3.00(m, 1H), 2.05(m, 1H), 1.73(m, 2H), 1.61(m, 4H), 1.18(d, 3H), 0.97(d,6H);). The diastereomers were separated by HPLC. Diastereomer 1: MS (M+H+): 571.2; Diastereomer 2: MS (M+H+): 571.2

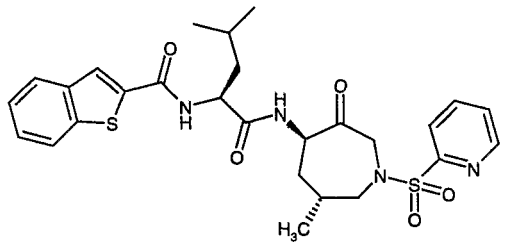
Example 2

Benzo[b]thiophene-2-carboxylic acid {(S)- 1-[(4S,6S)-6-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide



; and

benzo[b]thiophene-2-carboxylic acid {(S)- 1-[(4R,6R)-6-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide



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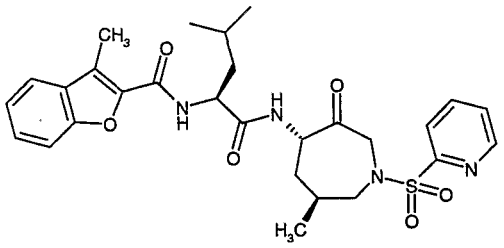
Following the procedure of Example 1 (a-i), except substituting " benzo[b]thiophene-2-carboxylic acid" for "5-methoxy-benzofuran-2-carboxylic acid " gave the title compound: MS (M+H+):; 1H-NMR (400Hz, CDCl3): d (ppm): 8.69(d, 1H), 7.97-7.78(m, 5H), 7.41-7.39(m, 3H), 6.95(d, 1H), 6.65(d, 1H), 5.25(m,1H), 4.71-4.60(m, 2H), 3.86(d, 1H), 3.80(m,1H), 2.98(d, 1H), 2.05(m, 2H), 1.75-1.55(m, 4H), 1.18(d, 3H), 0.97(d, 6H); The diastereomers were separated by HPLC. Diastereomer 1: MS (M+H+): 557.2; Diastereomer 2: MS (M+H+): 557.2

Example 3

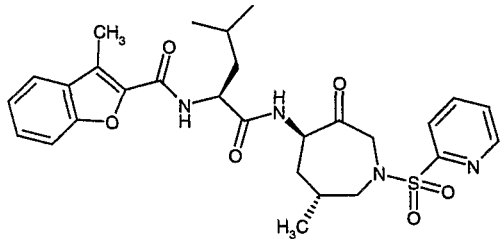
3-Methyl-benzofuran-2-carboxylic acid {(S)- 1-[(4S,6S)-6-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide



;

;and

3-methyl-benzofuran-2-carboxylic acid {(S)- 1-[(4R,6R)-6-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide

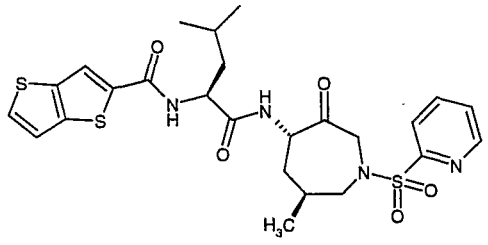


;

Following the procedure of Example 1 (a-i), except substituting " 3-methyl-benzofuran-2-carboxylic acid" for "5-methoxy-benzofuran-2-carboxylic acid " gave the title compound: MS (M+H+) 555.2; 1H-NMR (400Hz, CDCl3): d (ppm): 8.68(d, 1H), 7.93(m, 2H), 7.59-7.27(m, 5H), 7.03-6.96(dd, 2H), 5.26(m, 1H), 4.70-4.61(m, 1H), 3.82(d, 1H), 3.76(m, 1H), 2.99(d, 1H), 2.60(s, 3H), 2.05(m,2H), 1.76-1.58(m, 5H), 1.19(d, 3H), 0.97(d, 6H); The diastereomers were separated by HPLC. Diastereomer 1: MS (M+H+): 555.2; Diastereomer 2: MS (M+H+): 555.4

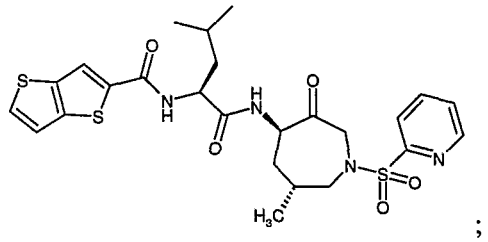
Example 4

Thieno[3,2-b]thiophene-2-carboxylic acid {(S)- 1-[(4S,6S)-6-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide



and;

thieno[3,2-b]thiophene-2-carboxylic acid {(S)- 1-[(4R,6R)-6-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide



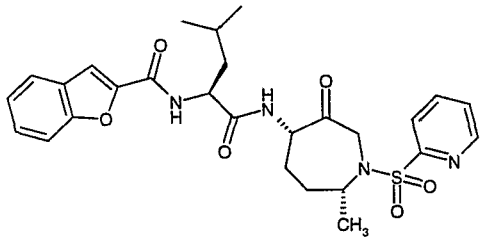
;

Following the procedure of Example 1 (a-i), except substituting "thieno[3,2-b]thiophene-2-carboxylic acid" for "5-methoxy-benzofuran-2-carboxylic acid " gave the title compound: MS (M+H+) 563.2; 1H-NMR (400Hz, CDCl3): d (ppm): 8.69(d, 1H), 7.97-7.78(m, 5H), 7.41-7.38(m, 3H), 6.95(d, 1H), 6.65(d,1H), 5.26(m, 1H), 4.69-4.60(m, 2H), 3.85(d, 1H), 3.80(m, 1H), 2.99(d, 1H), 2.04(m, 2H), 1.75-1.55(m, 4H), 1.18(d, 3H), 0.97(d, 6H); The diastereomers were separated by HPLC. Diastereomer 1: MS (M+H+): 563.2; Diastereomer 2:

MS (M+H+): 563.2

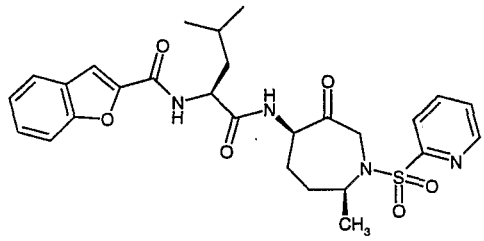
Example 5

Benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide



and;

benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(4R,7S)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide



a. Allyl-(1-methyl-pent-4-enylidene)-amine Allyl-(1-methyl-pent-4-enyl)-amine

Hex-5-en-2-one (9.8 g, 11.6 ml, 100 mmol) was added to a stirred solution of allylamine (8.55 mmol, 11.25 ml, 150 mmol), 4 Angstrom molecular sieves (52g), and p-toluene sulfonic acid (10 mg) in CH_2Cl_2 (200 ml) and was stirred overnight. The reaction mixture was concentrated *in vacuo* by rotary evaporation and was used in the next reaction without further purification (13 g, 95%). Electrospray mass spec: $M+H^+ = 137.9$

b. Racemic Allyl-(1-methyl-pent-4-enyl)-amine

Sodium borohydride (2.7 g, 71 mmol) was added portionwise to a stirred solution of allyl-(1-methyl-pent-4-enylidene)-amine (6.5 g, 47 mmol) in MeOH (100 ml) at 0 C. The reaction mixture was stirred for 30 minutes, then warmed to RT. Approximately 90 ml of MeOH was removed from the reaction mixture by rotary evaporation, then the reaction mixture was diluted with ether (200 ml), then extracted with water then brine. The combined organics were dried with $MgSO_4$, filtered, concentrated *in vacuo* by rotary evaporation to give a pale yellow liquid that was used in the next reaction without further purification (5.2 g, 80%).

c. Racemic Allyl-(1-methyl-pent-4-enyl)-carbamic acid benzyl ester

Carbobenzyloxy chloride (9.56 g, 8 ml) was added dropwise to a stirred solution of allyl-(1-methyl-pent-4-enyl)-amine (7 g, 50 mmol), triethylamine (5.5 g, 8.0 ml, 57.5 mmol) in CH_2Cl_2 (100 ml) at 0 C. The reaction mixture was warmed to RT, then was stirred for 2 h. The reaction mixture was diluted with CH_2Cl_2 (100 ml), then was extracted with water, then brine. The combined organics were dried with $MgSO_4$, filtered, concentrated *in vacuo* by rotary evaporation, then was chromatographed (silica gel, 4% EtOAc/ hexanes) to give the title compound (8.9 g, 65% yield): Liquid Chromatgraphy/Electrospray mass spec: $M+H^+ = 274.2$

d. Racemic 2-Methyl-2,3,4,7-tetrahydro-azepine-1-carboxylic acid benzyl ester

Allyl-(1-methyl-pent-4-enyl)-carbamic acid benzyl ester (1.036 g, 3.8 mmol) was dissolved in CH_2Cl_2 (10 ml) and a stream of argon gas was bubbled into the reaction mixture for 10 minutes. Then bis(tricyclohexylphosphine)benzylidine ruthenium(IV) dichloride (Strem Chemicals, Grubbs' catalyst, 22 mg, 0.027 mmol) was added and the reaction mixture was refluxed for 2 h. Additional bis(tricyclohexylphosphine)benzylidine ruthenium(IV) dichloride (11 mg, 0.014 mmol) was added and the reaction mixtrue was refluxed for an additional 1.5 hours. The reaction was cooled to RT under argon overnight, then was concentrated *in vacuo* by rotary evaporation, then was chromatographed (silica gel, 5% EtOAc/ hexanes) to give the title compound (0.83 g, 89%): 1H NMR: 7.35-7.20 (m, 5H), 5.65 (1H, m), 5.13 (2H, AB), 4.45-4.05 (m, 2H), 3.56 (1H, d), 2.25-2.10 (m, 2H), 1.90-1.60 (m, 2H), 1.12 (3H, d); Liquid Chromatgraphy/Electrospray mass spec: $M+H^+ = 246.2$.

e. Racemic (1S,4R,7R)-4-Methyl-8-oxa-3-aza-bicyclo[5.1.0]octane-3-carboxylic acid benzyl ester

m-Chloro-perbenzoic acid (1.05 g, 57-86% pure) was added to a solution of 2-methyl-2,3,4,7-tetrahydro-azepine-1-carboxylic acid benzyl ester (0.83 g, 3.34 mmol) in CH_2Cl_2 at 0 degrees C. The reaction mixture was stirred for half an hour, then was warmed to RT. Additional m-chloro-perbenzoic acid (0.3 g, 57-86% pure) was added and the reaction was stirred 2 h. The reaction mixture was concentrated *in vacuo* by rotary evaporation, then 80 ml of 9:1 hexanes/EtOAc was added and the reaction mixture was filtered. The filtrate was concentrated *in vacuo* by rotary evaporation, then was chromatographed (silica gel, 20% EtOAc:hexanes) to give racemic (1S,4R,7S)-4-methyl-8-

oxa-3-aza-bicyclo[5.1.0]octane-3-carboxylic acid benzyl ester (0.44 g, 50%) and the title compound as a racemic mixture of the title compound (0.15 g, 17% yield): 1H NMR: 7.42-7.22 (m, 5H), 5.13 (2H, s), 4.50-4.15 (m, 2H), 3.27 (1H, d), 3.12-2.95 (1H, m), 2.15-1.70 (m, 2H), 1.47 (m, 2H), 1.12 (3H, d); Liquid Chromatgraphy/Electrospray mass spec: $M+H^+$ = 262.0.

f. Racemic (2R,5S,6S)-5-Azido-6-hydroxy-2-methyl-azepane-1-carboxylic acid benzyl ester

Sodium azide (0.56 g, 8.62 mmol) was added to a solution of racemic (1S,4R,7R)-4-methyl-8-oxa-3-aza-bicyclo[5.1.0]octane-3-carboxylic acid benzyl ester (0.75 g, 2.87 mmol) and ammonium chloride (0.46 g, 8.62 mmol) in MeOH (5 ml) and H_2O (0.5 ml), then was refluxed for 6 h. The reaction mixture was concentrated *in vacuo* by rotary evaporation, then was diluted with water (5 ml) and extracted with EtOAc (10 ml). The organic layer was then extracted with water, brine, dried with $MgSO_4$, filtered, concentrated *in vacuo* by rotary evaporation, and chromatographed (silica gel, 20% EtOAc/hexanes) to yield the title compound (0.7g, 80%): 7.39-7.30 (m, 5H), 5.15 (2H, s), 4.10-3.67 (m, 2H), 3.10 (1H, d), 1.85-1.53 (m, 4H), 1.09 (3H, d); Liquid Chromatgraphy/Electrospray mass spec: $M+H^+$ = 305.2.

g. Racemic (2R,5S,6S)-5-Amino-6-hydroxy-2-methyl-azepane-1-carboxylic acid benzyl ester

Triphenylphosphine (1.94 g, 7.4 mmol) was added to a solution of racemic (2R,5S,6S)-5-azido-6-hydroxy-2-methyl-azepane-1-carboxylic acid benzyl ester (1. 5 g, 4.93 mmol) in THF (185 ml) and H_2O (0.7 ml), then was heated to 45 degrees C overnight. The reaction mixture was then diluted with toluene (100 ml x 2) and was azeotroped *in vacuo* by rotary evaporation twice. The resxulting oil was dissolved in MeOH and HCl in Et_2O and the resulting salt was collected following filtration and was used in the next reaction without further purification (1.4 g, 90%).

h. (2R,5S,6S)-5-((S)-2- tert -Butoxycarbonylamino-4-methyl-pentanoylamino)-6-hydroxy-2-methyl-azepane-1 -carboxylic acid benzyl ester and (2S,5R,6R)-5-((S)-2- tert -Butoxycarbonylamino-4-methyl-pentanoylamino)-6-hydroxy-2-methyl-azepane-1 -carboxylic acid benzyl ester

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide (0.33 g, 1.73 mmol) was added to a solution of Boc-leucine-hydrate (0.43 g, 1.7 mmol), diisopropylethylamine (0.22 g, 0.3 ml, 1.7 mmol), hydroxybenztriazole (0.25 g, 1.85 mmol), and racemic (2R,5S,6S)-5-Amino-6-hydroxy-2-methyl-azepane-1-carboxylic acid benzyl ester (0.5 g, 1.6 mmol) in DMF (10 ml). The reaction was stirred overnight at RT, then was diluted with EtOAc (100 ml), washed with H_2O (3x 50 ml), brine (50 ml), dried with magnesium sulfate, filtered, concentrated *in vacuo* by rotary evaporation, and chromatographed (silica gel, 50% EtOAc/hexanes) to yield the title compound (0.78g, 100%): 1H NMR: 7.40-7.29 (m, 5H), 6.75 (1H, bd), 5.12 (2H, AB), 5.0 (1H, bs), 4.15-3.72 (m, 2H), 3.06 (1H, d), 1.60-1.30 (m, 2H), 1.60-1.30 (m, 5H), 1.12 (3H, d), 0.97-0.87(6H, dd); Electrospray mass spec: $M+H^+$ = 492.0

i. [(S)-1-((3S,4S,7R)-3-Hydroxy-7-methyl-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid tert -butyl ester and . [(S)-1-((3R,4R,7S)-3-Hydroxy-7-methyl-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid tert -butyl ester

(2R,5S,6S)-5-((S)-2- tert -Butoxycarbonylamino-4-methyl-pentanoylamino)-6-hydroxy-2-methyl-azepane-1 -carboxylic acid benzyl ester and (2S,5R,6R)-5-((S)-2- tert -butoxycarbonylamino-4-methyl-pentanoylamino)-6-hydroxy-2-methyl-azepane-1 -carboxylic acid benzyl ester (0.77g, 1.57 mmol) was dissolved in EtOAc (27.5 ml), MeOH (5.5 ml). Then 10% Pd/C (0.39 g) was added and the reaction was stirred overnight under a balloon filled with hydrogen gas. The reaction mixture was filtered through Celite, concentrated *in vacuo* by rotary evaporation and was used in the next reaction without further purification (0.56 g): Electrospray mass spec: $M+H^+$ = 358.11.

j. [(S)-1-((3S,4S,7R)-1-Benzenesulfonyl-3-hydroxy-7-methyl-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid tert -butyl ester and [(S)-1-((3R,4R,7S)-1-Benzenesulfonyl-3-hydroxy-7-methyl-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid tert -butyl ester

2-Pyridine sulfonyl chloride (0.6 g, 3.4 mmol) was added to a solution of [(S)-1-((3S,4S,7R)-3-Hydroxy-7-methyl-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid tert -butyl ester and . [(S)-1-((3R,4R,7S)-3-hydroxy-7-methyl-azepan-4-ylcarbamoyl)-3-methyl-

butyl]-carbamic acid tert -butyl ester (1.0 g, 2.8 mmol), N-methyl morpholine (0.45 ml, 4.1 mmol) in CH_2Cl_2 (35 ml) and was stirred at RT overnight. The reaction mixture was diluted with EtOAc (100 ml), washed with H_2O, brine, dried with magnesium sulfate, filtered, concentrated *in vacuo* by rotary evaporation, and chromatographed (silica gel, 2.5% MeOH/ CH_2Cl_2) to yield the title compound (0.9g, 64%): 1H NMR: 8.68 (m, 1H), 8.05 (1H, d), 7.92 (1H, dd), 7.50 (1H, dd), 6.66 (1H, bd), 4.95-4.88 (dd), 4.20-3.87 (m, 3H), 3.65 (1H, bs), 3.40 (1H, d), 1.94-1.57 (m, 4H), 1.45-1.38 (m, 6H), 1.14 (3H, dd), 0.94 (6H, dd); Electrospray mass spec: $M+H^+ = 499.0$

k. (S)-2-Amino-4-methyl-pentanoic acid ((3S,4S,7R)-1-(2-pyridine)-sulfonyl-3-hydroxy-7-methyl-azepan-4-yl)-amide and (S)-2-Amino-4-methyl-pentanoic acid ((3R,4R,7S)-1-(2-pyridine)-sulfonyl-3-hydroxy-7-methyl-azepan-4-yl)-amide

HCl in dioxane (4.0 M, 15 ml) was added to a stirred solution of [(S)-1-((3S,4S,7R)-1-benzenesulfonyl-3-hydroxy-7-methyl-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid tert -butyl ester and [(S)-1-((3R,4R,7S)-1-benzenesulfonyl-3-hydroxy-7-methyl-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid tert -butyl ester (0.9 g, 1.8 mmol) in MeOH (15 ml). The reaction mixture was stirred for 2h at RT, then was concentrated *in vacuo* by rotary evaporation and was used in the next reaction without further purification (0.85 g).

l. Benzofuran-2-carboxylic acid {(S)-1-[(3S,4S,7R)-3-hydroxy-7-methyl-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide and benzofuran-2-carboxylic acid {(S)-1-[(3R,4R,7S)-3-hydroxy-7-methyl-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide (0.35 g, 1.85 mmol) was added to a solution of 2-benzofuran-carboxylic acid (0.3 g, 1.85 mmol), (S)-2-amino-4-methyl-pentanoic acid ((3S,4S,7R)-1-(2-pyridine)-sulfonyl-3-hydroxy-7-methyl-azepan-4-yl)-amide and (S)-2-amino-4-methyl-pentanoic acid ((3R,4R,7S)-1-(2-pyridine)-sulfonyl-3-hydroxy-7-methyl-azepan-4-yl)-amide (0.85 g, 1.8 mmol), diisopropylethylamine (0.48 g, 0.65 ml, 3.7 mmol), hydroxybenztriazole (0.25 g, 1.85 mmol) in DMF (10 ml) and was stirred at RT overnight. The reaction mixture was then warmed to RT and was stirred overnight. The reaction mixture was diluted with EtOAc (100 ml), washed with H_2O, brine, dried with magnesium sulfate, filtered, concentrated *in vacuo* by rotary evaporation, and chromatographed (silica gel, 2.5% MeOH/ CH_2Cl_2) to yield the title compound (0.8g,

82%): 1H NMR: 8.65 (m, 1H), 8.05 (m, 1H), 7.87 (dd, 1H), 7.62 (dd, 1H), 7.50-7.35 (m, 3H), 7.28-7.20 (m, 1H), 7.07 (m, 1H), 6.92 (1H, bd), 6.80 (bd, 1H), 4.65-4.48 (m, 1H), 4.20-3.87 (m, 3H), 3.65 (1H, bd), 3.40 (1H, dd), 1.94-1.57 (m, 4H), 1.45-1.38 (m, 6H), 1.14 (3H, dd), 0.94 (6H, m); Electrospray mass spec: $M+H^+ = 542.98$

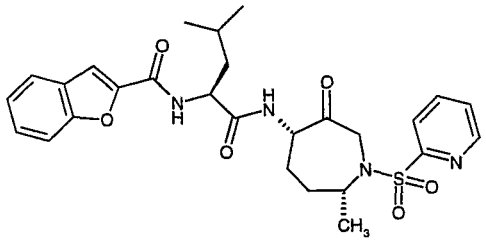
m. Benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide and Benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(4R,7S)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide

Dess-Martin periodinane (1.0 g, 2.36 mmol) was added to a solution of benzofuran-2-carboxylic acid {(S)-1-[(3S,4S,7R)-3-hydroxy-7-methyl-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide and benzofuran-2-carboxylic acid {(S)-1-[(3R,4R,7S)-3-hydroxy-7-methyl-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide (0.8 g, 1.48 mmol) in CH_2Cl_2 (20 ml) and was stirred at RT for 45 minutes. The solution was washed with 10% $NaHCO_3$ and brine. Purification by column chromatography (60% ethyl acetate/ hexanes) gave the title compound as a mixture of diastereomers (0.75 g, 94%); The diastereomers were separated by HPLC. Diastereomer 1: 1H NMR: 8.72 (m, 1H), 8.0 (d, 1H), 8.92 (dd, 1H), 7.65 (d, 1H), 7.56 (d, 1H), 7.45 (s, 1H), 7.42 (dd, 2H), 7.28 (d, 1H), 7.10 (d, 1H), 5.15 (m, 1H), 4.77 (d, 1H), 4.68 (m, 1H), 4.40 (m, 1H), 3.86 (d, 1H), 2.20-2.08 (m, 2H), 1.78-1.50 (m, 5H), 1.22 (dd, 3H), 0.98 (m, 6H); Electrospray mass spec: $M+H^+ = 541.2$; Diastereomer 2: 1H NMR: 8.68 (m, 1H), 8.04 (d, 1H), 8.92 (dd, 1H), 7.68 (d, 1H), 7.58 (d, 2H), 7.52 (s, 1H), 7.42 (dd, 1H), 7.29 (d, 1H), 7.05 (m, 2H), 5.12 (m, 1H), 4.75-4.68 (m, 1H), 4.43 (m, 1H), 3.83 (d, 1H), 2.25-2.12 (m, 2H), 1.88-1.50 (m, 5H), 0.98 (m, 9H); Electrospray mass spec: $M+H^+ = 541.2$

Example 6

Preparation of single diasteromer:

Benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide



a. ((R)-2-Iodo-1-methyl-ethyl)-carbamic acid benzyl ester

Triphenylphospine (24 g, 91.8 mmol) was added to a solution of imidazole (12.5 g, 184 mmol) in CH_2Cl_2 (231 ml), then was cooled to 0 degrees C. Iodine (23.3 g, 91.8 mmol) was added to the suspension. The reaction mixture turned yellow, then faintly brown. After 5 minutes ((R)-2-hydroxy-1-methyl-ethyl)-carbamic acid benzyl ester (9.59 g, 45.9 mmol) was added and the reaction mixture was warmed to RT then stirred for 3 h. Then, H_2O (7 ml) was added and the reaction mixture was partitioned between CH_2Cl_2 (300 ml) and H_2O (600 ml). The aqueous layer was extracted again with CH_2Cl_2 (200 ml). The combined organic layer was then washed with a solution of 1:9 aq. saturated $Na_2S_2O_3$: H_2O (140 ml), then brine (400 ml). The combined organics were dried with $MgSO_4$, filtered, concentrated *in vacuo*, then filtered through a plug of silica gel washing with 15% EtOAc/ hexanes (1.5 liter). The solution was concentrated *in vacuo*, then the solid was washed with hexane and the resultant white solid was used in the next reaction without further purification (11g, 75%).

b. ((R)-1-Methyl-pent-4-enyl)-carbamic acid benzyl ester

Copper (I) bromide-dimethyl sulfide (1.93 g, 9.4 mmol) was dissolved in distilled THF (24 ml), then was cooled to –78 degrees C. A solution of allyl magnesium chloride (9.4 ml, 2M in THF, Aldrich) was added dropwise, then the solution was stirred for 30 minutes. ((R)-2-Iodo-1-methyl-ethyl)-carbamic acid benzyl ester (1.5 g, 4.7 mmol) in distilled THF (3 ml) was added dropwise, then the reaction was warmed to –40 degrees C and was stirred for 2.5 h. The reaction mixture was quenched with aq. sat. NH_4Cl (4 ml) at –40 degrees C, warmed to RT and the gray reaction mixture turned sky blue. THF was removed *in vacuo*. Then, Et_2O was added and the reaction mixture was filtered to remove precipitated solids. The solids were washed with additional Et_2O. The combined organics

were extracted with 10% NH_4OH (3x), then brine. The combined organics were dried with $MgSO_4$, filtered, concentrated *in vacuo*, then filtered through a plug of silica gel washing with 20% EtOAc/ hexanes (100 ml). The solution was concentrated *in vacuo*, then the resultant colorless oil was used in the next reaction without further purification (0.8 g, 73%).

c. Allyl-((R)-1-methyl-pent-4-enyl)-carbamic acid benzyl ester

((R)-1-Methyl-pent-4-enyl)-carbamic acid benzyl ester (790 mg, 3.39 mmol) was dissolved in DMF (8 ml) and was cooled to 0 degrees C. Sodium hydride (60% dispersion, 271 mg, 6.78 mmol) was added and the reaction was stirred for 15 minutes. Allyl bromide (1.23 g, 0.88 ml, 10.17 mmol) was added and the reaction mixture was stirred for 3 h at 0 degrees C. H_2O (10 ml) was added, then 2N HCl was added dropwise adjusting the pH to 1. The reaction mixture was extracted with Et_2O (2 x 50 ml). The combined organics were washed with aq. 2N HCl, then aq. $NaHCO_3$, then brine. The combined organics were dried with $MgSO_4$, filtered, concentrated *in vacuo*, then chromatographed on silica gel (5% EtOAc/ hexanes) to yield the title compound as a colorless oil (883 mg, 95%).

d. 2-Methyl-2,3,4,7-tetrahydro-azepine-1-carboxylic acid benzyl ester

Allyl-(1-methyl-pent-4-enyl)-carbamic acid benzyl ester (0.872 g, 3.19 mmol) was dissolved in CH_2Cl_2 (10 ml) and a stream of argon gas was bubbled into the reaction mixture for 10 minutes. Then bis(tricyclohexylphosphine)benzylidine ruthenium(IV) dichloride (Strem Chemicals, Grubbs' catalyst, 19 mg, 0.0227 mmol) was added and the reaction mixture was refluxed for 2 h. Additional bis(tricyclohexylphosphine)benzylidine ruthenium(IV) dichloride (mg, 0.0108 mmol) was added and the reaction mixture was refluxed for an additional 1.5 hours. The reaction was cooled to RT under argon overnight, then was concentrated *in vacuo* by rotary evaporation, then was chromatographed (silica gel, 5% EtOAc/ hexanes) to give the title compound (0.72 g, 92%): 1H NMR: 7.35-7.20 (m, 5H), 5.65 (1H, m), 5.13 (2H, AB), 4.45-4.05 (m, 2H), 3.56 (1H, d), 2.25-2.10 (m, 2H), 1.90-1.60 (m, 2H), 1.12 (3H, d); Liquid Chromatgraphy/Electrospray mass spec: $M+H^+$ = 246.2.

e. (1S,4R,7R)-4-Methyl-8-oxa-3-aza-bicyclo[5.1.0]octane-3-carboxylic acid benzyl ester

m-Chloro-perbenzoic acid (1.10 g, 57-86% pure) was added to a solution of 2-methyl-2,3,4,7-tetrahydro-azepine-1-carboxylic acid benzyl ester (0.72 g, 2.94 mmol) in CH_2Cl_2 at 0 degrees C. The reaction mixture was stirred for half an hour, then was warmed to RT. Additional m-chloro-perbenzoic acid (0.660 g, 57-86% pure) was added and the reaction was stirred 2 h. The reaction mixture was concentrated *in vacuo* by rotary evaporation, then 80 ml of 9:1 hexanes/EtOAc was added and the reaction mixture was filtered. The filtrate was concentrated *in vacuo* by rotary evaporation, then was chromatographed (silica gel, 20% EtOAc:hexanes) to give (1S,4R,7S)-4-methyl-8-oxa-3-aza-bicyclo[5.1.0]octane-3-carboxylic acid benzyl ester (0.450 g, 75%) and the title compound (0.15 g, 25% yield): 1H NMR: 7.42-7.22 (m, 5H), 5.13 (2H, s), 4.50-4.15 (m, 2H), 3.27 (1H, d), 3.12-2.95 (1H, m), 2.15-1.70 (m, 2H), 1.47 (m, 2H), 1.12 (3H, d); Liquid Chromatgraphy/Electrospray mass spec: $M+H^+ = 262.0$.

f. (2R,5S,6S)-5-Azido-6-hydroxy-2-methyl-azepane-1-carboxylic acid benzyl ester

Sodium azide (0.139 g, 2.14 mmol) was added to a solution of (1S,4R,7R)-4-methyl-8-oxa-3-aza-bicyclo[5.1.0]octane-3-carboxylic acid benzyl ester (0.186 g, 0.71 mmol) and ammonium chloride (0.114 g, 2.14 mmol) in MeOH (1.5 ml) and H_2O (0.15 ml), then was refluxed for 6 h. The reaction mixture was concentrated *in vacuo* by rotary evaporation, then was diluted with water (5 ml) and extracted with EtOAc (10 ml). The organic layer was then extracted with water, brine, dried with $MgSO_4$, filtered, concentrated *in vacuo* by rotary evaporation, and chromatographed (silica gel, 20% EtOAc/hexanes) to yield the title compound (0.192 g, 89%): 7.39-7.30 (m, 5H), 5.15 (2H, s), 4.10-3.67 (m, 2H), 3.10 (1H, d), 1.85-1.53 (m, 4H), 1.09 (3H, d); Liquid Chromatgraphy/Electrospray mass spec: $M+H^+ = 305.2$.

g. (2R,5S,6S)-5-Amino-6-hydroxy-2-methyl-azepane-1-carboxylic acid benzyl ester

Triphenylphosphine (0.25 g, 0.952 mmol) was added to a solution of (2R,5S,6S)-5-azido-6-hydroxy-2-methyl-azepane-1-carboxylic acid benzyl ester (0.193 g, 0.635 mmol) in THF (10 ml) and H_2O (0.04 ml), then was heated to 45 degrees C overnight. The reaction mixture was then diluted with toluene (100 ml x 2) and was azeotroped *in vacuo* by rotary evaporation twice. The resulting oil was dissolved in MeOH and HCl in Et_2O and the

resulting salt was collected following filtration and was used in the next reaction without further purification (0.27 g, 90%).

h. (2R,5S,6S)-5-((S)-2- tert -Butoxycarbonylamino-4-methyl-pentanoylamino)-6-hydroxy-2-methyl-azepane-1 -carboxylic acid benzyl ester

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide (0.164 g, 0.22 mmol) was added to a solution of Boc-Leucine-hydrate (0.190 g, 0.76 mmol), diisopropylethylamine (0.164 g, 0.22 ml, 1.27 mmol), hydroxybenztriazole (0.114 g, 0.83 mmol), and racemic (2R,5S,6S)-5-Amino-6-hydroxy-2-methyl-azepane-1-carboxylic acid benzyl ester (0.27 g, 0.57 mmol) in DMF (3.2 ml). The reaction was stirred overnight at RT, then was diluted with EtOAc (100 ml), washed with H_2O (3x 50 ml), brine (50 ml), dried with magnesium sulfate, filtered, concentrated *in vacuo* by rotary evaporation, and chromatographed (silica gel, 50% EtOAc/hexanes) to yield the title compound (0.218 g, 72 %): 1H NMR: 7.40-7.29 (m, 5H), 6.75 (1H, bd), 5.12 (2H, AB), 5.0 (1H, bs), 4.15-3.72 (m, 2H), 3.06 (1H, d), 1.60-1.30 (m, 2H), 1.60-1.30 (m, 5H), 1.12 (3H, d), 0.97-0.87(6H, dd); Electrospray mass spec: $M+H^+$ = 492.0

i. [(S)-1-((3S,4S,7R)-3-Hydroxy-7-methyl-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid tert -butyl ester

(2R,5S,6S)-5-((S)-2- tert -Butoxycarbonylamino-4-methyl-pentanoylamino)-6-hydroxy-2-methyl-azepane-1 -carboxylic acid benzyl ester (0.169 g, 0.344 mmol) was dissolved in EtOAc (3 ml), MeOH (1 ml). Then 10% Pd/C (0.183 g, 0.172 mmol) was added and the reaction was stirred overnight under a balloon filled with hydrogen gas. The reaction mixture was filtered through Celite, concentrated *in vacuo* by rotary evaporation and was used in the next reaction without further purification (0.126 g): Electrospray mass spec: $M+H^+$ = 358.11.

j. [(S)-1-((3S,4S,7R)-2-Pyridinesulfonyl-3-hydroxy-7-methyl-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid tert -butyl ester

2-Pyridine sulfonyl chloride (0.71 g, 0.4 mmol) was added to a solution of . [(S)-1-((3S,4S,7R)-3-hydroxy-7-methyl-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid tert -butyl ester (0.126 g, 0.344 mmol), sodium bicarbonate (0.87 g, 1.03 mmol) in CH_2Cl_2 (3 ml) and H_2O (2 ml) and was stirred at RT for 30 minutes. The reaction mixture was diluted with EtOAc (100 ml), washed with H_2O, brine, dried with magnesium sulfate, filtered,

concentrated *in vacuo* by rotary evaporation, and chromatographed (silica gel, 3 % MeOH/ CH_2Cl_2) to yield the title compound (0.180 g, 70%): 1H NMR: 8.68 (m, 1H), 8.05 (1H, d), 7.92 (1H, dd), 7.50 (1H, dd), 6.66 (1H, bd), 4.95-4.88 (dd), 4.20-3.87 (m, 3H), 3.65 (1H, bs), 3.40 (1H, d), 1.94-1.57 (m, 4H), 1.45-1.38 (m, 6H), 1.14 (3H, dd), 0.94 (6H, dd); Electrospray mass spec: $M+H^+ = 499.0$

k. (S)-2-Amino-4-methyl-pentanoic acid ((3S,4S,7R)-1-(2-pyridine)-sulfonyl-3-hydroxy-7-methyl-azepan-4-yl)-amide

HCl in dioxane (4.0 M, 1.5 ml) was added to a stirred solution of [(S)-1-((3S,4S,7R)- 2-pyridinesulfonyl -3-hydroxy-7-methyl-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid tert -butyl ester (0.090 g, 0.18 mmol) in MeOH (1.5 ml). The reaction mixture was stirred for 2h at RT, then was concentrated *in vacuo* by rotary evaporation and was used in the next reaction without further purification (0.072 g).

l. Benzofuran-2-carboxylic acid {(S)-1-[(3S,4S,7R)-3-hydroxy-7-methyl-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide (0.046 g, 0.36 mmol) was added to a solution of 2-benzofuran-carboxylic acid (0.032 g, 0.198 mmol), (S)-2-Amino-4-methyl-pentanoic acid ((3S,4S,7R)-1-(2-pyridine)-sulfonyl-3-hydroxy-7-methyl-azepan-4-yl)-amide (0.072 g, 0.18 mmol), diisopropylethylamine (0.046 g, 0.06 ml, 0.36 mmol), hydroxybenztriazole (0.029 g, 0.36 mmol) in DMF (2 ml) and was stirred at RT overnight. The reaction mixture was then warmed to RT and was stirred overnight. The reaction mixture was diluted with EtOAc (10 ml), washed with H_2O, brine, dried with magnesium sulfate, filtered, concentrated *in vacuo* by rotary evaporation, and chromatographed (silica gel, 2.5% MeOH/ CH_2Cl_2) to yield the title compound (0.092 g, 94%): 1H NMR: 8.65 (m, 1H), 8.05 (m, 1H), 7.87 (dd, 1H), 7.62 (dd, 1H), 7.50-7.35 (m, 3H), 7.28-7.20 (m, 1H), 7.07 (m, 1H), 6.92 (1H, bd), 6.80 (bd, 1H), 4.65-4.48 (m, 1H), 4.20-3.87 (m, 3H), 3.65 (1H, bd), 3.40 (1H, dd), 1.94-1.57 (m, 4H), 1.45-1.38 (m, 6H), 1.14 (3H, dd), 0.94 (6H, m); Electrospray mass spec: $M+H^+ = 542.98$

m. Benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide

Dess-Martin periodinane (0.077 g, 0.182 mmol) was added to a solution of . Benzofuran-2-carboxylic acid {(S)-1-[(3S,4S,7R)-3-hydroxy-7-methyl-1-(pyridine-2-

sulfonyl)-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide (0.058 g, 0.107 mmol) in CH_2Cl_2 (10 ml) and was stirred at RT for 1 h. The solution was washed with 10% aq. $Na_2S_2O_3$, then aq. sat. $NaHCO_3$, then brine. Purification by column chromatography (50% to 80% ethyl acetate/ hexanes) gave the title compound (0.056 g, 97%): 1H NMR: 8.72 (m, 1H), 8.0 (d, 1H), 8.92 (dd, 1H), 7.65 (d, 1H), 7.56 (d, 1H), 7.45 (s, 1H), 7.42 (dd, 2H), 7.28 (d, 1H), 7.10 (d, 1H), 5.15 (m, 1H), 4.77 (d, 1H), 4.68 (m, 1H), 4.40 (m, 1H), 3.86 (d, 1H), 2.20-2.08 (m, 2H), 1.78-1.50 (m, 5H), 1.22 (dd, 3H), 0.98 (m, 6H); Electrospray mass spec: $M+H^+ = 541.2$.

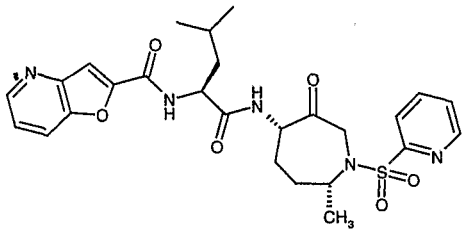
Example 7

2,2,4-Trideutero-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide

Benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide is dissolved in d4-methanol (CD_3OD) and D_2O (10:1), then triethyl amine is added and the reaction mixture is stirred for 3 days. Azeotroping with toluene by concentrating *in vacuo* provides the title compound.

Example 8

Furo[3,2-b]pyridine-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide



a. ((R)-2-Iodo-1-methyl-ethyl)-carbamic acid benzyl ester

Triphenylphospine (24 g, 91.8 mmol) was added to a solution of imidazole (12.5 g, 184 mmol) in CH_2Cl_2 (231 ml), then was cooled to 0 degrees C. Iodine (23.3 g, 91.8 mmol) was added to the suspension. The reaction mixture turned yellow, then faintly brown. After 5 minutes ((R)-2-hydroxy-1-methyl-ethyl)-carbamic acid benzyl ester (9.59 g, 45.9 mmol) was added and the reaction mixture was warmed to RT then stirred for 3 h. Then, H_2O (7 ml) was added and the reaction mixture was partitioned between CH_2Cl_2 (300 ml) and H_2O

(600 ml). The aqueous layer was extracted again with CH_2Cl_2 (200 ml). The combined organic layer was then washed with a solution of 1:9 aq. saturated $Na_2S_2O_3$: H_2O (140 ml), then brine (400 ml). The combined organics were dried with $MgSO_4$, filtered, concentrated *in vacuo*, then filtered through a plug of silica gel washing with 15% EtOAc/ hexanes (1.5 liter). The solution was concentrated *in vacuo*, then the solid was washed with hexane and the resultant white solid was used in the next reaction without further purification (11g, 75%).

b. ((R)-1-Methyl-pent-4-enyl)-carbamic acid benzyl ester

Copper (I) bromide-dimethyl sulfide (1.93 g, 9.4 mmol) was dissolved in distilled THF (24 ml), then was cooled to –78 degrees C. A solution of allyl magnesium chloride (9.4 ml, 2M in THF, Aldrich) was added dropwise, then the solution was stirred for 30 minutes. ((R)-2-Iodo-1-methyl-ethyl)-carbamic acid benzyl ester (1.5 g, 4.7 mmol) in distilled THF (3 ml) was added dropwise, then the reaction was warmed to –40 degrees C and was stirred for 2.5 h. The reaction mixture was quenched with aq. sat. NH_4Cl (4 ml) at –40 degrees C, warmed to RT and the gray reaction mixture turned sky blue. THF was removed *in vacuo*. Then, Et_2O was added and the reaction mixture was filtered to remove precipitated solids. The solids were washed with additional Et_2O. The combined organics were extracted with 10% NH_4OH (3x), then brine. The combined organics were dried with $MgSO_4$, filtered, concentrated *in vacuo*, then filtered through a plug of silica gel washing with 20% EtOAc/ hexanes (100 ml). The solution was concentrated *in vacuo*, then the resultant colorless oil was used in the next reaction without further purification (0.8 g, 73%).

c. Allyl-((R)-1-methyl-pent-4-enyl)-carbamic acid benzyl ester

((R)-1-Methyl-pent-4-enyl)-carbamic acid benzyl ester (790 mg, 3.39 mmol) was dissolved in DMF (8 ml) and was cooled to 0 degrees C. Sodium hydride (60% dispersion, 271 mg, 6.78 mmol) was added and the reaction was stirred for 15 minutes. Allyl bromide (1.23 g, 0.88 ml, 10.17 mmol) was added and the reaction mixture was stirred for 3 h at 0 degrees C. H_2O (10 ml) was added, then 2N HCl was added dropwise adjusting the pH to 1. The reaction mixture was extracted with Et_2O (2 x 50 ml). The combined organics were washed with aq. 2N HCl, then aq. $NaHCO_3$, then brine. The combined organics were dried with $MgSO_4$, filtered, concentrated *in vacuo*, then chromatographed on silica gel (5% EtOAc/ hexanes) to yield the title compound as a colorless oil (883 mg, 95%).

d. 2-Methyl-2,3,4,7-tetrahydro-azepine-1-carboxylic acid benzyl ester

Allyl-(1-methyl-pent-4-enyl)-carbamic acid benzyl ester (0.872 g, 3.19 mmol) was dissolved in CH_2Cl_2 (10 ml) and a stream of argon gas was bubbled into the reaction mixture for 10 minutes. Then bis(tricyclohexylphosphine)benzylidine ruthenium(IV) dichloride (Strem Chemicals, Grubbs' catalyst, 19 mg, 0.0227 mmol) was added and the reaction mixture was refluxed for 2 h. Additional bis(tricyclohexylphosphine)benzylidine ruthenium(IV) dichloride (mg, 0.0108 mmol) was added and the reaction mixture was refluxed for an additional 1.5 hours. The reaction was cooled to RT under argon overnight, then was concentrated *in vacuo* by rotary evaporation, then was chromatographed (silica gel, 5% EtOAc/ hexanes) to give the title compound (0.72 g, 92%): 1H NMR: 7.35-7.20 (m, 5H), 5.65 (1H, m), 5.13 (2H, AB), 4.45-4.05 (m, 2H), 3.56 (1H, d), 2.25-2.10 (m, 2H), 1.90-1.60 (m, 2H), 1.12 (3H, d); Liquid Chromatgraphy/Electrospray mass spec: $M+H^+$ = 246.2.

e. (1S,4R,7R)-4-Methyl-8-oxa-3-aza-bicyclo[5.1.0]octane-3-carboxylic acid benzyl ester

m-Chloro-perbenzoic acid (1.10 g, 57-86% pure) was added to a solution of 2-methyl-2,3,4,7-tetrahydro-azepine-1-carboxylic acid benzyl ester (0.72 g, 2.94 mmol) in CH_2Cl_2 at 0 degrees C. The reaction mixture was stirred for half an hour, then was warmed to RT. Additional m-chloro-perbenzoic acid (0.660 g, 57-86% pure) was added and the reaction was stirred 2 h. The reaction mixture was concentrated *in vacuo* by rotary evaporation, then 80 ml of 9:1 hexanes/EtOAc was added and the reaction mixture was filtered. The filtrate was concentrated *in vacuo* by rotary evaporation, then was chromatographed (silica gel, 20% EtOAc:hexanes) to give (1S,4R,7S)-4-methyl-8-oxa-3-aza-bicyclo[5.1.0]octane-3-carboxylic acid benzyl ester (0.450 g, 75%) and the title compound (0.15 g, 25% yield): 1H NMR: 7.42-7.22 (m, 5H), 5.13 (2H, s), 4.50-4.15 (m, 2H), 3.27 (1H, d), 3.12-2.95 (1H, m), 2.15-1.70 (m, 2H), 1.47 (m, 2H), 1.12 (3H, d); Liquid Chromatgraphy/Electrospray mass spec: $M+H^+$ = 262.0.

f. (2R,5S,6S)-5-Azido-6-hydroxy-2-methyl-azepane-1-carboxylic acid benzyl ester

Sodium azide (0.139 g, 2.14 mmol) was added to a solution of (1S,4R,7R)-4-methyl-8-oxa-3-aza-bicyclo[5.1.0]octane-3-carboxylic acid benzyl ester (0.186 g, 0.71 mmol) and ammonium chloride (0.114 g, 2.14 mmol) in MeOH (1.5 ml) and H_2O (0.15 ml), then was refluxed for 6 h. The reaction mixture was concentrated *in vacuo* by rotary

evaporation, then was diluted with water (5 ml) and extracted with EtOAc (10 ml). The organic layer was then extracted with water, brine, dried with $MgSO_4$, filtered, concentrated *in vacuo* by rotary evaporation, and chromatographed (silica gel, 20% EtOAc/hexanes) to yield the title compound (0.192 g, 89%): 7.39-7.30 (m, 5H), 5.15 (2H, s), 4.10-3.67 (m, 2H), 3.10 (1H, d), 1.85-1.53 (m, 4H), 1.09 (3H, d); Liquid Chromatgraphy/Electrospray mass spec: $M+H^+ = 305.2$.

g. (2R,5S,6S)-5-Amino-6-hydroxy-2-methyl-azepane-1-carboxylic acid benzyl ester

Triphenylphosphine (0.25 g, 0.952 mmol) was added to a solution of (2R,5S,6S)-5-azido-6-hydroxy-2-methyl-azepane-1-carboxylic acid benzyl ester (0.193 g, 0.635 mmol) in THF (10 ml) and H_2O (0.04 ml), then was heated to 45 degrees C overnight. The reaction mixture was then diluted with toluene (100 ml x 2) and was azeotroped *in vacuo* by rotary evaporation twice. The resulting oil was dissolved in MeOH and HCl in Et_2O and the resulting salt was collected following filtration and was used in the next reaction without further purification (0.27 g, 90%).

h. (2R,5S,6S)-5-((S)-2- tert -Butoxycarbonylamino-4-methyl-pentanoylamino)-6-hydroxy-2-methyl-azepane-1 -carboxylic acid benzyl ester

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide (0.164 g, 0.22 mmol) was added to a solution of Boc-Leucine-hydrate (0.190 g, 0.76 mmol), diisopropylethylamine (0.164 g, 0.22 ml, 1.27 mmol), hydroxybenztriazole (0.114 g, 0.83 mmol), and racemic (2R,5S,6S)-5-Amino-6-hydroxy-2-methyl-azepane-1-carboxylic acid benzyl ester (0.27 g, 0.57 mmol) in DMF (3.2 ml). The reaction was stirred overnight at RT, then was diluted with EtOAc (100 ml), washed with H_2O (3x 50 ml), brine (50 ml), dried with magnesium sulfate, filtered, concentrated *in vacuo* by rotary evaporation, and chromatographed (silica gel, 50% EtOAc/hexanes) to yield the title compound (0.218 g, 72 %): 1H NMR: 7.40-7.29 (m, 5H), 6.75 (1H, bd), 5.12 (2H, AB), 5.0 (1H, bs), 4.15-3.72 (m, 2H), 3.06 (1H, d), 1.60-1.30 (m, 2H), 1.60-1.30 (m, 5H), 1.12 (3H, d), 0.97-0.87(6H, dd); Electrospray mass spec: $M+H^+ = 492.0$

i. [(S)-1-((3S,4S,7R)-3-Hydroxy-7-methyl-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid tert -butyl ester

(2R,5S,6S)-5-((S)-2- tert -Butoxycarbonylamino-4-methyl-pentanoylamino)-6-hydroxy-2-methyl-azepane-1 -carboxylic acid benzyl ester (0.169 g, 0.344 mmol) was

dissovled in EtOAc (3 ml), MeOH (1 ml). Then 10% Pd/C (0.183 g, 0.172 mmol) was added and the reaction was stirred overnight under a balloon filled with hydrogen gas. The reaction mixture was filtered through Celite, concentrated *in vacuo* by rotary evaporation and was used in the next reaction without further purification (0.126 g): Electrospray mass spec: $M+H^+ = 358.11$.

j. [(S)-1-((3S,4S,7R)-2-Pyridinesulfonyl-3-hydroxy-7-methyl-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid tert -butyl ester

2-Pyridine sulfonyl chloride (0.71 g, 0.4 mmol) was added to a solution of . [(S)-1-((3S,4S,7R)-3-Hydroxy-7-methyl-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid tert -butyl ester (0.126 g, 0.344 mmol), sodium bicarbonate (0.87 g, 1.03 mmol) in CH_2Cl_2 (3 ml) and H_2O (2 ml) and was stirred at RT for 30 minutes. The reaction mixture was diluted with EtOAc (100 ml), washed with H_2O, brine, dried with magnesium sulfate, filtered, concentrated *in vacuo* by rotary evaporation, and chromatographed (silica gel, 3 % MeOH/ CH_2Cl_2) to yield the title compound (0.180 g, 70%): 1H NMR: 8.68 (m, 1H), 8.05 (1H, d), 7.92 (1H, dd), 7.50 (1H, dd), 6.66 (1H, bd), 4.95-4.88 (dd), 4.20-3.87 (m, 3H), 3.65 (1H, bs), 3.40 (1H, d), 1.94-1.57 (m, 4H), 1.45-1.38 (m, 6H), 1.14 (3H, dd), 0.94 (6H, dd); Electrospray mass spec: $M+H^+ = 499.0$

k. (S)-2-Amino-4-methyl-pentanoic acid ((3S,4S,7R)-1-(2-pyridine)-sulfonyl-3-hydroxy-7-methyl-azepan-4-yl)-amide

HCl in dioxane (4.0 M, 1.5 ml) was added to a stirred solution of [(S)-1-((3S,4S,7R)- 2-pyridinesulfonyl -3-hydroxy-7-methyl-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid tert -butyl ester (0.090 g, 0.18 mmol) in MeOH (1.5 ml). The reaction mixture was stirred for 2h at RT, then was concentrated *in vacuo* by rotary evaporation and was used in the next reaction without further purification (0.072 g).

l. Furo[3,2-b]pyridine-2-carboxylic acid {(S)-1-[(3S,4S,7R)-3-hydroxy-7-methyl-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide (0.035 g, 0.185 mmol) was added to a solution of Furo[3,2-b]pyridine-2-carboxylic acid (0.034 g, 0.2 mmol, as described in Shiotani, Shunsaku; Morita, Hiroyuki *J.Heterocycl.Chem.* **1991**, 28 (6), 1469-1480), (S)-2-Amino-4-methyl-pentanoic acid ((3S,4S,7R)-1-(2-pyridine)-sulfonyl-3-hydroxy-7-methyl-azepan-4-yl)-amide (0.077 g, 0.16 mmol), diisopropylethylamine (0.05 g, 0.07 ml, 0.4

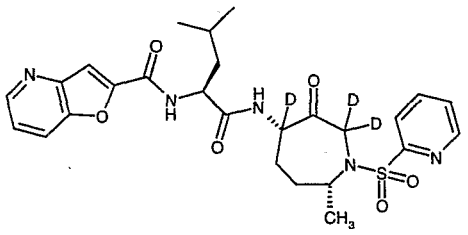
mmol), hydroxybenztriazole (0.025 g, 0.185 mmol) in DMF (1.5 ml) and was stirred at RT overnight. The reaction mixture was then warmed to RT and was stirred overnight. The reaction mixture was diluted with EtOAc (20 ml), washed with H_2O, brine, dried with magnesium sulfate, filtered, concentrated *in vacuo* by rotary evaporation, and chromatographed (silica gel, 2.5% MeOH/ CH_2Cl_2) to yield the title compound (0.056 g, 64%): 1H NMR: 8.68 (1H, d), 7.96 (1H, d), 7.87 (1H, d), 7.82 (1H, dd), 7.65 (1H, d), 7.61 (1H, s), 7.45 (1H, dd), 7.33 (1H, dd), 7.08 (d, 1H), 4.69 (q, 1H), 3.90-3.45 (m, 3H), 3.71 (q, 1H), 3.12-3.04 (m, 1H), 2.04-1.95 (m, 1H), 1.88-1.65 (m, 3H), 1.55-1.45 (m, 2H), 0.95 (m, 9H); Electrospray mass spec: $M+H^+ = 543.86$

m. Furo[3,2-b]pyridine-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide

Sulfur trioxide-pyridine complex (0.050 g, 0.31 mmol) was added to a solution of Furo[3,2-b]pyridine-2-carboxylic acid {(S)-1-[(3S,4S,7R)-3-hydroxy-7-methyl-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide (0.056 g, 0.103 mmol) in DMSO (1.0 ml) and triethylamine (0.085 ml, 0.6 mmol) was stirred at RT for 1 h. The reaction was incomplete; therefore, additional triethyl amine (0.04 ml, 0.3 mmol) and sulfur trioxide-pyridine complex (0.0.025 g, 0.15 mmol) was added ant the reaction was stirred an additional hour. The reaction mixture was diluted with water, then was extracted with EtOAc. Then, the organic layer was was extracted with brine. The combined organics were dried with magnesium sulfate, filtered, concentrated in vacuo, and purified by column chromatography (50% to 80% ethyl acetate/ hexanes) gave the title compound (12.5 mg, 22%): 1H NMR: 1H NMR: 8.72 (1H, d), 8.66 (1H, d), 8.02 (1H, d), 7.93 (1H, dd), 7.85 (1H, d), 7.53 (1H, dd), 7.40 (1H, dd), 7.25 (d, 1H), 6.95 (1H, d), 5.15 (m, 1H), 4.77 (m, 2H), 3.72 (q, 1H), 2.20-2.08 (m, 2H), 1.78-1.50 (m, 5H), 1.22 (dd, 3H), 0.98 (m, 6H); Electrospray mass spec: $M+H^+ = 542.2$

Example 9

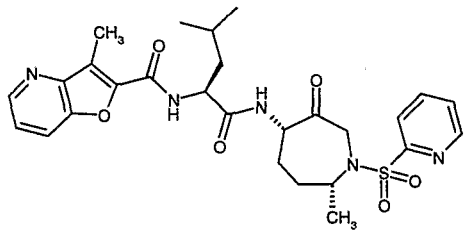
Preparation of 2,2,4-Trideutero-furo[3,2-b]pyridine-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide



Furo[3,2-b]pyridine-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide is dissolved in d4-methanol (CD_3OD) and D_2O (10:1), then triethyl amine is added and the reaction mixture is stirred for 3 days. Azeotroping with toluene by concentrating *in vacuo* provides the title compound.

Example 10

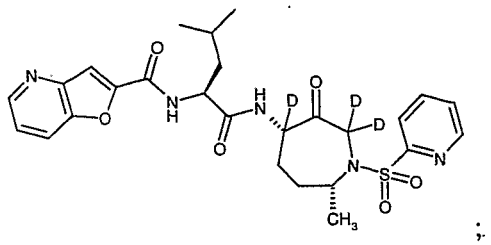
Preparation of 3-methyl-furo[3,2-b]pyridine-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide



Following the procedure of Example 8 (a-m), except substituting "3-methyl-furo[3,2-b]pyridine-2-carboxylic acid (as described in Shiotani, Shunsaku; Morita, Hiroyuki *J.Heterocycl.Chem.* **1991**, 28 (6), 1469-1480)" for "furo[3,2-b]pyridine-2-carboxylic acid" gave the title compound: MS (M+H+):; 1H NMR: 8.72 (d, 1H), 8.66 (d, 1H), 8.02 (d, 1H), 7.93 (dd, 1H), 7.80 (d, 1H), 7.53 (dd, 1H), 7.39 (dd, 1H), 7.66 (d, 1H), 6.90 (d, 1H), 5.56-5.12 (m, 1H), 4.72 (q, 1H), 4.42 (q, 1H), 3.87 (d, 1H), 2.70 (s, 3H), 2.24-2.14 (m, 2H), 1.75 (m, 2H), 1.65-1.42 (m, 4H), 1.2-0.95 (m, 9H); Electrospray mass spec: $M+H^+ = 556.2$.

Example 11

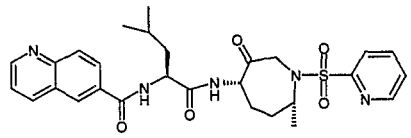
Preparation of 2,2,4-Trideutero-3-methyl-furo[3,2-b]pyridine-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide



Following the procedure of Example 9, except substituting 3-methyl-furo[3,2-b]pyridine-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide" for "furo[3,2-b]pyridine-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide " gives the title compound.

Example 12

Preparation of Quinoline-6-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide



a. ((R)-2-Iodo-1-methyl-ethyl)-carbamic acid benzyl ester

Triphenylphospine (24 g, 91.8 mmol) was added to a solution of imidazole (12.5 g, 184 mmol) in CH_2Cl_2 (231 ml), then was cooled to 0 degrees C. Iodine (23.3 g, 91.8 mmol) was added to the suspension. The reaction mixture turned yellow, then faintly brown. After 5 minutes ((R)-2-hydroxy-1-methyl-ethyl)-carbamic acid benzyl ester (9.59 g, 45.9 mmol) was added and the reaction mixture was warmed to RT then stirred for 3 h. Then, H_2O (7 ml) was added and the reaction mixture was partitioned between CH_2Cl_2 (300 ml) and H_2O (600 ml). The aqueous layer was extracted again with CH_2Cl_2 (200 ml). The combined organic layer was then washed with a solution of 1:9 aq. saturated $Na_2S_2O_3$: H_2O (140 ml), then brine (400 ml). The combined organics were dried with $MgSO_4$, filtered, concentrated *in vacuo*, then filtered through a plug of silica gel washing with 15% EtOAc/ hexanes (1.5 liter). The solution was concentrated *in vacuo*, then the solid was washed with hexane and the resultant white solid was used in the next reaction without further purification (11g, 75%).

b. ((R)-1-Methyl-pent-4-enyl)-carbamic acid benzyl ester

Copper (I) bromide-dimethyl sulfide (1.93 g, 9.4 mmol) was dissolved in distilled THF (24 ml), then was cooled to –78 degrees C. A solution of allyl magnesium chloride (9.4 ml, 2M in THF, Aldrich) was added dropwise, then the solution was stirred for 30 minutes. ((R)-2-Iodo-1-methyl-ethyl)-carbamic acid benzyl ester (1.5 g, 4.7 mmol) in distilled THF (3 ml) was added dropwise, then the reaction was warmed to –40 degrees C and was stirred for 2.5 h. The reaction mixture was quenched with aq. sat. NH_4Cl (4 ml) at –40 degrees C, warmed to RT and the gray reaction mixture turned sky blue. THF was removed *in vacuo*. Then, Et_2O was added and the reaction mixture was filtered to remove precipitated solids. The solids were washed with additional Et_2O. The combined organics were extracted with 10% NH_4OH (3x), then brine. The combined organics were dried with $MgSO_4$, filtered, concentrated *in vacuo*, then filtered through a plug of silica gel washing with 20% EtOAc/ hexanes (100 ml). The solution was concentrated *in vacuo*, then the resultant colorless oil was used in the next reaction without further purification (0.8 g, 73%).

c. Allyl-((R)-1-methyl-pent-4-enyl)-carbamic acid benzyl ester

((R)-1-Methyl-pent-4-enyl)-carbamic acid benzyl ester (790 mg, 3.39 mmol) was dissolved in DMF (8 ml) and was cooled to 0 degrees C. Sodium hydride (60% dispersion, 271 mg, 6.78 mmol) was added and the reaction was stirred for 15 minutes. Allyl bromide (1.23 g, 0.88 ml, 10.17 mmol) was added and the reaction mixture was stirred for 3 h at 0 degrees C. H_2O (10 ml) was added, then 2N HCl was added dropwise adjusting the pH to 1. The reaction mixture was extracted with Et_2O (2 x 50 ml). The combined organics were washed with aq. 2N HCl, then aq. $NaHCO_3$, then brine. The combined organics were dried with $MgSO_4$, filtered, concentrated *in vacuo*, then chromatographed on silica gel (5% EtOAc/ hexanes) to yield the title compound as a colorless oil (883 mg, 95%).

d. 2-Methyl-2,3,4,7-tetrahydro-azepine-1-carboxylic acid benzyl ester

Allyl-(1-methyl-pent-4-enyl)-carbamic acid benzyl ester (0.872 g, 3.19 mmol) was dissolved in CH_2Cl_2 (10 ml) and a stream of argon gas was bubbled into the reaction mixture for 10 minutes. Then bis(tricyclohexylphosphine)benzylidine ruthenium(IV) dichloride (Strem Chemicals, Grubbs' catalyst, 19 mg, 0.0227 mmol) was added and the reaction mixture was refluxed for 2 h. Additional bis(tricyclohexylphosphine)benzylidine ruthenium(IV) dichloride (mg, 0.0108 mmol) was added and the reaction mixture was

refluxed for an additional 1.5 hours. The reaction was cooled to RT under argon overnight, then was concentrated *in vacuo* by rotary evaporation, then was chromatographed (silica gel, 5% EtOAc/ hexanes) to give the title compound (0.72 g, 92%): 1H NMR: 7.35-7.20 (m, 5H), 5.65 (1H, m), 5.13 (2H, AB), 4.45-4.05 (m, 2H), 3.56 (1H, d), 2.25-2.10 (m, 2H), 1.90-1.60 (m, 2H), 1.12 (3H, d); Liquid Chromatgraphy/Electrospray mass spec: $M+H^+$ = 246.2.

e. (1S,4R,7R)-4-Methyl-8-oxa-3-aza-bicyclo[5.1.0]octane-3-carboxylic acid benzyl ester

m-Chloro-perbenzoic acid (1.10 g, 57-86% pure) was added to a solution of 2-methyl-2,3,4,7-tetrahydro-azepine-1-carboxylic acid benzyl ester (0.72 g, 2.94 mmol) in CH_2Cl_2 at 0 degrees C. The reaction mixture was stirred for half an hour, then was warmed to RT. Additional m-chloro-perbenzoic acid (0.660 g, 57-86% pure) was added and the reaction was stirred 2 h. The reaction mixture was concentrated *in vacuo* by rotary evaporation, then 80 ml of 9:1 hexanes/EtOAc was added and the reaction mixture was filtered. The filtrate was concentrated *in vacuo* by rotary evaporation, then was chromatographed (silica gel, 20% EtOAc:hexanes) to give (1S,4R,7S)-4-methyl-8-oxa-3-aza-bicyclo[5.1.0]octane-3-carboxylic acid benzyl ester (0.450 g, 75%) and the title compound (0.15 g, 25% yield): 1H NMR: 7.42-7.22 (m, 5H), 5.13 (2H, s), 4.50-4.15 (m, 2H), 3.27 (1H, d), 3.12-2.95 (1H, m), 2.15-1.70 (m, 2H), 1.47 (m, 2H), 1.12 (3H, d); Liquid Chromatgraphy/Electrospray mass spec: $M+H^+$ = 262.0.

f. (2R,5S,6S)-5-Azido-6-hydroxy-2-methyl-azepane-1-carboxylic acid benzyl ester

Sodium azide (0.139 g, 2.14 mmol) was added to a solution of (1S,4R,7R)-4-methyl-8-oxa-3-aza-bicyclo[5.1.0]octane-3-carboxylic acid benzyl ester (0.186 g, 0.71 mmol) and ammonium chloride (0.114 g, 2.14 mmol) in MeOH (1.5 ml) and H_2O (0.15 ml), then was refluxed for 6 h. The reaction mixture was concentrated *in vacuo* by rotary evaporation, then was diluted with water (5 ml) and extracted with EtOAc (10 ml). The organic layer was then extracted with water, brine, dried with $MgSO_4$, filtered, concentrated *in vacuo* by rotary evaporation, and chromatographed (silica gel, 20% EtOAc/hexanes) to yield the title compound (0.192 g, 89%): 7.39-7.30 (m, 5H), 5.15 (2H, s), 4.10-3.67 (m, 2H), 3.10 (1H, d), 1.85-1.53 (m, 4H), 1.09 (3H, d); Liquid Chromatgraphy/Electrospray mass spec: $M+H^+$ = 305.2.

g. (2R,5S,6S)-5-Amino-6-hydroxy-2-methyl-azepane-1-carboxylic acid benzyl ester

Triphenylphosphine (0.25 g, 0.952 mmol) was added to a solution of (2R,5S,6S)-5-azido-6-hydroxy-2-methyl-azepane-1-carboxylic acid benzyl ester (0.193 g, 0.635 mmol) in THF (10 ml) and H_2O (0.04 ml), then was heated to 45 degrees C overnight. The reaction mixture was then diluted with toluene (100 ml x 2) and was azeotroped *in vacuo* by rotary evaporation twice. The resulting oil was dissolved in MeOH and HCl in Et_2O and the resulting salt was collected following filtration and was used in the next reaction without further purification (0.27 g, 90%).

h. (2R,5S,6S)-5-((S)-2- tert -Butoxycarbonylamino-4-methyl-pentanoylamino)-6-hydroxy-2-methyl-azepane-1 -carboxylic acid benzyl ester

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide (0.164 g, 0.22 mmol) was added to a solution of Boc-Leucine-hydrate (0.190 g, 0.76 mmol), diisopropylethylamine (0.164 g, 0.22 ml, 1.27 mmol), hydroxybenztriazole (0.114 g, 0.83 mmol), and racemic (2R,5S,6S)-5-Amino-6-hydroxy-2-methyl-azepane-1-carboxylic acid benzyl ester (0.27 g, 0.57 mmol) in DMF (3.2 ml). The reaction was stirred overnight at RT, then was diluted with EtOAc (100 ml), washed with H_2O (3x 50 ml), brine (50 ml), dried with magnesium sulfate, filtered, concentrated *in vacuo* by rotary evaporation, and chromatographed (silica gel, 50% EtOAc/hexanes) to yield the title compound (0.218 g, 72 %): 1H NMR: 7.40-7.29 (m, 5H), 6.75 (1H, bd), 5.12 (2H, AB), 5.0 (1H, bs), 4.15-3.72 (m, 2H), 3.06 (1H, d), 1.60-1.30 (m, 2H), 1.60-1.30 (m, 5H), 1.12 (3H, d), 0.97-0.87(6H, dd); Electrospray mass spec: $M+H^+$ = 492.0

i. [(S)-1-((3S,4S,7R)-3-Hydroxy-7-methyl-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid tert -butyl ester

(2R,5S,6S)-5-((S)-2- tert -Butoxycarbonylamino-4-methyl-pentanoylamino)-6-hydroxy-2-methyl-azepane-1 -carboxylic acid benzyl ester (0.169 g, 0.344 mmol) was dissovled in EtOAc (3 ml), MeOH (1 ml). Then 10% Pd/C (0.183 g, 0.172 mmol) was added and the reaction was stirred overnight under a balloon filled with hydrogen gas. The reaction mixture was filtered through Celite, concentrated *in vacuo* by rotary evaporation and was used in the next reaction without further purification (0.126 g): Electrospray mass spec: $M+H^+$ = 358.11.

j. [(S)-1-((3S,4S,7R)-2-Pyridinesulfonyl-3-hydroxy-7-methyl-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid tert -butyl ester

Pyridine-2-sulfonyl chloride (0.71 g, 0.4 mmol) was added to a solution of [(S)-1-((3S,4S,7R)-3-Hydroxy-7-methyl-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid tert -butyl ester (0.126 g, 0.344 mmol), sodium bicarbonate (0.87 g, 1.03 mmol) in CH_2Cl_2 (3 ml) and H_2O (2 ml) and was stirred at RT for 30 minutes. The reaction mixture was diluted with EtOAc (100 ml), washed with H_2O, brine, dried with magnesium sulfate, filtered, concentrated *in vacuo* by rotary evaporation, and chromatographed (silica gel, 3 % MeOH/ CH_2Cl_2) to yield the title compound (0.180 g, 70%): 1H NMR: 8.68 (m, 1H), 8.05 (1H, d), 7.92 (1H, dd), 7.50 (1H, dd), 6.66 (1H, bd), 4.95-4.88 (dd), 4.20-3.87 (m, 3H), 3.65 (1H, bs), 3.40 (1H, d), 1.94-1.57 (m, 4H), 1.45-1.38 (m, 6H), 1.14 (3H, dd), 0.94 (6H, dd); Electrospray mass spec: $M+H^+ = 499.0$

k. (S)-2-Amino-4-methyl-pentanoic acid ((3S,4S,7R)-1-(2-pyridine)-sulfonyl-3-hydroxy-7-methyl-azepan-4-yl)-amide

HCl in dioxane (4.0 M, 1.5 ml) was added to a stirred solution of [(S)-1-((3S,4S,7R)- 2-pyridinesulfonyl -3-hydroxy-7-methyl-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid tert -butyl ester (0.090 g, 0.18 mmol) in MeOH (1.5 ml). The reaction mixture was stirred for 2h at RT, then was concentrated *in vacuo* by rotary evaporation and was used in the next reaction without further purification (0.072 g).

l. Quinoline-6-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide

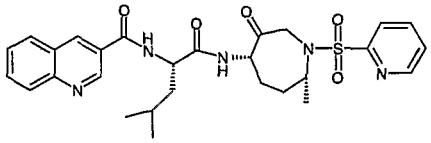
1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide (76 mg, 0.4 mmol) was added to a solution of Quinoline-6-carboxylic acid (64 mg, 0.37 mmol), (S)-2-Amino-4-methyl-pentanoic acid ((3S,4S,7R)-1-(2-pyridine)-sulfonyl-3-hydroxy-7-methyl-azepan-4-yl)-amide (160 mg, 0.37 mmol), diisopropylethylamine (56 mg, 0.075 ml, 0.43 mmol), hydroxybenztriazole (50 mg, 0.37 mmol) in DMF (3 ml) and was stirred at RT overnight. The reaction mixture was then warmed to RT and was stirred overnight. The reaction mixture was diluted with EtOAc (20 ml), washed with H_2O, brine, dried with magnesium sulfate, filtered, concentrated *in vacuo* by rotary evaporation, and chromatographed (silica gel, 4.5% MeOH/ CH_2Cl_2) to yield the title compound (138 mg, 69%): 1H NMR: 8.90 (s, 1), 8.60 (s, 1H), 8.30 (s, 1H), 7.95-8.10 (m, 4H), 7.85-7.95 (m, 1H), 7.70 (d, 1H), 7.35-7.50 (m, 3H), 4.75-4.85 (m, 1H), 4.10 (d, 1H), 4.0 (bs, 1H), 3.85 (bs, 1H), 3.80 (s, 1H), 3.45 (d, 1H), 1.60-1.75 (m, 3H), 1.40-1.50 (m, 1H), 0.90-1.0 (m, 9H); Electrospray mass spec: $M+H^+ = 554.28$ ($M+H^+$); 1107.38 ($2M + H^+$).

m. Quinoline-6-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide

Sulfur trioxide-pyridine complex (11 mg, 0.7 mmol) was added to a solution of quinoline-6-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide (130 mg, 0.235 mmol) in DMSO (2.0 ml) and triethylamine (0.2 ml, 1.4 mmol) was stirred at RT for 1 h. The reaction was incomplete; therefore, additional triethyl amine (0.2 ml, 1.4 mmol) and sulfur trioxide-pyridine complex (11 mg, 0.7 mmol) was added and the reaction was stirred an additional hour. The reaction mixture was diluted with water, then was extracted with EtOAc. Then, the organic layer was was extracted with brine. The combined organics were dried with magnesium sulfate, filtered, concentrated in vacuo, and purified by column chromatography (3% MeOH/CH_2Cl_2) gave the title compound (100 mg, 77%): 1H NMR:9.0 (sm 1H), 8.70 (s, 1H), 7.90-8.30 (m, 6H), 7.50-7.55 (m, 2H), 7.10 (d, 1H), 7.0 (d, 1H), 5.10-5.15 (m, 1H), 4.70-4.80 (m,2H), 4.35-4.40 (m, 1H), 3.85 (d, 1H), 2.0-2.25 (m, 3H), 1.70-1.80 (m, 2H), 1.60-1.70 (m, 2H), 0.90-1.10 (m, 9H); Electrospray mass spec: $M+H^+ = 552.4$

Example 13

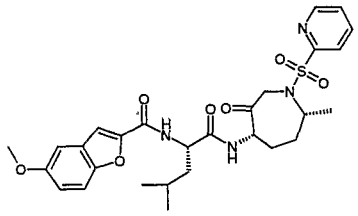
Preparation of Quinoline-3-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide



Following the procedure of Example 12 (a-m), except substituting "quinoline-3-carboxylic acid" for "quinoline-6-carboxylic acid" gave the title compound: 1H NMR: 9.30 (s, 1H), 8.70 (s, 1H), 8.60 (s, 1H), 8.20 (d, 1H), 7.80-8.0 (m, 4H), 7.65 (t, 1H), 7.50 9d, 1H), 7.20 (d, 1H), 7.10 (d, 1H), 5.70-5.85 (m, 2H), 5.10-5.20 (m, 1H), 4.35-4.45 (m, 1H), 3.85 (d, 1H), 2.10-2.25 (m, 2H), 1.70-1.80 (m, 3H), 1.45-1.65 (m, 2H), 0.90-1.10 (m, 9H); Electrospray mass spec: $M+H^+ = 552.4$.

Example 14

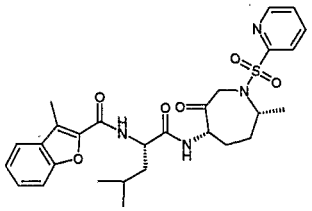
Preparation of 5-Methoxy-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide



Following the procedure of Example 12 (a-m), except substituting "5-methoxy-benzofuran-2-carboxylic acid" for "quinoline-6-carboxylic acid" gave the title compound: 1H NMR: 8.73 (d,1H), 7.95(m,2H), 7.55(m,1H), 7.43(m,2H), 7.09 (m,3H), 6.93(d,1H), 5.15(m,1H), 4.78(d,1H), 4.71(m,1H), 4.43(m,1H), 3.89(d,1H), 3.86(s,3H), 2.18(m,2H), 1.56-1.77(m,5H), 0.95(m,9H). Electrospray mass spec: $M+H^+ = 571.4$ $(M+H)^+$.

Example 15

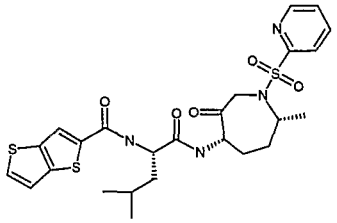
Preparation of 3-Methyl-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide



Following the procedure of Example 12 (a-m), except substituting "3-methyl-benzofuran-2-carboxylic acid" for "quinoline-6-carboxylic acid" gave the title compound: 1H NMR: 8.74(d,1H), 8.02(d,1H), 7.95(m, 1H), 7.62(d,1H), 7.54(m,3H), 7.05(d,1H), 6.93(d,1H), 5.14(m,1H), 4.78(d,1H), 4.71(m,1H), 4.43(m,1H), 3.87(d,1H), 2.64(s,3H), 2.19 (m,2H), 1.5-1.76(m,5H), 1.0(m, 10H); Electrospray mass spec: $M+H^+ = 555.2$ $(M+1)^+$.

Example 16

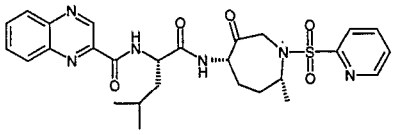
Preparation of Thieno[3,2-b]thiophene-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide



Following the procedure of Example 12 (a-m), except substituting "thieno[3,2-b]thiophene-2-carboxylic acid" for "quinoline-6-carboxylic acid" gave the title compound: 1H NMR: 8.74(d,1H), 8.02(d,1H), 7.95(m,1H), 7.78(s,1H), 7.54(m,2H), 6.90(d,1H), 6.59(d,1H), 5.15(m,1H), 4.78(d,1H), 4.70(m,1H), 4.43(m,1H), 3.88(d,1H), 2.19(m,2H), 1.50-1.72(m.5H), 1.00(m, 10H) ; Electrospray mass spec: $M+H^+ = 563.2$ $(M+1)^+$.

Example 17

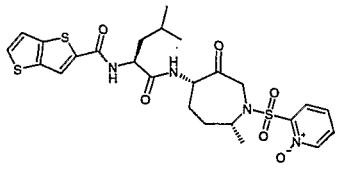
Preparation of Quinoxaline-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide



Following the procedure of Example 12 (a-m), except substituting "quinoxaline-2-carboxylic acid" for "quinoline-6-carboxylic acid" gave the title compound: 1H NMR: 9.70 (s, 1H), 8.70 (s, 1H), 8.40 (d, 1H), 8.20 (d, 2H), 7.85-8.0 (m, 1H), 7.50 (d, 1H), 7.0 (d, 1H), 5.10-5.15 (m, 1H), 4.70-4.80 (m, 2H), 4.40-4.50 (m, 1H), 3.90 (d, 1H), 2.10-2.20 (m, 2H), 1.70-1.90 (m, 3H), 1.40-1.70 (m, 2H), 0.90-1.05 (m, 9H); Electrospray mass spec: $M+H^+ = 553.4$.

Example 18

Preparation of Thieno[3,2-b] thiophene-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide

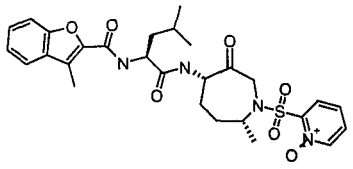


Following the procedure of Example 12 (a-m), except substituting "1-oxy-pyridine-2-sulfonyl chloride" for "pyridine-2-sulfonyl chloride" and "Thieno[3,2-b] thiophene-2-carboxylic acid" for "quinoline-6-carboxylic acid" gave the title compound: 1H NMR: 8.27 (d, 1H), 8.13 (dd, 1H), 7.55-7.41 (m, 3H), 7.28 (m, 2H), 6.95 (m, 1H), 6.65 (m, 1H), 5.03

(m, 1H), 4.89 (d, 1H), 4.68 (m, 1H), 4.36 (m, 1H), 3.98 (d, 1H), 2.30-2.12 (m, 2H), 1.74 (m, 5H), 1.06 (d, 3H), 1.00 (m, 6H); Electrospray mass spec: $M+H^+ = 579.2$.

Example 19

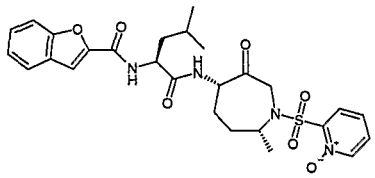
Preparation of 3-Methyl-benzofuran-2-carboxylicacid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide



Following the procedure of Example 12 (a-m), except substituting "1-oxy-pyridine-2-sulfonyl chloride" for "pyridine-2-sulfonyl chloride" and "3-methyl-benzofuran-2-carboxylic acid" for "quinoline-6-carboxylic acid" gave the title compound: 1H NMR: 8.25 (d, 1H), 8.12 (dd, 1H), 7.61 (d, 1H), 7.50-7.39 (m, 3H), 7.30 (m, 1H), 7.05 (d, 1H), 6.95 (d, 1H), 5.03 (m, 1H), 4.89 (d, 1H), 4.71 (m, 1H), 4.36 (m, 1H), 3.98 (d, 1H), 2.62 (s, 3H), 2.25-2.12 (m, 2H), 1.89 (m, 2H), 1.75 (m, 2H), 1.63 (m, 1H), 1.53 (m, 1H), 1.05 (d, 3H), 1.00 (m, 6H); Electrospray mass spec: $M+H^+ = 571.4$.

Example 20

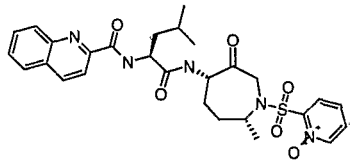
Preparation of Benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide



Following the procedure of Example 12 (a-m), except substituting "1-oxy-pyridine-2-sulfonyl chloride" for "pyridine-2-sulfonyl chloride" and "benzofuran-2-carboxylic acid" for "quinoline-6-carboxylic acid" gave the title compound: 1H NMR: 8.23 (d, 1H), 8.12 (dd, 1H), 7.67 (d, 1H), 7.52 (d, 1H), 7.48-7.39 (m, 3H), 7.31 (m, 1H), 7.08 (d, 1H), 6.93 (d, 1H), 5.05 (m, 1H), 4.91 (d, 1H), 4.71 (m, 1H), 4.37 (m, 1H), 3.99 (d, 1H), 2.30-2.10 (m, 2H), 1.75-1.50 (m, 6H), 1.05 (d, 3H), 1.01 (m, 6H); Electrospray mass spec: $M+H^+ = 557.2$.

Example 21

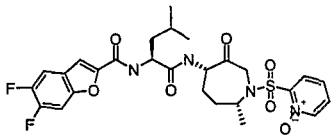
Preparation of Quinoline-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide



Following the procedure of Example 12 (a-m), except substituting "1-oxy-pyridine-2-sulfonyl chloride" for "pyridine-2-sulfonyl chloride" and "quinoline-2-carboxylic acid" for "quinoline-6-carboxylic acid" gave the title compound: 1H NMR: 8.65 (m, 2H), 8.49 (d, 1H), 8.23 (d, 1H), 8.11 (d, 1H), 8.05-7.95 (m, 2H), 7.80 (t, 1H), 7.46 (t, 1H), 7.39 (t, 1H), 5.02 (m, 1H), 4.85 (d, 1H), 4.75 (m, 1H), 4.39 (m, 1H), 3.93 (d, 1H), 2.30-2.08 (m, 3H), 1.97-1.80 (m, 4H), 1.70-1.52 (m, 2H), 1.07-0.99 (m, 9H); Electrospray mass spec: $M+H^+ = 568.2$.

Example 22

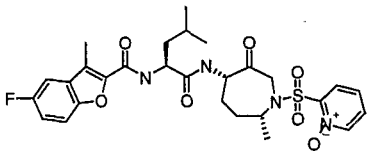
Preparation of 5,6-Difluoro-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide



Following the procedure of Example 12 (a-m), except substituting "1-oxy-pyridine-2-sulfonyl chloride" for "pyridine-2-sulfonyl chloride" and "5,6-Difluoro-benzofuran-2-carboxylic acid" for "quinoline-6-carboxylic acid" gave the title compound: 1H NMR: 8.16 (1H, d), 8.04 (1H,d), 7.26-7.40 (m, 4H), 7.02 (1H, d), 6.89 (1H,d), 4.96 (m, 1H), 4.63 (m, 1H), 4.28 (m,1H), 2.10-2.25 (m, 2H), 1.44-1.65 (m, 3H), 1.17-1.20 (m, 3H), 0.93-0.97 (m, 9H); Liquid/Chromatgraphy/Electrospray mass spec: $M+H^+ = 593.23$

Example 23

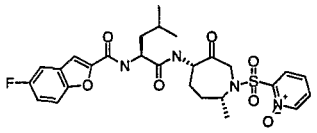
Preparation of 5-Fluoro-3-methyl-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide



Following the procedure of Example 12 (a-m), except substituting "1-oxy-pyridine-2-sulfonyl chloride" for "pyridine-2-sulfonyl chloride" and "5-Fluoro-3-methyl-benzofuran-2-carboxylic acid" for "quinoline-6-carboxylic acid" gave the title compound: 1H NMR: 8.15 (1H, d), 8.03 (1H, d), 7.31-7.39(m, 3H), 7.18 (m, 1H), 7.17 (m, 1H), 7.07 (d, 1H), 7.06 (d, 1H), 4.85 (m, 1H), 4.62 (m, 1H), 4.31 (m, 1H), 2.05-2.22 (m, 3H), 1.44-1.66 (m, 4H), 0.92-0.99 (m, 12H); Liquid/Chromatgraphy/Electrospray mass spec: $M+H^+ = 589.21$

Example 24

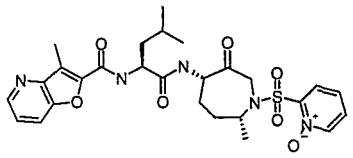
Preparation of 5-Fluoro-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide



Following the procedure of Example 12 (a-m), except substituting "1-oxy-pyridine-2-sulfonyl chloride" for "pyridine-2-sulfonyl chloride" and "5-Fluoro-benzofuran-2-carboxylic acid" for "quinoline-6-carboxylic acid" gave the title compound: 1H NMR: 8.22 (1H, d), 8.12 (1H, d), 7.32-7.46 (m, 7H), 7.13 (m, 1H), 6.98 (m, 1H), 5.05 (m, 1H), 4.76 (m, 1H), 4.36 (m, 1H), 2.11-2.28 (m, 2H), 1.51-1.78 (m, 3H), 0.99-1.02 (m, 12H); Liquid/Chromatgraphy/Electrospray mass spec: $M+H^+ = 575.16$

Example 25

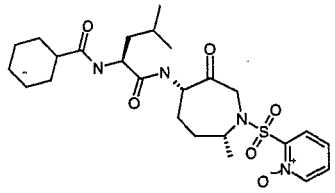
Preparation of 3-Methyl-furo[3,2-b]]pyridine-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide



Following the procedure of Example 12 (a-m), except substituting "1-oxy-pyridine-2-sulfonyl chloride" for "pyridine-2-sulfonyl chloride" and "3-Methyl-furo[3,2-b]]pyridine-2-carboxylic acid" for "quinoline-6-carboxylic acid" gave the title compound: 1H NMR: 8.56 (1H, d), 8.16 (1H, d), 8.03 (d, 1H), 7.73 (d, 1H), 7.38 (m, 1H), 7.29-7.34 (m, 2H), 7.13 (d, 1H), 6.93 (d, 1H), 4.97 (m, 1H), 4.66 (m, 1H), 4.26 (m, 1H), 2.05-2.13 (m, 2H), 1.46-1.67 (m, 3H), 1.11-1.16 (m, 3H), 0.92-0.97 (m, 9H); Liquid/ Chromatgraphy/ Electrospray mass spec: $M+H^+ = 572.23$

Example 26

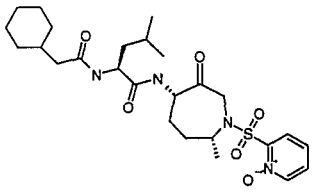
Preparation of Cyclohexanecarboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide



Following the procedure of Example 12 (a-m), except substituting "1-oxy-pyridine-2-sulfonyl chloride" for "pyridine-2-sulfonyl chloride" and "Cyclohexanecarboxylic acid" for "quinoline-6-carboxylic acid" gave the title compound: 1H NMR: 8.23 (d, 1H), 8.11 (dd, 1H), 7.46 (m, 1H), 7.39 (t, 1H), 6.90 (m, 1H), 5.91 (m, 1H), 4.98 (m, 1H), 4.87 (d, 1H), 4.48 (m, 1H), 4.36 (m, 1H), 3.96 (d, 1H), 2.24-2.08 (m, 2H), 1.90-1.62 (m, 10H), 1.54-1.39 (m, 3H), 1.33-1.21 (m, 3H), 1.05 (d, 3H), 0.95 (m, 6H); Electrospray mass spec: $M+H^+ =$ 523.4.

Example 27

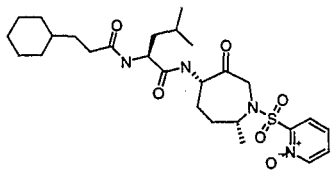
Preparation of (S)-2-(2-Cyclohexyl-ethanoylamino)-4-methyl-pentanoic acid [(4S,7R)-7-methyl-3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-yl]-amide



Following the procedure of Example 12 (a-m), except substituting "1-oxy-pyridine-2-sulfonyl chloride" for "pyridine-2-sulfonyl chloride" and " Cyclohexyl-acetic acid" for "quinoline-6-carboxylic acid" gave the title compound: 1H NMR: 8.23 (d, 1H), 8.11 (dd, 1H), 7.45 (t, 1H), 7.39 (t, 1H), 6.95 (m, 1H), 5.95 (m, 1H), 4.99 (m, 1H), 4.87 (d, 1H), 4.48 (m, 1H), 4.36 (m, 1H), 3.96 (d, 1H), 2.18 (m, 2H), 2.07 (m, 2H), 1.91 (m, 2H), 1.74-1.58 (m, 10H), 1.53 (m, 2H), 1.34-1.12 (m, 3H), 1.05 (d, 3H), 0.95 (m, 6H); Electrospray mass spec: $M+H^+ = 537.4$.

Example 28

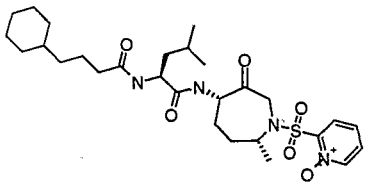
Preparation of (S)-2-(3-Cyclohexyl-propanoylamino)-4-methyl-pentanoic acid [(4S,7R)-7-methyl-3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-yl]-amide



Following the procedure of Example 12 (a-m), except substituting "1-oxy-pyridine-2-sulfonyl chloride" for "pyridine-2-sulfonyl chloride" and "3-cyclohexyl-propionic acid" for "quinoline-6-carboxylic acid" gave the title compound: 1H NMR: 8.23 (d, 1H), 8.11 (dd, 1H), 7.45 (m, 1H), 7.39 (t, 1H), 6.90 (m, 1H), 5.93 (m, 1H), 4.99 (m, 1H), 4.87 (d, 1H), 4.48 (m, 1H), 4.38 (m, 1H), 3.97 (d, 1H), 2.25-2.19 (m, 4H), 1.80 (m, 2H), 1.71-1.50 (m, 12H), 1.28-1.15 (m, 4H), 1.05 (d, 3H), 0.95 (m, 6H); Electrospray mass spec: $M+H^+ =$ 551.4.

Example 29

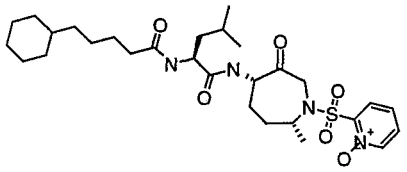
Preparation of (S)-2-(4-Cyclohexyl-butanoylamino)-4-methyl-pentanoic acid [(4S,7R)-7-methyl-3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-yl]-amide



Following the procedure of Example 12 (a-m), except substituting "1-oxy-pyridine-2-sulfonyl chloride" for "pyridine-2-sulfonyl chloride" and "4-cyclohexyl-butyric acid" for "quinoline-6-carboxylic acid" gave the title compound: 1H NMR: 8.22 (d, 1H), 8.11 (dd, 1H), 7.44 (m, 1H), 7.39 (t, 1H), 6.86 (d, 1H), 5.87 (d, 1H), 5.00 (m, 1H), 4.87 (d, 1H), 4.50 (m, 1H), 4.39 (m, 1H), 3.97 (d, 1H), 2.18 (m, 4H), 1.74-1.50 (m, 12H), 1.28-1.12 (m, 6H), 1.05 (d, 3H), 0.95 (m, 6H), 0.91-0.86 (m, 2H); Electrospray mass spec: $M+H^+ = 565.4$.

Example 30

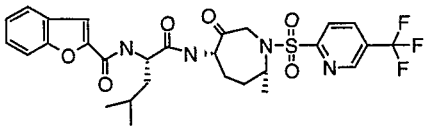
Preparation of (S)-2-(5-Cyclohexyl-pentanoylamino)-4-methyl-pentanoic acid [(4S,7R)-7-methyl-3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-yl]-amide



Following the procedure of Example 12 (a-m), except substituting "1-oxy-pyridine-2-sulfonyl chloride" for "pyridine-2-sulfonyl chloride" and "5-cyclohexyl-pentanoic acid" for "quinoline-6-carboxylic acid" gave the title compound: 1H NMR: 8.23 (d, 1H), 8.11 (d, 1H), 7.46 (m, 1H), 7.39 (t, 1H), 6.88 (d, 1H), 5.88 (m, 1H), 5.01 (m, 1H), 4.88 (d, 1H), 4.50 (m, 1H), 4.38 (m, 1H), 3.97 (d, 1H), 2.20 (m, 4H), 1.71-1.50 (m, 12H), 1.34 (m, 2H), 1.26-1.13 (m, 6H), 1.05 (d, 3H), 0.95 (m, 6H), 0.91-0.85 (m, 2H); Electrospray mass spec: $M+H^+ = 579.4$.

Example 31

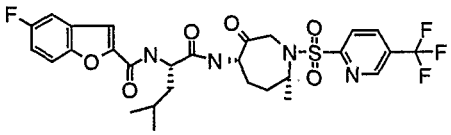
Preparation of Benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(5-trifluoromethyl-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide



Following the procedure of Example 12 (a-m), except substituting "5-trifluoromethyl-pyridine-2-sulfonyl chloride" for "pyridine-2-sulfonyl chloride" and "benzofuran-2-carboxylic acid" for "quinoline-6-carboxylic acid" gave the title compound: 1H NMR: 8.95 (s, 1H), 8.10-8.20 (m, 2H), 7.65 (d, 1H), 7.30-7.60 (m, 3H), 7.20-7.30 (m, 1H), 7.10 (d, 1H), 6.90 (d, 1H), 5.05-5.15 (m, 1H), 4.70-4.80 (m, 2H), 4.30-4.45 (m, 1H), 3.80 (d, 1H), 2.10-2.20 (m, 2H), 1.40-1.80 (m, 5H), 0.90-1.10 (m, 9H); Electrospray mass spec: $M+H^+ = 609.2$.

Example 32

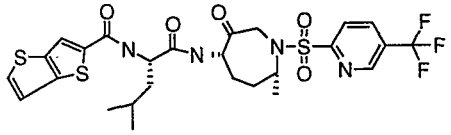
Preparation of 5-Fluoro-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(5-trifluoromethyl-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide



Following the procedure of Example 12 (a-m), except substituting "5-trifluoromethyl-pyridine-2-sulfonyl chloride" for "pyridine-2-sulfonyl chloride" and "5-fluoro-benzofuran-2-carboxylic acid" for "quinoline-6-carboxylic acid" gave the title compound: 1H NMR: 9.0 (s, 1H), 8.20 (d, 1H), 8.12 (d, 1H), 7.40-7.50 (m, 2H), 7.30 (d, 1H), 7.20 (d, 1H), 6.90 (d, 1H), 5.05-5.15 (m, 1H), 4.65-5.75 (m, 2H), 4.40-4.50 (m, 1H), 3.90 (d, 1H), 2.00-2.30 (m, 2H), 1.50-1.80 (m, 5H), 0.95-1.10 (m, 9H); Electrospray mass spec: $M+H^+ = 627.2$.

Example 33

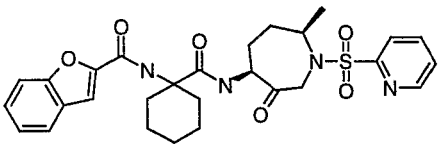
Preparation of Thieno[3,2-b] thiophene-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(5-trifluoromethyl-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide



Following the procedure of Example 12 (a-m), except substituting "5-trifluoromethyl-pyridine-2-sulfonyl chloride" for "pyridine-2-sulfonyl chloride" and "thieno[3,2-b] thiophene-2-carboxylic acid" for "quinoline-6-carboxylic acid" gave the title compound: 1H NMR: 9.0 (s, 1H), 8.10-8.20 (m, 2H), 7.80 (s, 1H), 7.50 (s, 1H), 7.25 (s, 1H), 7.0 (d, 1H), 6.80 (d, 1H), 5.0-5.10 (m, 1H), 4.60-4.80 (m, 2H), 4.40-4.50 (m, 1H), 3.90 (d, 1H), 2.10-2.20 (m, 2H), 1.50-1.80 (m, 5H), 0.9-1.0 (m, 9H); Electrospray mass spec: $M+H^+ = 631.2$.

Example 34

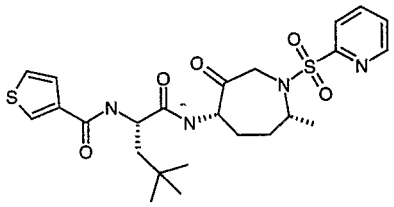
Preparation of Benzofuran-2-carboxylic acid {1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-cyclohexyl}-amide



Following the procedure of Example 12 (a-m), except substituting "N-Boc-amino-cyclohexane carboxylic acid" for "Boc-L-leucine" and "benzofuran-2-carboxylic acid" for "quinoline-6-carboxylic acid" gave the title compound: 1H NMR: 8.74-8.73 (s, 1H), 8.02-7.91(m, 2H), 7.71-7.69(d, 1H), 7.58-7.28(m, 6H), 6.73(s, 1H) 5.10-5.08(m, 1H), 4.78-4.73(d,1H), 4.44-4.13(m, 1H), 3.86-3.81(d, 1H), 2.33-2.01 (m, 6H), 1.98-1.40(m,8H), 0.99-0.97(d, 3H); Electrospray mass spec: $M+H^+ = 553.4$.

Example 35

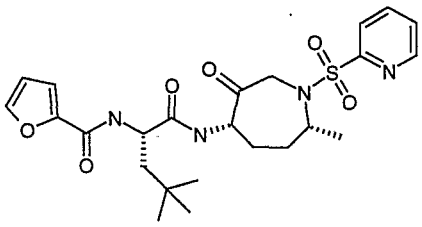
Preparation of Thiophene-3-carboxylic acid {(S)-3,3-dimethyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide



Following the procedure of Example 12 (a-m), except substituting "N-Boc-tert-butylalanine" for "Boc-L-leucine" and "thiophene-3-carboxylic acid" for "quinoline-6-carboxylic acid" gave the title compound: 1H NMR: 8.72(m, 1 H), 7.96(m, 2 H), 7.48(m, 2 H), 7.00(m, 3 H), 6.60(m, 2 H), 5.18(m, 1 H), 4.67(m, 2 H), 4.42(m, 1 H), 3.88(m, 1H), 2.87(m, 2 H), 2.22(m, 2 H), 1.95(m, 1 H), 1.70(m, 2 H), 1.01(m, 12 H); Electrospray mass spec: $M+H^+ = 521.4$.

Example 36

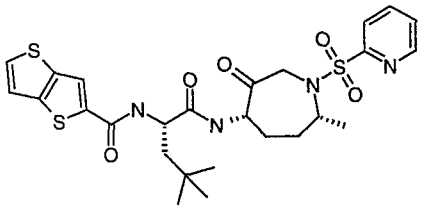
Preparation of Furan-2-carboxylic acid {(S)-3,3-dimethyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide



Following the procedure of Example 12 (a-m), except substituting "N-Boc-tert-butylalanine" for "Boc-L-leucine" and "furan-2-carboxylic acid" for "quinoline-6-carboxylic acid" gave the title compound: 1H NMR: 8.73(d, 1 H), 7.95(m, 3 H), 7.54(m, 1 H), 7.41(m, 1H), 7.32(m, 1H), 7.26(s, 1 H), 7.01(d, 1 H), 6.56(d, 1 H), 5.08(m, 1 H), 4.73(m, 2 H), 4.43(m, 1 H), 3.88(d, 1 H), 2.18(m, 2 H), 1.70(m, 3 H), 1.04(s, 9 H), 0.98(d, 3 H); Electrospray mass spec: $M+H^+ = 505.4$.

Example 37

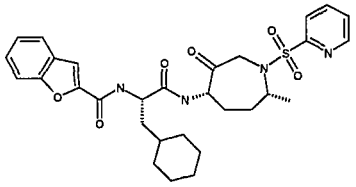
Preparation of Thieno[3,2-b] thiophene-2-carboxylic acid {(S)-3,3-dimethyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide



Following the procedure of Example 12 (a-m), except substituting "N-Boc-tert-butylalanine" for "Boc-L-leucine" and "thieno[3,2-b] thiophene-2-carboxylic acid" for "quinoline-6-carboxylic acid" gave the title compound: 1H NMR: 8.73(d, 1 H), 7.92(m, 3 H), 7.52(m, 2 H), 7.27(m, 1H), 7.09(br, 1 H), 6.80(br, 1 H), 5.10(m, 1 H), 4.77(m, 2 H), 4.40(m, 1 H), 3.87(d, 1 H), 1.90(m, 5 H), 1.05(s, 9 H), 0.95(d, 3 H); Electrospray mass spec: $M+H^+ = 577.2$.

Example 38

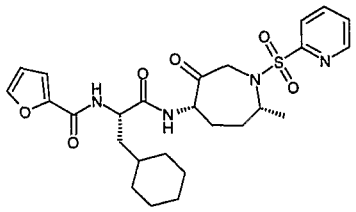
Preparation of Benzofuran-2-carboxylic acid {(S)-2-cyclohexyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide



Following the procedure of Example 12 (a-m), except substituting "N-Boc-L-cyclohexylalanine" for "Boc-L-leucine" and "benzofuran-2-carboxylic acid" for "quinoline-6-carboxylic acid" gave the title compound: 1H NMR: 8.74(d, 1 H), 7.96(m, 3 H), 7.55(m, 1 H), 7.42(m, 2 H), 7.28(m, 2 H), 6.77(d, 1 H), 6.51(m, 1 H), 5.14(m, 1 H), 4.77(d, 1 H), 4.69(m, 1 H), 4.43(m, 1 H), 3.85(d, 1 H), 2.18(m, 2 H), 1.85-0.98(m, 18 H); Electrospray mass spec: $M+H^+ = 581.3$.

Example 39

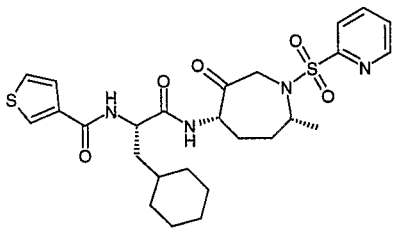
Preparation of Furan-2-carboxylic acid {(S)-2-cyclohexyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide



Following the procedure of Example 12 (a-m), except substituting "N-Boc-L-cyclohexylalanine" for "Boc-L-leucine" and "furan-2-carboxylic acid" for "quinoline-6-carboxylic acid" gave the title compound: 1H NMR: 8.73(d, 1 H), 7.62(m, 2 H), 7.53(m, 2 H), 7.13(s, 1 H), 6.94(d, 1 H), 6.77(d, 1 H), 6.51(m, 1 H), 5.18(m, 1 H), 4.77(d, 1 H), 4.63(m, 1 H), 4.25(m, 1 H), 3.86(d, 1 H), 2.10(m, 2 H), 1.87-0.93(m, 18 H); Electrospray mass spec: $M+H^+ = 531.2$.

Example 40

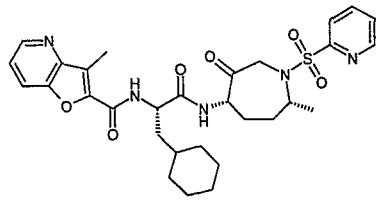
Preparation of Thiophene-3-carboxylic acid {(S)-2-cyclohexyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide



Following the procedure of Example 12 (a-m), except substituting "N-Boc-L-cyclohexylalanine" for "Boc-L-leucine" and "thiophene-3-carboxylic acid" for "quinoline-6-carboxylic acid" gave the title compound: 1H NMR: 8.74(d, 1 H), 8.00(m, 2 H), 7.66(d, 1 H), 7.46(m, 3 H), 7.28(d, 1 H), 6.90(d, 1 H), 5.14(m, 1 H), 4.43(m, 1 H), 3.82(d, 1 H), 2.16(m, 2 H), 1.90-0.96(m, 18 H); Electrospray mass spec: $M+H^+ = 547.2$.

Example 41

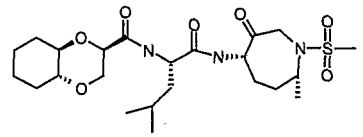
Preparation of 3-Methyl-furo[3,2-b]- pyridine-2-carboxylic acid {(S)-2-cyclohexyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide



Following the procedure of Example 12 (a-m), except substituting "N-Boc-L-cyclohexylalanine" for "Boc-L-leucine" and "3-Methyl-furo[3,2-b]- pyridine-2-carboxylic acid" for "quinoline-6-carboxylic acid" gave the title compound: 1H NMR: 8.75(d, 1 H), 7.98(m, 2 H), 7.55(m, 1 H), 7.40(m, 2 H), 7.33(m, 1 H), 6.75(d, 1 H), 6.50(m, 1 H), 5.09(m, 1 H), 4.79(d, 1 H), 4.68(m, 1 H), 4.47(m, 1 H), 3.87(d, 1 H), 2.55(s,3 H), 2.17(m, 1 H), 1.93-0.93(m, 19 H); Electrospray mass spec: $M+H^+ = 596.4$.

Example 42

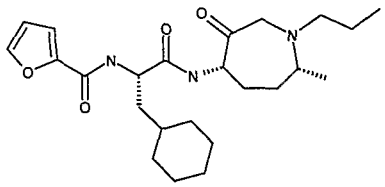
Preparation of (2R,4aR,8aR)-Octahydro-benzo[1,4]dioxine-2-carboxylic acid [(S)-1-((4S,7R)-1-methanesulfonyl-7-methy l-3-oxo-azepan-4-ylcarbamoyl)-3-methyl-butyl]-amide



Following the procedure of Example 12 (a-m), except substituting "methyl sulfonylchloride" for "pyridine-2-sulfonyl chloride" and "(2R,4aR,8aR)-Octahydro-benzo[1,4]dioxine-2-carboxylic acid" for "quinoline-6-carboxylic acid" gave the title compound: 1H NMR: 7.65 (d, 1H), 5.0 (d, 1H), 4.45-4.50 (m, 1H), 4.30-4.35 (m, 1H), 4.25 (d, 1H), 4.0 (d, 1H), 3.80 (d, 1H), 3.50 (t, 1H), 3.30 (s, 2H), 3.15-3.2 (m, 1H), 3.30 (s, 1H), 1.3-2.2 (m, 15H), 1.20 (d, 3H), .0 (t, 6H); Electrospray mass spec: $M+H^+ = 502.4$.

Example 43

Preparation of Furan-2-carboxylic acid [(S)-2-cyclohexyl-1-((4S,7R)-7-methyl-3-oxo-1-propyl-azepan-4-ylcarbamoyl)-ethyl]-amide



a. [(S)-2-Cyclohexyl-1-((3S,4S,7R)-3-hydroxy-7-methyl-1-propyl-azepan-4-ylcarbamoyl)-ethyl]-carbamic acid tert-butyl ester

[(S)-2-Cyclohexyl-1-((3S,4S,7R)-3-hydroxy-7-methyl-azepan-4-ylcarbamoyl)-ethyl]-carbamic acid-tert-butyl ester (Example 12 a-e, except substituting "Boc-L-cyclohexylalanine" for "Boc-L-leucine", 1.5 g, 3.78 mmol) was dissolved in CH_2Cl_2(30 mL), then propionaldehyde (0.41 mL, 5.67 mmol) was added. Then, sodium borohydride (1.6 g, 7.56 mmol) was added and the reaction mixture was stirred at RT for 1 h. The reaction mixture was concentrated *in vacuo* by rotary evaporation, then the filtrate (silica gel, 1-4% MeOH/ CH_2Cl_2) to yield the title compound as a white solid (84%, 1.4 g): Electrospray mass spec: $M+H^+ = 440.4$.

b. (S)-2-Amino-3-cyclohexyl-N-((3S,4S,7R)-3-hydroxy-7-methyl-1-propyl-azepan-4-yl)-propionamide

HCl in dioxane (4.0 M, 15 ml) was added to a stirred solution of [(S)-2-Cyclohexyl-1-((3S,4S,7R)-3-hydroxy-7-methyl-1-propyl-azepan-4-ylcarbamoyl)-ethyl]-carbamic acid tert-butyl ester (1.4 g, 3.0 mmol) in MeOH (5 ml). The reaction mixture was stirred for 2h at RT, then was concentrated *in vacuo* by rotary evaporation and was used in the next reaction without further purification (1.4 g).

c. Furan-2-carboxylic acid [(S)-2-cyclohexyl-1-((3S,4S,7R)-3-hydroxy-7-methyl-1-propyl-azepan-4-ylcarbamoyl)-ethyl]-amide

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide (0.10 g, 0.53 mmol) was added to a solution of furan-2-carboxylic acid (0.059 g, 0.53 mmol), (S)-2-Amino-3-cyclohexyl-N-((3S,4S,7R)-3-hydroxy-7-methyl-1-propyl-azepan-4-yl)-propionamide (0.15 g, 0.36 mmol), 4-methylmorpholine (0.14 g, 0.16 ml, 1.44 mmol), hydroxybenztriazole (0.071 g, 0.53 mmol) in DMF (2.0 ml) and was stirred at RT overnight. The reaction mixture was then warmed to RT and was stirred overnight. The reaction mixture was diluted with EtOAc (30

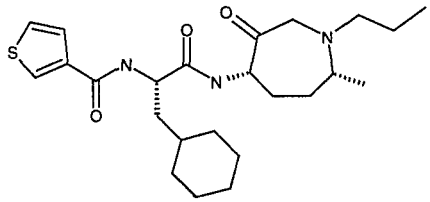
ml), washed with H_2O, brine, dried with magnesium sulfate, filtered, concentrated *in vacuo* by rotary evaporation, and chromatographed (silica gel, 2.5% MeOH/ CH_2Cl_2) to yield the title compound (0.12 g, 76%): Electrospray mass spec: $M+H^+ = 434.2$.

d. Furan-2-carboxylic acid [(S)-2-cyclohexyl-1-((4S,7R)-7-methyl-3-oxo-1-propyl-azepan-4-ylcarbamoyl)-ethyl]-amide

Sulfur trioxide-pyridine complex (0.0.35 g, 2.2 mmol) was added to a solution of Furan-2-carboxylic acid [(S)-2-cyclohexyl-1-((3S,4S,7R)-3-hydroxy-7-methyl-1-propyl-azepan-4-ylcarbamoyl)-ethyl]-amide (0.19 g, 0.44 mmol) in DMSO (4.0 ml) and triethylamine (0.61 ml, 4.4 mmol) was stirred at RT for 1 h. The reaction mixture was diluted with water, then was extracted with EtOAc. Then, the organic layer was was extracted with brine. The combined organics were dried with magnesium sulfate, filtered, concentrated in vacuo, and purified by column chromatography (3% methanol/ methylene chloride) gave the title compound (0.15 mg, 79%): 1H NMR: 7.44(s, 1 H), 7.11(d, 1 H), 7.04(d, 1 H), 6.92(d, 1 H), 6.49(d, 1 H), 5.29(m, 1 H), 4.69(m, 1 H), 3.40(d, 1 H), 3.08(m, 2 H), 2.51(m, 2 H), 1.88-0.81(m, 29 H); Electrospray mass spec: $M+H^+ = 432.2$.

Example 44

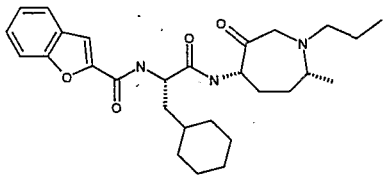
Preparation of Thiophene-3-carboxylic acid [(S)-2-cyclohexyl-1-((4S,7R)-7-methyl-3-oxo-1-propyl-azepan-4-ylcarbamoyl)-ethyl]-amide



Following the procedure of Example 43 (a-d), except substituting "thiophene-3-carboxylic acid" for "furan-2-carboxylic acid" gave the title compound: 1H NMR: 7.62(d, 1 H), 7.40(d, 1 H), 7.04(d, 1 H), 6.80(d, 1 H), 6.45(d, 1 H), 5.27(m, 1 H), 4.66(m, 1 H), 3.44(d, 1 H), 3.09(m, 2 H), 2.54(m, 2 H), 1.87-0.87(m, 29 H); Electrospray mass spec: $M+H^+ = 448.4$.

Example 45

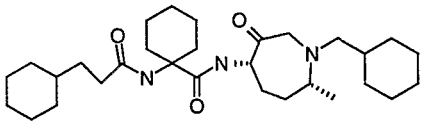
Preparation of Benzofuran-2-carboxylic acid [(S)-2-cyclohexyl-1-((4S,7R)-7-methyl-3-oxo-1-propyl-azepan-4-ylcarbamoyl)-ethyl]-amide



Following the procedure of Example 43 (a-d), except substituting "benzofuran-2-carboxylic acid" for "furan-2-carboxylic acid" gave the title compound: 1H NMR: 7.98(d, 1 H), 7.45(m, 2 H), 7.27(s, 2 H), 6.90(d, 1 H), 6.50(d, 1 H), 5.28(m, 1 H), 4.67(m, 1 H), 3.40(d, 1 H), 3.06(m, 2 H), 2.56(m, 2 H), 1.88-0.80(m, 29 H); Electrospray mass spec: $M+H^+$ = 482.4.

Example 46

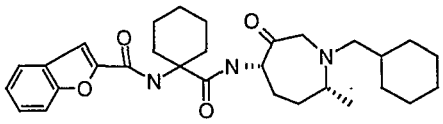
Preparation of 1-(3-Cyclohexyl-propanoylamino)-cyclohexanecarboxylic acid ((4S,7R)-1-cyclohexylmethyl-7-methyl-3-oxo-azepan-4-yl)-amide



Following the procedure of Example 43 (a-d), except substituting "N-Boc-amino-cyclohexane carboxylic acid" for "Boc-L-cyclohexylalanine" and "cyclohexanecarbaldehyde" for "propionaldehyde" and "cyclohexyl-3-propionic acid" for "furan-2-carboxylic acid" gave the title compound: 1H NMR: 7.40 (d, 1H), 7.15 (d, 1H), 5.10-5.20 (m, 1H), 3.40 (d, 1H), 3.00-3.10 (m, 2H), 0.80-2.40 (m, 45H) ; Electrospray mass spec: $M+H^+$ = 502.4.

Example 47

Preparation of Benzofuran-2-carboxylic acid [1-((4S,7R)-1-cyclohexylmethyl-7-methyl-3-oxo-azepan-4-ylcarbamoyl)-cyclohexyl]-amide

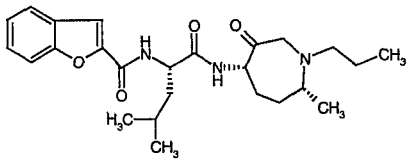


Following the procedure of Example 43 (a-d), except substituting "N-Boc-amino-cyclohexane carboxylic acid" for "Boc-L-cyclohexylalanine" and

"cyclohexanecarbaldehyde" for "propionaldehyde" and "benzofuran-2-carboxylic acid" for "furan-2-carboxylic acid" gave the title compound: 1H NMR: 7.60 (d, 1H), 7.30-7.50 (m, 3H), 7.15-7.25 (m, 2H), 6.60 (s, 1H), 5.00-5.10 (m, 1H), 3.35 (d, 1H), 2.90-3.05 (m, 3H), 1.05-2.40 (m, 26 H),0.80 (d, 3H); Electrospray mass spec: $M+H^+$ = 508.4.

Example 48

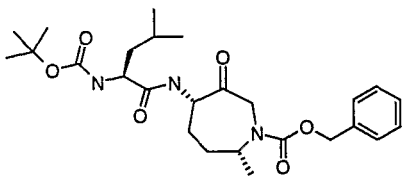
Preparation of Benzofuran-2-carboxylic acid [(S)-3-methyl-1-((4S,7R)-7-methyl-3-oxo-1-propyl-azepan-4-ylcarbamoyl)- butyl]-amide



Following the procedure of Example 43 (a-d), except substituting "N-Boc-L-leucine" for "Boc-L-cyclohexylalanine" and "benzofuran-2-carboxylic acid" for "furan-2-carboxylic acid" gave the title compound: Electrospray mass spec: $M+H^+$ = 442.05 (M + H).

Example 49

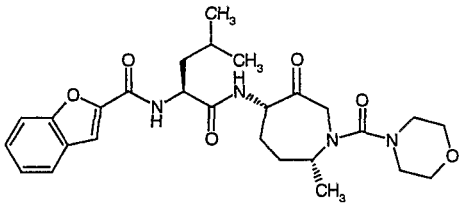
Preparation of (2R,5S)-5-((S)-2-tert-Butoxycarbonylamino-4-methyl-pentanoylamino)-2-methyl-6-oxo-azepane-1-carboxylic acid benzyl ester



Following the procedure of Example 12 (m), except substituting "(2R,5S)-5-((S)-2-tert-Butoxycarbonylamino-4-methyl-pentanoylamino)-2-methyl-6-hydroxy-azepane-1-carboxylic acid benzyl ester" for "quinoline-6-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide gave the title compound: 1H NMR: 7.40-7.35 (m, 5H), 5.26 (m, 1H), 5.13 (dd, 1H), 4.91-4.78 (m, 2H), 4.47 (m, 1H), 4.12 (m, 1H), 3.64 (dd, 1H), 2.32 (m, 1H), 2.10 (m, 1H), 1.70-1.52 (m, 5H), 1.45 (s, 9H), 1.12 (d, 3H), 0.96 (s, 3H), 0.94 (s, 3H); Electrospray mass spec: $M+H^+$ = 512.2.

Example 50

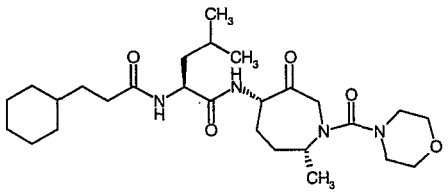
Preparation of Benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-1-(1-morpholin-4-yl-methanoyl)-3-oxo- azepan-4-ylcarbamoyl]-butyl}-amide



Following the procedure of Example 12 (a-m), except "morpholine-4-carbonyl chloride" for "pyridine-2-sulfonyl chloride" and "benzofuran-2-carboxylic acid" for "quinoline-6-carboxylic acid" gave the title compound: 1H NMR: 7.62 (d, 1H), 7.51 (d, 1H), 7.38 (m, 1H), 7.22 (m, 1H), 7.11 (d, 1H), 4.69 (m, 1H), 3.87 (m, 1H), 3.51 (m, 2H), 3.21 (m, 2H), 3.07 (m, 1H), 2.14 (m, 1H), 1.66-1.85 (m, 3H), 1.26 (m, 3H), 1.17 (m, 3H), 0.94 (m, 6H); Liquid/Chromatgraphy/Electrospray mass spec: $M+H^+ = 513.21$

Example 51

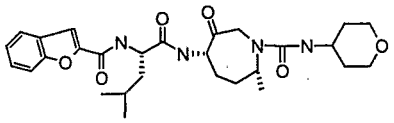
Preparation of (S)-2-(3-Cyclohexyl-propanoylamino)-4-methyl-pentanoic acid [(4S,7R)-7-methyl-1-(1-morpholin-4-yl-me thanoyl)-3-oxo-azepan-4-yl]-amide



Following the procedure of Example 12 (a-m), except "morpholine-4-carbonyl chloride" for "pyridine-2-sulfonyl chloride" and "cyclohexyl-3-propionic acid" for "quinoline-6-carboxylic acid" gave the title compound: 1H NMR: 6.94 (d, 1H), 5.85 (d, 1H), 4.59 (m, 1H), 4.40 (m, 1H), 3.61 (m, 4H), 3.19 (m, 2H), 3.10 (m, 2H), 2.02-2.28 (m, 4H), 1.77 (m, 1H), 1.50-1.69 (m, 6H), 1.32-1.46 (m, 4H), 1.25 (d, 2H), 1.01-1.19 (m, 4H), 0.87 (m, 6H); Liquid/Chromatgraphy/Electrospray mass spec: $M+H^+ = 507.27$.

Example 52

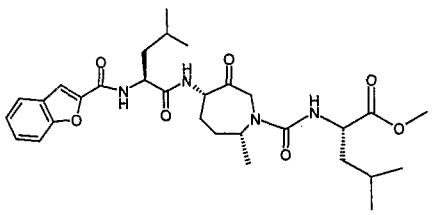
Preparation of (2R,5S)-5-{(S)-2-[(1-Benzofuran-2-yl-methanoyl)-amino]-4-methyl-pentanoylamino}-2-methyl-6-oxo-azepane-1-carboxylic acid (tetrahydro-pyran-4-yl)-amide



Following the procedure of Example 12 (a-m), except "tetrahydro-pyran-4-amino-carbonyl chloride" for "pyridine-2-sulfonyl chloride" and "benzofuran-2-carboxylic acid" for "quinoline-6-carboxylic acid" gave the title compound: 1H NMR: 7.65 (d, 1H), 7.40-7.50 (m, 3H), 7.20-7.30 (m, 1H), 7.05 (d, 1H), 6.90 (d, 1H), 5.00 (d, 1H), 4.80-4.90 (m, 1H), 4.65-4.80 (m, 1H), 4.50 (d, 1H), 3.85-4.00 (m, 4H), 3.40-3.50 (m, 5H), 2.30-2.40 (m, 1H), 1.90-2.05 (m, 3H), 1.40-1.75 (m, 5H), 1.20 (d, 3H), 1.00 (d, 6H); Electrospray mass spec: $M+H^+ = 527.4$.

Example 53

Preparation of (S)-2-{[1-((2R,5S)-5-{(S)-2-[(1-Benzofuran-2-yl-methanoyl)-amino]-4-methyl-pentanoylamino}-2-methyl-6-oxo-azepan-1-yl)-methanoyl]-amino}-4-methyl-pentanoic acid methyl ester



a. (S)-2-({1-[(2R,5S)-5-((S)-2-tert-Butoxycarbonylamino-4-methyl-pentanoylamino)-2-methyl-6-hydroxy-azepan-1-yl]-methanoyl}-amino)-4-methyl-pentanoic acid methyl ester

[(S)-3-Methyl-1-((4S,7R)-7-methyl-3-hydroxy-azepan-4-ylcarbamoyl)-butyl]-carbamic acid tert-butyl ester (Example 12a-i, 500 mg, 1.4 mmol) was dissolved in THF (7 ml), then (S)-(-)-2-isocyanato-4-methylvaleric acid methyl ester (180 mg, 1.05 mmol) was added and the reaction mixture was stirred at RT for 2 h. The reaction mixture was concentrated *in vacuo* by rotary evaporation, and chromatographed (silica gel, 1 % to 2 % MeOH/ CH_2Cl_2) to yield the title compound as a white solid (91 %, 506 mg): LC/Electrospray mass spec: $M+H^+ = 529.4$.

b. (S)-2-({1-[(2R,5S)-5-((S)-2-Amino-4-methyl-pentanoylamino)-2-methyl-6-hydroxy-azepan-1-yl]-methanoyl}-amino)-4-methyl-pentanoic acid methyl ester

4.0 M HCl in dioxane (8 ml) was added to a stirred solution (S)-2-({1-[(2R,5S)-5-((S)-2-tert-Butoxycarbonylamino-4-methyl-pentanoylamino)-2-methyl-6-hydroxy-azepan-1-yl]-methanoyl}-amino)-4-methyl-pentanoic acid methyl ester (490 mg, 0.93 mmol) in MeOH (8 ml). The reaction mixture was stirred for 2.5 h at RT, then was concentrated *in vacuo* by rotary evaporation and was used in the next reaction without further purification (430 mg).

c.(S)-2-{[1-((2R,5S,6S)-5-{(S)-2-[(1-Benzofuran-2-yl-methanoyl)-amino]-4-methyl-pentanoylamino}-6-hydroxy-2-methyl-azepan-1-yl)-methanoyl]-amino}-4-methyl-pentanoic acid methyl ester

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide (214 g, 1.12 mmol) was added to a solution of benzofuran-2-carboxylic acid (166 g, 1.02 mmol), (S)-2-({1-[(2R,5S)-5-((S)-2-Amino-4-methyl-pentanoylamino)-2-methyl-6-hydroxy-azepan-1-yl]-methanoyl}-amino)-4-methyl-pentanoic acid methyl ester (430 mg, 0.93 mmol), diisopropylethylamine (240 mg, 0.32 ml, 1.86 mmol), hydroxybenztriazole (151 mg, 1.12 mmol) in DMF (5 ml) and was stirred at RT overnight. The reaction mixture was stirred overnight. The reaction mixture was diluted with EtOAc (30 ml), washed with cold aq. 1N HCl , aq. sat. $NaHCO_3$, and brine, and then dried with magnesium sulfate, filtered, concentrated *in vacuo* by rotary evaporation, and chromatographed (silica gel, 2% to 3% MeOH/ CH_2Cl_2) to yield the title compound (478 mg, 84 % for two steps): electrospray MS: 572.4

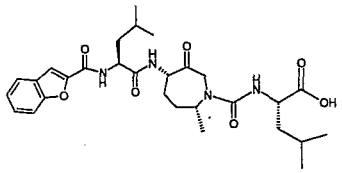
d.(S)-2-{[1-((2R,5S,6S)-5-{(S)-2-[(1-Benzofuran-2-yl-methanoyl)-amino]-4-methyl-pentanoylamino}-6-oxo-2-methyl-azepan-1-yl)-methanoyl]-amino}-4-methyl-pentanoic acid methyl ester

Dess-Martin periodinane (500 mg, 1.18 mmol) was added to a solution of (S)-2-{[1-((2R,5S,6S)-5-{(S)-2-[(1-Benzofuran-2-yl-methanoyl)-amino]-4-methyl-pentanoylamino}-6-hydroxy-2-methyl-azepan-1-yl)-methanoyl]-amino}-4-methyl-pentanoic acid methyl ester (450 mg, 0.79 mmol) in CH_2Cl_2 (16 ml) and was stirred at RT for 3 h. The solution was washed with 10% aq. $Na_2S_2O_3$, aq. sat. $NaHCO_3$, and brine. Purification by column chromatography (silica gel, 1% to 2% MeOH/CH_2Cl_2) gave the title compound (405 mg, 90%): 1H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, 1H), 7.54 (d, 1H), 7.49 (s, 1H), 7.44 (t,

1H), 7.31(t, 1H), 7.08 (d, 1H), 6.91 (d, 1H), 5.03-4.95 (m, 2H), 4.84 (q, 1H), 4.71-4.62 (m, 1H), 4.57 (q, 1H), 4.10-4.02 (m, 1H), 3.77 (s, 3H), 3.57 (d, 1H), 2.46-2.36 (m, 1H), 2.07-1.99(m, 1H), 1.82-1.41 (m, 8H), 1.25 (d, 3H), 1.02 (d, 12H); Electrospray mass spec: $M+H^+$ = 571.4.

Example 54

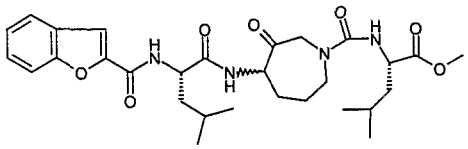
Preparation of (S)-2-{[1-((2R,5S)-5-{(S)-2-[(1-Benzofuran-2-yl-methanoyl)-amino]-4-methyl-pentanoylamino}-2-methyl-6-oxo-azepan-1-yl)-methanoyl]-amino}-4-methyl-pentanoic acid



a. (S)-2-{[1-((2R,5S,6S)-5-{(S)-2-[(1-Benzofuran-2-yl-methanoyl)-amino]-4-methyl-pentanoylamino}-6-oxo-2-methyl-azepan-1-yl)-methanoyl]-amino}-4-methyl-pentanoic acid methyl ester (58 mg, 0.1 mmol) was dissolved in MeOH (1.0 ml) and H_2O (0.5 ml), then potassium carbonate (28 mg, 0.2 mmol) was added and the reaction mixture was stirred at RT for 20 h. The reaction mixture was acidified with cold aq. 1N HCl, extracted with CH_2Cl_2, washed with brine, and then dried with magnesium sulfate. Following filtration, concentration by rotary evaporation, and purification by column chromatography (silica gel, 2% MeOH/ CH_2Cl_2 to 5% MeOH/CH_2Cl_2), the title compound (28 mg, 50%) was obtained as a white solid: 1H NMR (400 MHz, DMSO-d_6): δ 8.65 (d, 1H), 8.11 (d, 1H), 7.79 (d, 1H), 7.69 (d, 1H), 7.63(s, 1H), 7.48 (t, 1H), 7.35 (t, 1H), 6.60 (br s, 1H), 4.67-4.48 (m, 3H), 4.24 (m, 1H), 4.11 (m, 1H), 3.62-3.49 (m, 2H), 2.01-1.09 (m, 10H), 1.09 (d, 3H), 0.93-0.81 (m, 12H); Electrospray mass spec: $M+H^+$ = 557.4.

Example 55

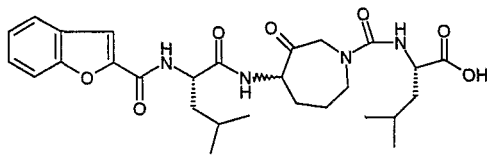
Preparation of (S)-2-{[1-(4-{(S)-2-[(1-Benzofuran-2-yl-methanoyl)-amino]-4-methyl-pentanoylamino}-3-oxo-azepan-1-yl)-methanoyl]-amino}-4-methyl-pentanoica cid methyl ester



Following the procedure of Example 53 (a-d), except substituting "(3S,4S)-4-Amino-3-hydroxy-azepane-1-carboxylic acid benzyl ester (Marquis, R. *J. Med. Chem.*, **2001**)" for "(2R,5S,6S)-5-Amino-6-hydroxy-2-methyl-azepane-1-carboxylic acid benzyl ester" the title compound was obtained: 1H NMR (400 MHz, $CDCl_3$): δ7.69 (d, 1H), 7.54 (d, 1H), 7.49 (s, 1H), 7.44 (t, 1H), 7.31 (t, 1H), 7.08 (d, 1H), 6.96 (d, 1H), 5.06-4.97 (m, 2H), 4.77-4.64 (m, 1H), 4.55 (m, 1H), 3.93 (d, 1H), 3.77 (s, 3H), 3.61 (d, 1H), 2.93 (t, 1H), 2.28 (m, 1H), 2.09 (m, 1H), 1.88 (m, 1H), 1.81-1.24 (m, 7H), 1.01 (d, 12H); Electrospray mass spec: $M+H^+$ = 557.4.

Example 56

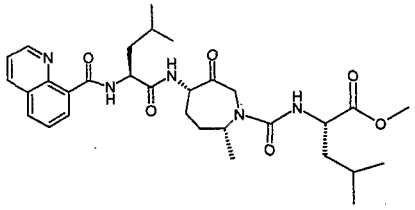
Preparation of (S)-2-{[1-(4-{(S)-2-[(1-Benzofuran-2-yl-methanoyl)-amino]-4-methyl-pentanoylamino}-3-oxo-azepan-1-yl)-methanoyl]-amino}-4-methyl-pentanoic acid



Following the procedure of Example 54 (a), except substituting "(S)-2-{[1-(4-{(S)-2-[(1-Benzofuran-2-yl-methanoyl)-amino]-4-methyl-pentanoylamino}-3-oxo-azepan-1-yl)-methanoyl]-amino}-4-methyl-pentanoic acid methyl ester" for (S)-2-{[1-((2R,5S,6S)-5-{(S)-2-[(1-Benzofuran-2-yl-methanoyl)-amino]-4-methyl-pentanoylamino}-6-oxo-2-methyl-azepan-1-yl)-methanoyl]-amino}-4-methyl-pentanoic acid methyl ester" the title compound was obtained: 1H NMR (400 MHz, $CDCl_3$): δ7.69 (d, 1H), 7.58-7.37 (m, 3H), 7.32 (t, 1H), 7.06 (br s, 1H), 5.00 (br s, 1H), 4.79-4.63 (m, 2H), 4.58-4.46 (m, 1H), 4.35-4.22 (m, 1H), 3.61-3.22 (m, 2H), 2.21-0.69 (m, 24H); Electrospray mass spec: $M+H^+$ = 543.4.

Example 57

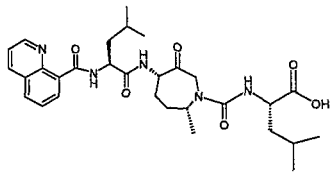
Preparation of (S)-4-Methyl-2-{[1-((2R,5S)-2-methyl-5-{(S)-4-methyl-2-[(1-quinolin-8-yl-methanoyl)-amino]-pentanoylamino}-6-oxo-azepan-1-yl)-methanoyl]-amino}-pentanoic acid methyl ester



Following the procedure of Example 53 (a-d), except substituting "Quinoline-8-carboxylic acid" for "Benzofuran-2-carboxylic acid" the title compound was obtained: 1H NMR (400 MHz, $CDCl_3$): δ11.70 (d, 1H), 8.98 (d, 1H), 8.87 (d, 1H), 8.32 (d, 1H), 8.01 (d, 1H), 7.71 (t, 1H), 7.53 (dd, 1H), 7.34 (d, 1H), 5.05-4.74 (m, 4H), 4.61-4.52 (m, 1H), 4.12-4.01 (m, 1H), 3.76 (s, 3H), 3.54 (d, 1H), 2.50-2.33 (m, 1H), 2.09-1.97 (m, 1H), 1.93-1.39 (m, 8H), 1.22 (d, 3H), 1.05-0.92 (m, 12H); Electrospray mass spec: $M+H^+ = 582.4$.

Example 58

Preparation of (S)-4-Methyl-2-{[1-((2R,5S)-2-methyl-5-{(S)-4-methyl-2-[(1-quinolin-8-yl-methanoyl)-amino]-pentanoylamino}-6-oxo-azepan-1-yl)-methanoyl]-amino}-pentanoic acid

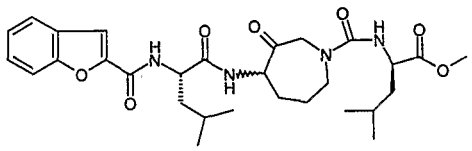


Following the procedure of Example 54 (a), except substituting "(S)-4-Methyl-2-{[1-((2R,5S)-2-methyl-5-{(S)-4-methyl-2-[(1-quinolin-8-yl-methanoyl)-amino]-pentanoylamino}-6-oxo-azepan-1-yl)-methanoyl]-amino}-pentanoic acid methyl ester" for (S)-2-{[1-((2R,5S,6S)-5-{(S)-2-[(1-Benzofuran-2-yl-methanoyl)-amino]-4-methyl-pentanoylamino}-6-oxo-2-methyl-azepan-1-yl)-methanoyl]-amino}-4-methyl-pentanoic acid methyl ester" the title compound was obtained: 1H NMR (400 MHz, $CDCl_3$): δ11.78 (d, 1H), 8.93 (d, 1H), 8.86 (d, 1H), 8.32 (d, 1H), 8.01 (d, 1H), 7.70 (t, 1H), 7.53 (dd, 1H), 7.29

(d, 1H), 4.94-4.12 (m, 5H), 3.96-3.48 (m, 2H), 2.48-0.78 (m, 25H); Electrospray mass spec: $M+H^+ = 568.2$.

Example 59

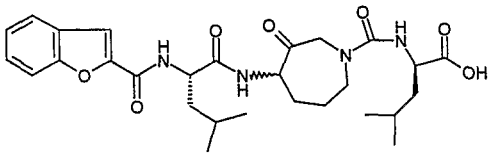
Preparation of (R)-2-{[1-(4-{(S)-2-[(1-Benzofuran-2-yl-methanoyl)-amino]-4-methyl-pentanoylamino}-3-oxo-azepan-1-yl)-methanoyl]-amino}-4-methyl-pentanoic acid methyl ester



Following the procedure of Example 53 (a-d), except substituting "(3S,4S)-4-Amino-3-hydroxy-azepane-1-carboxylic acid benzyl ester" for "(2R,5S,6S)-5-Amino-6-hydroxy-2-methyl-azepane-1-carboxylic acid benzyl ester" and "(R)-(+)-2-isocyanato-4-methylvaleric acid methyl ester" for "(S)-(-)-2-isocyanato-4-methylvaleric acid methyl ester" the title compound was obtained: 1H NMR of a 1:1 mixture of diastereomers (400 MHz, $CDCl_3$): δ7.69 (d, two 1H), 7.57-7.41 (m, two 3H), 7.37-7.30 (m, two 1H), 7.16-7.08 (m, two 1H), 7.00 and 6.93 (two d, two 1H), 5.11-4.89 (m, two 2H), 4.78-4.49 (m, two 3H), 3.97-3.88 (m, two 1H), 3.81-3.75 (two s, two 3H), 3.62 and 3.60 (two d, two 1H), 2.97-2.85 (m, two 1H), 2.33-2.02 (m, two 2H), 1.88-1.24 (m, two 8H), 1.01 and 0.99 (two d, two 12H); Electrospray mass spec: $M+H^+ = 571.4$.

Example 60

Preparation of (R)-2-{[1-(4-{(S)-2-[(1-Benzofuran-2-yl-methanoyl)-amino]-4-methyl-pentanoylamino}-3-oxo-azepan-1-yl)-methanoyl]-amino}-4-methyl-pentanoic acid

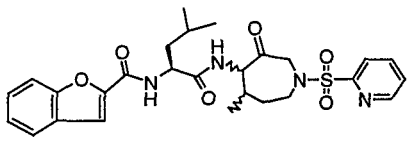


Following the procedure of Example 54 (a), except substituting (R)-2-{[1-(4-{(S)-2-[(1-Benzofuran-2-yl-methanoyl)-amino]-4-methyl-pentanoylamino}-3-oxo-azepan-1-yl)-methanoyl]-amino}-4-methyl-pentanoic acid methyl ester" for (S)-2-{[1-((2R,5S,6S)-5-{(S)-2-[(1-Benzofuran-2-yl-methanoyl)-amino]-4-methyl-pentanoylamino}-6-oxo-2-methyl-

azepan-1-yl)-methanoyl]-amino}-4-methyl-pentanoic acid methyl ester" the title compound was obtained: 1H NMR (400 MHz, $CDCl_3$): δ7.68 (d, 1H), 7.56-7.27 (m, 4H), 7.15-7.05 (m, 2H), 5.55 (d, 1H), 5.06 (d, 1H), 4.84 (m, 1H), 4.70 (m, 1H), 4.53 (m, 1H), 3.97 (d, 1H), 3.53 (d, 1H), 2.83 (t, 1H), 2.41-2.26 (m, 1H), 2.22-2.10 (m, 1H), 1.83-1.38 (m, 8 H), 1.07-0.82 (m, 12H); Electrospray mass spec: $M+H^+ = 543.4$.

Example 61

Preparation of 4,5(R,S)-Benzofuran-2-carboxylic acid {(S)-3-methyl-1-[5-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide



;

a. 3-Methyl-4-nitro-butyric acid ethyl ester

Ethyl 2-crotonate (10 g, 87 mmol) dissolved in nitromethane (23 mL, 438 mmol) was added 1,1,3,3,-tetramethylguanidine (2 g, 17 mmol). The solution was stirred at RT for 24h. Ether was added (500 mL) and the organic phase was washed with 1N HCl (100 mL) and dried over sodium sulfate. The solution was filtered, concentrated and product purified on a silica gel column to yield 14 g of the tile compound: ^1H NMR (400 MHz, $CDCl_3$) δ 4.6 (2H), 4.2 (q, 2H), 2.9 (m, 1H), 2.4 (2H), 1.3 (m, 3H), 1.01(d, 3H). MS (ESI) 174.0 (M +H)$^+$.

b. 3-Methyl-4-nitro-butyraldehyde

To a solution of 3-methyl-4-nitro-butyric acid ethyl ester of Example 61a (1.0 g, 5.71 mmol) in dry toluene at –78°C was slowly added a cold solution Dibal-H (4 mL, of a 1.5 M solution) so as to maintain the internal temperature below –65°C. The reaction was stirred for an additional 2h. The reaction was then quenched by slowly adding cold (-78°C) MeOH. again by keeping the internal temperature below –65°C. The resulting white emulsion was slowly poured into ice-cold 1 N HCl with swirling over 15 minutes and the aqueous mixture was then extracted with EtOAc (3 times). The combined organic layers were washed with brine, dried over sodium sulfate and concentrated to give the crude product which was then purified on a silica gel column to give the pure product as a pale

yellow oil. 0.73 g: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.9 (s, 1H), 4.5 (dq, 2H), 2.9 (m, 2H), 2.6 (dq, 1H), 1.1(d, 3H).

c. 2-[Benzyl-(3-methyl-4-nitro-butyl)-amino]-ethanol

To a solution of 3-methyl-4-nitro-butyaldehyde (0.73 g, 5.57 mmol) of Example 61b in methylene chloride (6.0 ml) was added sodium triacetoxyborohydride (1.57 g, 7.4 mmol) and N-Benzyl ethanolamine (0.55 g, 3.67 mmol). The reaction was stirred for 16h whereupon it was quenched with water, diluted with EtOAc, washed with $NaHCO_3$ and brine. The organic layer was dried over sodium sulfate, concentrated and used directly in the following reaction: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.4 (m, 6H), 4.2 (dq, 2H), 3.6 (m, 4H), 2.3-2.8 (m, 4H), 1.5 (dm, 4H), 1.01(d, 3H). MS (ESI) 265.3 $(M+H)^+$.

d. 3,4,5-(R,S)-1-Benzyl-5-methyl-4-nitro-azepan-3-ol

To a stirring solution of oxalyl chloride (2M in CH_2Cl_2) (3.38 mL) in methylene chloride at –78 was added DMSO (1.25 mL, 17.6 mmol) slowly. After a 15 min stirring, the alcohol (0.60 g, 2.25 mmol) dissolved in methylene chloride was added slowly. The reaction was continued for a further 1h at –78. Triethylamine (4.7 mL, 33.8 mmol) was added and the reaction mixture bought to RT, quenched with water and the product extracted into methylene chloride. The organic layer was dried over sodium sulfate, filtered and concentrated. To the crude product in THF was added triethyl amine and the mixture stirred for 16h to give title compound. The crude product was purified on a silica gel column: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.4 (m, 5H), 4.2 (d, 1H), 3.8 (s, 1H), 1.4-3 (m, 4H), 1.1 (d, 3H), MS (ESI) 265.24 $(M+H)^+$.

e. 3,4,5-(R,S)-4-Amino-1-benzyl-5-methyl-azepan-3-ol

To a 10:1 solution of methanol (56 mL) and 12N HCl (5.60 mL) was slowly added Zn dust (0.43 g, 6.47 mmol). The compound of Example 61d (171 mg, 0.65 mmol) was added and the reaction was heated to reflux for 18h whereupon it was concentrated *in vacuo* to remove the methanol. The residue was diluted with ethyl acetate and water and made basic with solid KOH. The mixture was washed with brine, dried over sodium sulfate, filtered and concentrated to give 120 mg of the title compound: MS (ESI) 235.2 $(M+H)^+$.

f. [(S)-1-(1-Benzyl-3-hydroxy-5-methyl-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid tert-butyl ester

To a solution of the compound from Example 61e (1.12 g, 4.76 mmol) in methylene chlorode was added Boc-leucine (1.3 g, 4.76 mmol), EDC (1 g, 4.76 mmol) and HOBt (0.13 g, 0.96 mmol). This mixture was stirred at room temperature for 3 hours whereupon it was diluted with ethyl acetate and washed with an aqueous solution of sodium bicarbonate, the organic layer was dried over sodium sulfate, filtered and concentrated. The crude product was purified on a silica gel column to yield the title compound: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.1 (d, 2H), 7.3 (m, 3H), 1.5 (d, 9H), 1.1 (m, 3H), MS (ESI) 448.4 $(M+H)^+$.

g. [(S)-1-(3-hydroxy-5-methyl-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid tert-butyl ester

To a solution of the compound of Example 61f in methanol: EtOAc, 1:3 was added 10% Pd/C. This mixture was shaken for 16h on a Parr Hydrogenation apparatus at 45 psi of hydrogen gas. The reaction mixture was filtered through a pad of celite and concentrated to give the title compound: MS (ESI) 358.4 $(M+H)^+$.

h. {(S)-1-[3-Hydroxy-5-methyl-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-3-methyl-butyl}-carbamic acid tert-butyl ester

To a solution of Example 61g (6 g, 16.8 mmol) in methylene chloride was added 2-pyridinesulfonyl chloride (3 g, 16.9 mmol) and triethylamine (3 mL, 22.5 mmol) . The reaction was allowed to stir at room temperature for 16h whereupon it was washed with $NaHCO_3$. The organic layer was dried over sodium sulfate, filtered, concentrated and purified on a silica gel column to yield 5.36 g of the title compound: ^{1}H NMR (400 MHz, $CDCl_3$), δ: 8.7 (d, 1H), 7.9 (m, 2H), 7.4 (m, 1H), 1.7-4.4 (m, 19H), 1.4 (d, 9H), 1.01(d, 6H); MS (ESI) 499.1 $(M+H)^+$.

i. (S)-2-Amino-4-methyl-pentanoic acid [3-hydroxy-5-methyl-1-(pyridine-2-sulfonyl)-azepan-4-yl]-amide

To a solution of the compound of Example 61h (5.36 g, 11.57 mmol) in MeOH (2 mL) was added 4M HCl/dioxane (25 mL) and stirred for 2h. Excess HCl was removed *in vacuo* and the residue was azeotropically dried with toluene (2 x's) to yield the title compound as the hydrochloride salt 5.37 g: MS (ESI) 399.2 $(M+H)^+$.

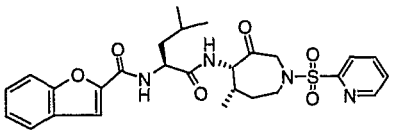
j. 3,4,5 (R,S)-Benzofuran-2-carboxylic acid {(S)-3-methyl-1-[5-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

To a solution of the compound of Example 61i (0.66 g, 1.26 mmoL) in methylene chlorode was added 2-benzofuran carboxylic acid (0.24 g, 1.51 mmol), EDC (0.29 g, 1.51 mmol), HOBt (0.04 g, 0.29 mmol), Et_3N (1 mL). The reaction was stirred at room temperature for 3 hours whereupon it was washed with an aqueous solution of sodium bicarbonate. The organic layer was dried over sodium sulfate, filtered and concentrated. The crude product was purified on a silica gel column to yield the title compound: ^1H NMR (400 MHz, $CDCl_3$), δ: 8.7 (d, 1H), 7.1-7.9 (m, 8H), 1.7-4.4 (m, 11H), 0.9-1.5 (m, 13H). MS (ESI) 565.08 $(M+Na)^+$.

k. 4,5 (R,S) Benzofuran-2-carboxylic acid {(S)-3-methyl-1-[5-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}amide

To a solution of the compound of Example 61j (0.15 g, 0.27 mmol) in methylene chloride was added Dess-Martin reagent (0.17 g, 0.41 mmol). The reaction was stirred at room temperature for 1 hour, diluted with methylene chloride then washed with sodium thiosulfate, sodium bicarbonate and brine. The organic layer was washed dried over sodium sulfate, filtered, concentrated and purified on a silica gel column to provide (0.1 g) of the title compound as a mixture of four diastereomers: ^1H NMR (400 MHz, $CDCl_3$), δ: 8.7 (d, 1H), 7.1-7.9 (m, 8H), 1.7-4.4 (m, 10H), 0.9-1.5 (m, 13H). MS (ESI) 540.08 (M +H).

This mixture was separated by HPLC to provide the 4 individual diastereomers as white powders.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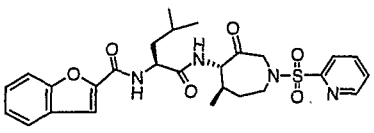
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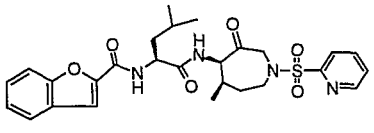
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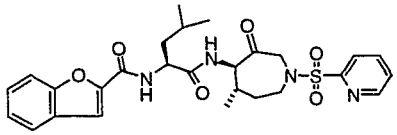

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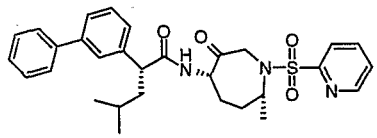
Example 62

Preparation of (R)-2-Biphenyl-3-yl-4-methyl-pentanoic acid [(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-yl]-amide



a. (2R,5R,6R)-5-Azido-6-hydroxy-2-methyl-azepane-1-carboxylic acid benzyl ester

Sodium azide (1.8 g, 27.7 mmol) was added to a (1R,4R,7S)-4-Methyl-8-oxa-3-aza-bicyclo[5.1.0]octane-3-carboxylic acid benzyl ester (2.4 g, 9.2 mmol, Example 1e) and ammonium chloride (1.48 g, 27.7 mmol) in MeOH (16 ml) and H_2O (1.6 ml), then was refluxed overnight. The reaction mixture was concentrated *in vacuo* by rotary evaporation, then was diluted with water (5 ml) and extracted with EtOAc (10 ml). The organic layer was then extracted with water, brine, dried with $MgSO_4$, filtered, concentrated *in vacuo* by rotary evaporation, and chromatographed (silica gel, 25% EtOAc/hexanes) to yield the title compound (1.76 g, 63%); Liquid chromatgraphy/ Electrospray mass spec: $M+H^+ = 305.2$.

b. (2R,5R,6R)-5-Amino-6-hydroxy-2-methyl-azepane-1-carboxylic acid benzyl ester

Triphenylphosphine (2.13 g, 8.14 mmol) was added to a solution (2R,5R,6R)-5-Azido-6-hydroxy-2-methyl-azepane-1-carboxylic acid benzyl ester (1.65 g, 5.43 mmol) in THF (200 ml) and H_2O (0.8 ml), then was heated to 45 degrees C overnight. The reaction mixture was then diluted with toluene (100 ml x 2) and was azeotroped *in vacuo* by rotary evaporation twice. The resulting oil was dissolved in MeOH and HCl in Et_2O and the resulting salt was collected following filtration and was used in the next reaction without further purification (1.7 g, quantitative).

c. (2R,5R,6R)-5-tert-Butoxycarbonylamino-6-hydroxy-2-methyl-azepane-1-carboxylic acid benzyl ester

Boc anhydride (0.9 g, 4.13 mmol) was added to a solution of (2R,5R,6R)-5-Amino-6-hydroxy-2-methyl-azepane-1-carboxylic acid benzyl ester (1.0 g, 3.18 mmol), triethylamine (0.38 g, 0.53 ml, 3.82 mmol) in THF (5 ml) and H_2O (5 ml) and was stirred at RT for 1 H. The THF and excess triethylamine were removed *in vacuo*, then the reaction mixture was diluted with H_2O (10 ml), extracted with EtOAc (3 x 20 ml), then the combined organics were extracted with H_2O (30 ml), brine (30 ml), dried with MgSO4, filtered through silica gel, concentrated, then used in the next reaction without further purification (1.0 g, 83%): Electrospray mass spec: $M+H^+ = 379.2$.

d. ((3R,4R,7R)-3-Hydroxy-7-methyl-azepan-4-yl)-carbamic acid tert-butyl ester

(2R,5R,6R)-5-tert-Butoxycarbonylamino-6-hydroxy-2-methyl-azepane-1-carboxylic acid benzyl ester (0.9 g, 2.4 mmol) was dissolved in EtOAc (40 ml), then 10% Pd/C (0.45 g) was added and the reaction mixture was degasses by bubbling argon for 5 minutes. Then, the reaction was stirred overnight under a balloon filled with hydrogen gas. The reaction mixture was filtered through Celite, concentrated *in vacuo* by rotary evaporation and was azeotroped with toluene (20 ml), then was used in the next reaction without further purification (0.58 g, quantitative): Electrospray mass spec: $M+H^+ = 245.2$.

e. [(3R,4R,7R)-3-Hydroxy-7-methyl-1-(pyridine-2-sulfonyl)-azepan-4-yl]-carbamic acid tert-butyl ester

Pyridine-2-sulfonyl chloride (0.55 g, 3.1 mmol) was added to a solution ((3R,4R,7R)-3-Hydroxy-7-methyl-azepan-4-yl)-carbamic acid tert-butyl ester (0.58 g, 0.2.4 mmol), sodium bicarbonate (0.84 g, 10 mmol) in CH_2Cl_2 (10 ml) and H_2O (3 ml) and was stirred at RT for 30 minutes. The reaction mixture was diluted with EtOAc (100 ml), washed with H_2O, brine, dried with magnesium sulfate, filtered, concentrated *in vacuo* by rotary evaporation, and chromatographed (silica gel, 45:55 EtOAC/hexanes) to yield the title compound (0.6 g, 65%): Electrospray mass spec: $M+H^+ = 386.27$.

f. (3R,4R,7R)-4-Amino-7-methyl-1-(pyridine-2-sulfonyl)-azepan-3-ol

HCl in dioxane (4.0 M, 10 ml) was added to a stirred solution . [(3R,4R,7R)-3-Hydroxy-7-methyl-1-(pyridine-2-sulfonyl)-azepan-4-yl]-carbamic acid tert-butyl ester (0.6 g, 1.55 mmol) in MeOH (10 ml). The reaction mixture was stirred for 1h at RT, then was

diluted with toluene (20 ml), concentrated *in vacuo* by rotary evaporation and was used in the next reaction without further purification (0.5 g, quantitative): Electrospray mass spec: $M+H^+ = 286.2$.

g. 2-Biphenyl-3-yl-4-methyl-pentanoic acid [(3R, 4R,7R)-7-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-yl]-amide

2-Biphenyl-3-yl-4-methyl-pentanoic acid (270 mg, 1.0 mmol, preparation described in *J. Am. Chem. Soc.* **1997**, *120*, 9114), and (3R,4R,7R)-4-Amino-7-methyl-1-(pyridine-2-sulfonyl)-azepan-3-ol (320 mg, 1.0 mmol, Example 1k), EDCI (190 mg, 1.0 mmol), HOBT (135 mg, 1.0 mmol) and diisopropylethylamine (1.7 g, 0.23 ml, 1.3 mmol) in DMF (5 ml) were stirred at RT for 4 h. The reaction mixture was diluted with EtOAc (20 ml), washed with H_2O, brine, dried with magnesium sulfate, filtered, concentrated *in vacuo* by rotary evaporation, and chromatographed (silica gel, 40% EtOAc/ hexanes) to yield the title compound (330 mg, 62%): ^1H NMR (400 MHz, $CDCl_3$): δ 8.55-8.60 (m, 1H), 8.00 (t, 1H), 7.80-7.90 (m, 1H), 7.65 (d, 2H), 7.25-7.55 (m, 8H), 5.50-5.60 (m, 1H), 4.00-4.10 (m, 1H), 3.70-3.85 (m, 1H), 3.50-3.70 (m, 2H), 2.90-3.05 (m, 1H), 2.00-2.10 (m, 2H), 1.30-1.85 (m, 5H), 0.90-0.95 (d, 9H); ESMS: 536.4 ($M+H^+$)

h. (R)-2-Biphenyl-3-yl-4-methyl-pentanoic acid [(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-yl]-amide

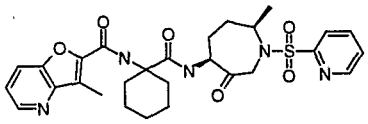
Dess-Martin periodinane (400 mg, 0.93 mmol) was added to a solution 2-Biphenyl-3-yl-4-methyl-pentanoic acid [(3R, 4R,7R)-7-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-yl]-amide (330 mg, 0.62 mmol) in CH_2Cl_2 (15 ml) and was stirred at RT for 4 h. The solution was washed with 10% aq. $Na_2S_2O_3$, aq. sat. $NaHCO_3$, and brine, then concentrated *in vacuo*, then chromatographed (silica gel, 50% EtOAc/ hexanes) to provide a mixture of diasteromers (260 mg, 60%), which was then dissolved in MeOH (12 ml) and triethylamine (0.44 g, 0.6 ml, 4.4 mmol), and was stirred at RT for 3 days. The reaction mixture was concentrated in vacuo, then chromatographed to yield a mixure of primarily (R)- and (S)-2-Biphenyl-3-yl-4-methyl-pentanoic acid [(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-yl]-amides (200 mg, 77%). The diastereomers were separated using HPLC (R,R-Whelk-O preparative column, 40% EtOH/ hexanes): Diastereomer 1 (retention time 13 min): ^1H NMR (400 MHz, $CDCl_3$): δ 8.70 (d, 1H), 8.00 (d, 1H), 7.90 (t, 1H), 7.60 (d, 2H), 7.25-7.55 (m, 8H), 6.52 (d, 1H), 5.05-5.15 (m, 1H), 4.75 (d, 1H), 4.35-4.45 (m,

1H), 3.82 (d, 1H), 3.50 (t, 1H), 2.00-2.20 (m, 3H), 1.70-1.80 (m, 1H), 1.40-1.65 (m, 2H), 1.25-1.40 (m, 1H), 0.9-1.0 (m, 9H); ESMS: 534.2 ($M+H^+$);

Diastereomer 2 (retention time 21 min): ^1H NMR (400 MHz, $CDCl_3$): δ 8.65 (d, 1H), 8.00 (d, 1H), 7.90 (t, 1H), 7.60 (d, 2H), 7.25-7.60 (m, 8H), 6.60 (d, 1H), 4.95-5.02 (m, 1H), 4.70 (d, 1H), 4.40-4.50 (m, 1H), 3.85 (d, 1H), 3.50 (t, 1H), 2.12-2.30 (m, 2H), 2.00-2.10 (m, 1H), 1.70-1.80 (m, 1H), 1.60-1.70 (m, 1H), 1.40-1.60 (m, 2H), 1.00 (d, 3H), 0.95 (d, 6H); ESMS: 534.2 ($M+H^+$)

Example 63

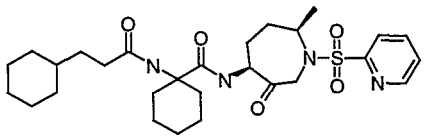
Preparation of 3-Methyl-furo[3,2-b]-pyridine-2-carboxylic acid {1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-cyclohexyl}-amide



Following the procedure of Example 12 (a-m), except substituting "N-Boc-amino-cyclohexane carboxylic acid" for "Boc-L-leucine" and "3-Methyl-furo[3,2-b]-pyridine-2-carboxylic acid" for "quinoline-6-carboxylic acid" gave the title compound: 1H NMR: 8.72(d, 1 H), 8.65(d, 1 H), 7.98(m, 1 H), 7.90(m, 1 H), 7.80(d, 1 H), 5.11(m, 1 H), 4.76(d, 1 H), 4.43(m, 1 H), 3.81(d, 1 H), 2.82(s, 3 H), 2.32-1.35(m, 14 H), 0.95(d, 3 H); Electrospray mass spec: $M+H^+$ = 568.2.

Example 64

Preparation of 1-(3-Cyclohexyl-propanoylamino)-cyclohexanecarboxylic acid [(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-yl]-amide

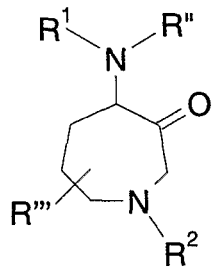


Following the procedure of Example 12 (a-m), except substituting "N-Boc-amino-cyclohexane carboxylic acid" for "Boc-L-leucine" and "3-Cyclohexyl-propananoic acid" for "quinoline-6-carboxylic acid" gave the title compound: 1H NMR: 8.71(d, 1 H), 7.97(m, 2 H), 7.72(m, 3 H), 6.60(s, 1 H), 5.04(m, 1 H), 4.71(d, 1 H), 4.42(m, 1 H), 3.81(d, 1 H), 2.27-0.73(m, 31 H); Electrospray mass spec: $M+H^+$ = 544.4.

The above specification and Examples fully disclose how to make and use the compounds of the present invention. However, the present invention is not limited to the particular embodiments described hereinabove, but includes all modifications thereof within the scope of the following claims. The various references to journals, patents and other publications which are cited herein comprise the state of the art and are incorporated herein by reference as though fully set forth.

We claim:

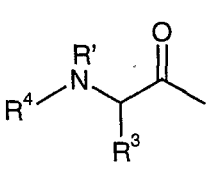
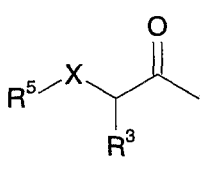
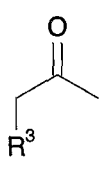
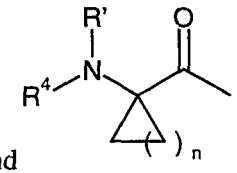
1. A compound of Formula I:

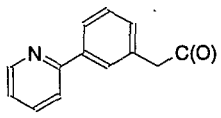
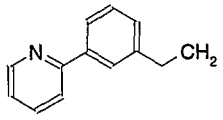
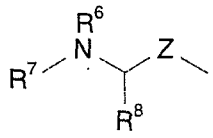


I

wherein:

R^1 is selected from the group consisting of:

 ;  ;  and  ;

R^2 is selected from the group consisting of: H, C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, $R^9C(O)$-, $R^9C(S)$-, R^9SO_2-, $R^9OC(O)$-, $R^9R^{11}NC(O)$-, $R^9R^{11}NC(S)$-, $R^9(R^{11})NSO_2$-  ,  and  ;

R^3 is selected from the group consisting of: H, C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, HetC_{0-6}alkyl, ArC_{0-6}alkyl, Ar-ArC_{0-6}alkyl, Ar-HetC_{0-6}alkyl, Het-ArC_{0-6}alkyl, and Het-HetC_{0-6}alkyl;

R^3 and R' may be connected to form a pyrrolidine, piperidine or morpholine ring;

R^4 is selected from the group consisting of: H, C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, $R^5C(O)$-, $R^5C(S)$-, R^5SO_2-, $R^5OC(O)$-, $R^5R^{12}NC(O)$-, and $R^5R^{12}NC(S)$-;

R^5 is selected from the group consisting of: H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, C_{2-6}alkanonyl, Ar-C_{0-6}alkyl and Het-C_{0-6}alkyl;

R^6 is selected from the group consisting of: H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl;

R^7 is selected from the group consisting of: H, C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, $R^{10}C(O)$-, $R^{10}C(S)$-, $R^{10}SO_2$-, $R^{10}OC(O)$-, $R^{10}R^{13}NC(O)$-, and $R^{10}R^{13}NC(S)$-;

R^8 is selected from the group consisting of: H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, HetC_{0-6}alkyl and ArC_{0-6}alkyl;

R^9 is selected from the group consisting of: C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl and Het-C_{0-6}alkyl;

R^{10} is selected from the group consisting of: C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl and Het-C_{0-6}alkyl;

R^{11} is selected from the group consisting of: H, C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, and Het-C_{0-6}alkyl;

R^{12} is selected from the group consisting of: H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, and Het-C_{0-6}alkyl;

R^{13} is selected from the group consisting of: H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, and Het-C_{0-6}alkyl;

R' is selected from the group consisting of: H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, and Het-C_{0-6}alkyl;

R" is selected from the group consisting of: H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl;

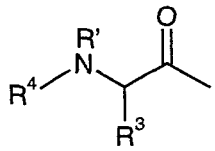
R‴ is C_{1-6}alkyl;

X is selected from the group consisting of: CH_2, S, and O; and

Z is selected from the group consisting of: C(O) and CH_2;

n is an integer from 1 to 5;

and pharmaceutically acceptable salts, hydrates and solvates thereof.

2. A compound according to Claim 1 wherein R^1 is 

3. A compound according to Claim 1 wherein R^3 is selected from the group consisting of: C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, and ArC_{0-6}alkyl.

4. A compound according to Claim 3 wherein R^3 is selected from the group consisting of:

H, methyl, ethyl, n-propyl, prop-2-yl, n-butyl, isobutyl, but-2-yl, cyclopropylmethyl, cyclohexylmethyl, 2-methanesulfinyl-ethyl, 1-hydroxyethyl, toluyl, naphthalen-2-ylmethyl, benzyloxymethyl, and hydroxymethyl.

5. A compound according to Claim 4 wherein R^3 is selected from the group consisting of: toluyl, isobutyl and cyclohexylmethyl.

6. A compound according to Claim 5 wherein R^3 is isobutyl.

7. A compound according to Claim 1 wherein R^4 is selected from the group consisting of: $R^5OC(O)$-, $R^5C(O)$- or R^5SO_2-.

8. A compound according to Claim 7 wherein R^4 is $R^5C(O)$-.

9. A compound according to Claim 8 wherein R^5 is selected from the group consisting of: C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, C_{2-6}alkanonyl, Ar-C_{0-6}alkyl and Het-C_{0-6}alkyl.

10. A compound according to Claim 9 wherein R^5 is selected from the group consisting of:

methyl, halogenated methyl, C_{1-6} alkoxy and aryloxy substituted methyl, heterocycle substituted methyl;

butyl, aryl substituted butyl;

isopentyl;

cyclohexyl;

butenyl, aryl substituted butenyl;

pentanonyl;

phenyl, phenyl substituted with one or more halogens, phenyl substituted with one or more C_{1-6}alkoxy groups, phenyl substituted with one or more sulfonyl groups;

benzyl;

naphthylenyl;

benzo[1,3]dioxolyl;

furanyl, halogen substituted furanyl, aryl substituted furanyl;

tetrahydrofuranyl;

benzofuranyl, C_{1-6}alkoxy substituted benzofuranyl, halogen substituted benzofuranyl, C_{1-6}alkyl substituted benzofuranyl;

benzo[*b*]thiophenyl, C_{1-6} alkoxy substituted benzo[*b*]thiophenyl;

quinolinyl;

quinoxalinyl;

1,8 naphthyridinyl;

indolyl, C_{1-6}alkyl substituted indolyl;

pyridinyl, C_{1-6}alkyl substituted pyridinyl, 1-oxy-pyridinyl;

furo[3,2-b]pyridinyl, C_{1-6}alkyl substituted furo[3,2-b]pyridinyl;

thiophenyl, C_{1-6}alkyl substituted thiophenyl, halogen substituted thiophenyl;

thieno[3,2-*b*]thiophenyl;

isoxazolyl, C_{1-6}alkyl substituted isoxazolyl; and

oxazolyl.

11. A compound according to Claim 9 wherein R^5 is selected from the group consisting of:

4-pentanonyl;

naphthylen-2-yl;

benzo[1,3]dioxol-5-yl,

tetrahydrofuran-2-yl

furan-2-yl;

benzofuran-2-yl;

benzo[*b*]thiophen-2-yl;

quinolin-2-yl, quinolin-3-yl, quinolin-4-yl, quinolin-6-yl, and quinolin-8-yl;

quinoxalin-2-yl;
1,8 naphthyridin-2-yl;
indol-3-yl, indol-5-yl;
pyridin-2-yl , pyridin-5-yl;
furo[3,2-b]pyridin-2-yl;
thiophen-3-yl;
thieno[3,2-*b*]thiophene-2-yl;
isoxazol-4-yl; and
oxazol-4-yl.

12. A compound according to Claim 9 wherein R^5 is selected from the group consisting of:

trifluoromethyl, phenoxy-methyl, 4-fluoro-phenoxy-methyl, 2-thiophenyl-methyl;
4-(4-methoxy)phenyl-butyl;
4,4-bis(4-methoxyphenyl)-but-3-enyl;
3,4-dichlorophenyl, 4-fluorophenyl, 3,4-dimethoxy-phenyl, 3-benzyloxy-4-methoxy-phenyl, 4-methanesulfonyl-phenyl;
5-nitro-furan-2-yl, 5-(4-nitrophenyl)-furan-2-yl, 5-(3-triflouromethyl-phenyl)-furan-2-yl, 5-bromo-furan-2-yl, 5-(4-chloro-phenyl)-furan-2-yl;
5-(2-piperazin-4-carboxylic acid *tert*-butyl ester- ethoxy) benzofuran-2-yl, 5-(2-morpholino-4-yl-ethoxy)-benzofuran-2-yl, 5-(2-piperazin-1-yl-ethoxy)benzofuran-2-yl, 5-(2-cyclohexyl-ethoxy)-benzofuran-2-yl, 7-methoxy-benzofuran-2-yl, 5-methoxy-benzofura-2-yl, 5,6-dimethoxy-benzofuran-2-yl, 5-fluoro-benzofuran-2-yl, 5,6-difluoro-benzofuran-2-yl, 3-methyl-benzofuran-2-yl;
5,6-dimethoxy- benzo[*b*]thiophen-2-yl;
N-methyl-indol-2-yl;
1-oxy-pyridin-2-yl, 2-methyl-pyridin-5-yl;
3-methyl-furo[3,2-b]pyridin-2-yl;
5-methyl-thiophen-2-yl, 4,5-dibromo-thiophen-2-yl;
5-*tert*-butyl-3-methyl thieno[3,2-*b*]thiophen-2-yl;
3,5-dimethyl- isoxazol-4-yl; and
5-methyl-2-phenyl oxazol-4-yl, and 2-phenyl-5-trifluoromethyl-oxazol-4-yl.

13. A compound according to Claim 9 wherein R^5 is selected from the group consisting of: 5-methoxybenzofuran-2-yl, benzo[*b*]thiophen-2-yl, 3-methyl-benzofuran-2-yl, thieno[3,2-b]thiophen-2-yl, benzofuran-2-yl, furo[3,2-b]pyridin-2-yl, and 3-methyl-furo[3,2-b]pyridin-2-yl.

14. A compound according to Claim 1 wherein R' is selected from the group consisting of H and naphthalen-2-yl-methyl.

15. A compound according to Claim 14 wherein R' is H.

16. A compound according to Claim 1 wherein R" is H.

17. A compound according to Claim 1 wherein R‴ is selected from the group consisting of: methyl, ethyl, propyl, butyl, pentyl, and hexyl.

18. A compound according to Claim 17 wherein R‴ is methyl.

19. A compound according to Claim 1 wherein R" is H and R‴ is methyl.

20. A compound according to Claim 1 wherein R‴ is selected from the group consisting of: 5-, 6- and 7-C_{1-6}alkyl.

21. A compound according to Claim 20 wherein 5-, 6- and 7-C_{1-6}alkyl is selected from the group consisting of: 5-, 6- or 7-methyl, -ethyl, -propyl, -butyl, -pentyl, and -hexyl.

22. A compound according to Claim 21 wherein 5-, 6- and 7-C_{1-6}alkyl is selected from the group consisting of: 5-, 6- and 7-methyl.

23. A compound according to Claim 20 wherein R‴ is selected from the group consisting of: 6- and 7-C_{1-6}alkyl.

24. A compound according to Claim 23 wherein 6- and 7-C_{1-6}alkyl is selected from the group consisting of: 6- or 7-methyl, -ethyl, -propyl, -butyl, -pentyl, and -hexyl.

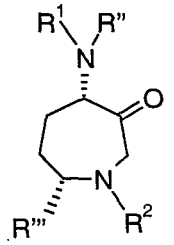
25. A compound according to Claim 24 wherein 6- and 7-C_{1-6}alkyl is selected from the group consisting of: 6- and 7-methyl.

26. A compound according to Claim 23 wherein R"' is 7-C_{1-6}alkyl.

27. A compound according to Claim 26 wherein 7-C_{1-6}alkyl is selected from the group consisting of: 7-methyl, -ethyl, -propyl, -butyl, -pentyl, and -hexyl.

28. A compound according to Claim 27 wherein 7-C_{1-6}alkyl is 7-methyl.

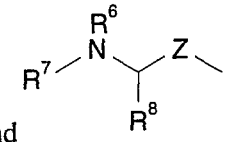
29. A compound according to Claim 26 of Formula Ia:



Ia

wherein R"' is *cis*-7-C_{1-6}alkyl.

30. A compound according to Claim 29 wherein R"' is *cis*-7-methyl.

31. A compound according to Claim 1 wherein R^2 is selected from the group consisting of: Ar-C_{0-6}alkyl, $R^9C(O)$-, R^9SO_2, $R^9R^{11}NC(O)$-, and  .

32. A compound according to Claim 31 wherein R^2 is selected from the group consisting of: Ar-C_{0-6}alkyl, $R^9C(O)$-, and R^9SO_2.

33. A compound according to Claim 32 wherein R^2 is R^9SO_2.

34. A compound according to Claim 31 wherein R^6 is H.

35. A compound according to Claim 31 wherein R^7 is $R^{10}OC(O)$.

36. A compound according to Claim 31 wherein R^8 is C_{1-6}alkyl.

37. A compound according to Claim 36 wherein R^8 is isobutyl.

38. A compound according to Claim 33 wherein R^9 is selected from the group consisting of: C_{1-6}alkyl, Ar-C_{0-6}alkyl and Het-C_{0-6}alkyl.

39. A compound according to Claim 38 wherein R^9 is selected from the group consisting of:

methyl;

ethyl, and C_{1-6}alkyl-substituted ethyl;

butyl, C_{1-6}alkyl-substituted butyl;

tert-butyl;

isopentyl;

phenyl, halogen substituted phenyl,C_{1-6}alkoxy phenyl, cyanophenyl;

toluyl, Het-substituted toluyl;

benzoyl;

naphthylenyl;

benzo[1,3]dioxolyl;

benzo[1,2,5]oxadiazolyl;

pyridinyl, 1-oxy-pyridinyl, C_{1-6}alkyl pyridinyl;

furo[3,2-b]pyridinyl, C_{1-6}alkyl substituted furo[3,2-b]pyridinyl;

thiophenyl;

thiazolyl;

1H-imidazolyl, C_{1-6}alkyl substituted imidazolyl;

1H-[1,2,4]triazolyl, C_{1-6}alkyl substituted 1H-[1,2,4]triazolyl; and

quinolinyl.

40. A compound according to Claim 39 wherein R^9 is selected from the group consisting of:

2-cyclohexyl-ethyl;

3-methylbutyl;

3,4-dichlorophenyl, 4-bromophenyl, 2-fluorophenyl, 4-fluorophenyl, 3-chlorophenyl, 4-chlorophenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl, 2-cyanophenyl;

2-benzoyl;

naphthylen-2-yl;

benzo[1,3]dioxol-5-yl;

benzo[1,2,5]oxadiazol-4-yl;

pyridin-2-yl, pyridin-3-yl , 1-oxy-pyridin-2-yl, 1-oxy-pyridin-3-yl, 3-methyl-pyridin-2-yl, 6-methyl-pyridin-2-yl;

furo[3,2-b]pyridin-2-yl, 3-methyl-furo[3,2-b]pyridin-2-yl;

thiophene-2-yl;

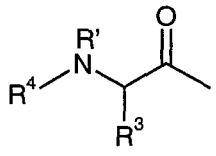
thiazol-2-yl;

1H-imidazol-2-yl, 1H-imidazol-4-yl, 1-methyl-1H-imidazol-2-yl, 1-methyl-1H-imidazol-4-yl;

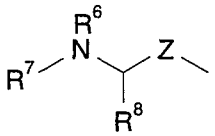
1H-[1,2,4]triazol-3-yl, 5-methyl-1H-[1,2,4]triazol-3-yl; and

quinolin-2-yl.

41. A compound according to Claim 1 wherein:

R^1 is  ;

R^2 is selected from the group consisting of:

Ar-C_{0-6}alkyl, $R^9C(O)$-, R^9SO_2, $R^9R^{11}NC(O)$-, and  ;

R^3 is selected from the group H, C_{1-6}alkyl and Ar C_{0-6}alkyl;

R^4 is selected from the group consisting of: $R^5OC(O)$-, $R^5C(O)$- or R^5SO_2-;

R^5 is selected from the group consisting of: C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, C_{2-6}alkanonyl, Ar-C_{0-6}alkyl and Het-C_{0-6}alkyl;

R^6 is H;

R^7 is $R^{10}OC(O)$;

R^8 is C_{1-6}alkyl;

R' is H; and

R" is H.

42. A compound according to Claim 41 wherein:

R^2 is selected from the group consisting of: Ar-C_{0-6}alkyl, $R^9C(O)$- and R^9SO_2;

R^3 is selected from the group consisting of: H, methyl, ethyl, n-propyl, prop-2-yl, n-butyl, isobutyl, but-2-yl, cyclopropylmethyl, cyclohexylmethyl, 2-methanesulfinyl-ethyl, 1-hydroxyethyl, toluyl, naphthalen-2-ylmethyl, benzyloxymethyl, and hydroxymethyl;

R^4 is $R^5C(O)$-;

R^5 is selected from the group consisting of:

methyl, halogenated methyl, C_{1-6}alkoxy substituted methyl, heterocycle substituted methyl;

butyl, aryl substituted butyl;

isopentyl;

pentanonyl;

cyclohexyl;

butenyl, aryl substituted butenyl;

phenyl, phenyl substituted with one or more halogens, phenyl substituted with one or more C_{1-6}alkoxy or aryloxy groups, phenyl substituted with one or more sulfonyl groups;

benzyl;

naphthylenyl;

benzo[1,3]dioxolyl;

furanyl, halogen substituted furanyl, aryl substituted furanyl;

tetrahydrofuran-2-yl;

benzofuranyl, C_{1-6}alkoxy substituted benzofuranyl, halogen substituted benzofuranyl, C_{1-6}alkyl substituted benzofuranyl;

benzo[*b*]thiophenyl, C_{1-6}alkoxy substituted benzo[*b*]thiophenyl;

quinolinyl;

quinoxalinyl;

1,8 naphthyridinyl;

indolyl , C_{1-6}alkyl substituted indolyl;

pyridinyl, C_{1-6}alkyl substituted pyridinyl, 1-oxy-pyridinyl;
furo[3,2-b]pyridinyl, C_{1-6}alkyl substituted furo[3,2-b]pyridin-2-yl;
thiophenyl, C_{1-6}alkyl substituted thiophenyl, halogen substituted thiophenyl;
thieno[3,2-*b*]thiophenyl, C_{1-6}alkyl thieno[3,2-*b*]thiophenyl;
isoxazolyl, C_{1-6}alkyl substituted isoxazolyl; and
oxazolyl; and

R^9 is selected from the group consisting of:
methyl;
ethyl, C_{1-6}alkyl substituted ethyl;
butyl, C_{1-6}alkyl substituted butyl;
tert-butyl;
isopentyl;
phenyl, halogen substituted phenyl,C_{1-6}alkoxy phenyl, cyanophenyl;
toluyl, Het-substituted toluyl;
benzoyl;
naphthylenyl;
benzo[1,3]dioxolyl;
benzo[1,2,5]oxadiazolyl;
pyridinyl, 1-oxy-pyridinyl, C_{1-6}alkyl pyridinyl;
thiophenyl;
thiazolyl;
1H-imidazolyl, C_{1-6}alkyl substituted imidazolyl;
1H-[1,2,4]triazolyl, C_{1-6}alkyl substituted 1H-[1,2,4]triazolyl; and
quinolinyl.

43. A compound according to Claim 41 wherein: R^5 is selected from the group consisting of:
4-pentanonyl;
naphthylen-2-yl;
benzo[1,3]dioxol-5-yl,
furan-2-yl;
benzofuran-2-yl;
benzo[*b*]thiophen-2-yl;

quinolin-2-yl, quinolin-3-yl, quinolin-4-yl, quinolin-6-yl, and quinolin-8-yl;
quinoxalin-2-yl;
1,8 naphthyridin-2-yl;
indol-3-yl, indol-5-yl;
pyridin-2-yl , pyridin-5-yl,
furo[3,2-b]pyridin-2-yl;
thiophen-3-yl;
thieno[3,2-*b*]thiophene-2-yl;
isoxazol-4-yl; and
oxazol-4-yl.

44. A compound according to Claim 41 wherein R^5 is selected from the group consisting of:

trifluoromethyl, phenoxy-methyl, 4-fluoro-phenoxy-methyl , 2-thiophenyl-methyl;
4-(4-methoxy)phenyl-butyl;
4,4-bis(4-methoxyphenyl)-but-3-enyl;
3,4-dichlorophenyl, 4-fluorophenyl, 3,4-dimethoxy-phenyl, 3-benzyloxy-4-methoxy-phenyl, 4-methanesulfonyl-phenyl;
5-nitro-furan-2-yl, 5-(4-nitrophenyl)-furan-2-yl, 5-(3-triflouromethyl-phenyl)-furan-2-yl, 5-bromo-furan-2-yl, 5-(4-chloro-phenyl)-furan-2-yl;
5-(2-piperazin-4-carboxylic acid *tert*-butyl ester- ethoxy) benzofuran-2-yl, 5-(2-morpholino-4-yl-ethoxy)-benzofuran-2-yl, 5-(2-piperazin-1-yl-ethoxy)benzofuran-2-yl, 5-(2-cyclohexyl-ethoxy)-benzofuran-2-yl, 7-methoxy-benzofuran-2-yl, 5-methoxy-benzofura-2-yl, 5,6-dimethoxy-benzofuran-2-yl, 5-fluoro-benzofuran-2-yl, 5,6-difluoro-benzofuran-2-yl, 3-methyl-benzofuran-2-yl;
5,6-dimethoxy- benzo[*b*]thiophen-2-yl;
N-methyl-indol-2-yl;
1-oxy-pyridin-2-yl, 2-methyl-pyridin-5-yl;
3-methyl-furo[3,2-b]pyridin-2-yl;
5-methyl-thiophen-2-yl, 4,5-dibromo-thiophen-2-yl;
5-*tert*-butyl-3-methyl thieno[3,2-*b*]thiophen-2-yl;
3,5-dimethyl- isoxazol-4-yl;
5-methyl-2-phenyl oxazol-4-yl, and 2-phenyl-5-trifluoromethyl-oxazol-4-yl.

45. A compound according to Claim 41 wherein R^9 is selected from the group consisting of:

2-cyclohexyl-ethyl;

3-methylbutyl;

3,4-dichlorophenyl, 4-bromophenyl, 2-fluorophenyl, 4-fluorophenyl, 3-chlorophenyl, 4-chlorophenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl, 2-cyanophenyl;

2-benzoyl;

naphthylen-2-yl;

benzo[1,3]dioxol-5-yl;

benzo[1,2,5]oxadiazol-4-yl;

pyridin-2-yl, pyridin-3-yl, 1-oxy-pyridin-2-yl, 1-oxy-pyridin-3-yl , 3-methyl-pyridin-2-yl, 6-methyl-pyridin-2-yl;

thiophene-2-yl;

thiazol-2-yl;

1H-imidazol-2-yl, 1H-imidazol-4-yl, 1-methyl-1H-imidazol-2-yl, 1-methyl-1H-imidazol-4-yl;

1H-[1,2,4]triazol-3-yl, 5-methyl-1H-[1,2,4]triazol-3-yl; and

quinolin-2-yl.

46. A compound according to Claim 41 wherein:

R^2 is R^9SO_2;

R^3 is C_{1-6}alkyl;

R^4 is $R^5C(O)$;

R^5 is Het-C_{0-6}alkyl;

R^9 is Het-C_{0-6}alkyl; and

$R^{"'}$ is 7-C_{1-6}alkyl.

47. A compound according to Claim 46 wherein:

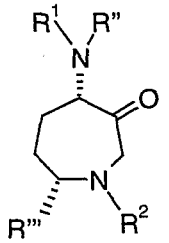
R^3 is isobutyl;

R^5 is selected from the group consisting of: 5-methoxybenzofuran-2-yl, benzo[*b*]thiophen-2-yl, 3-methyl-benzofuran-2-yl, thieno[3,2-b]thiophen-2-yl, benzofuran-2-yl, furo[3,2-b]pyridin-2-yl, and 3-methyl-furo[3,2-b]pyridin-2-yl;

R^9 is selected from the group consisting of: pyridin-2-yl and 1-oxy-pyridin-2-yl; and

R''' is is 7-C_{1-6}alkyl.

48. A compound according to Claim 47 of Formula Ia:



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wherein R''' is *cis*-7-C_{1-6}alkyl.

49. A compound according to Claim 48 wherein R''' is *cis*-7-methyl.

50. A compound according to Claim 49 wherein R^5 is benzofuran-2-yl.

51. A compound according to Claim 50 wherein R^9 is pyridin-2-yl.

52. A compound according to Claim 1 selected from the group consisting of:
5-methoxy-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(4S,6S)-6-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

5-methoxy-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(4R,6R)-6-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

benzo[b]thiophene-2-carboxylic acid {(S)- 1-[(4S,6S)-6-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide;

benzo[b]thiophene-2-carboxylic acid {(S)- 1-[(4R,6R)-6-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide;

3-methyl-benzofuran-2-carboxylic acid {(S)- 1-[(4S,6S)-6-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide;

3-methyl-benzofuran-2-carboxylic acid {(S)- 1-[(4R,6R)-6-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide;

thieno[3,2-b]thiophene-2-carboxylic acid {(S)- 1-[(4S,6S)-6-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide;

thieno[3,2-b]thiophene-2-carboxylic acid {(S)- 1-[(4R,6R)-6-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide;

benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(4R,7S)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(4S,7S)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(4R,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

furo[3,2-b]pyridine-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

2,2,4-trideutero-furo[3,2-b]pyridine-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

3-methyl-furo[3,2-b]pyridine-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

2,2,4-trideutero-3-methyl-furo[3,2-b]pyridine-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

quinoline-6-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

quinoline-3-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

5-methoxy-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

3-methyl-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

thieno[3,2-b]thiophene-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

quinoxaline-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

thieno[3,2-b] thiophene-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide
Ki = 0.05 nM;

3-methyl-benzofuran-2-carboxylicacid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

quinoline-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

5,6-difluoro-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

5-fluoro-3-methyl-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

5-fluoro-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

3-methyl-furo[3,2-b]]pyridine-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide

cyclohexanecarboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

(S)-2-(2-cyclohexyl-ethanoylamino)-4-methyl-pentanoic acid [(4S,7R)-7-methyl-3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-yl]-amide;

(S)-2-(3-cyclohexyl-propanoylamino)-4-methyl-pentanoic acid [(4S,7R)-7-methyl-3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-yl]-amide;

(S)-2-(4-cyclohexyl-butanoylamino)-4-methyl-pentanoic acid [(4S,7R)-7-methyl-3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-yl]-amide;

(S)-2-(5-cyclohexyl-pentanoylamino)-4-methyl-pentanoic acid [(4S,7R)-7-methyl-3-oxo-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-yl]-amide;

benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(5-trifluoromethyl-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

5-fluoro-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(5-trifluoromethyl-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-;

thieno[3,2-b] thiophene-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(5-trifluoromethyl-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

benzofuran-2-carboxylic acid {1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-cyclohexyl}-amide;

thiophene-3-carboxylic acid {(S)-3,3-dimethyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

furan-2-carboxylic acid {(S)-3,3-dimethyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

thieno[3,2-b] thiophene-2-carboxylic acid {(S)-3,3-dimethyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

benzofuran-2-carboxylic acid {(S)-2-cyclohexyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide;

furan-2-carboxylic acid {(S)-2-cyclohexyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide;

thiophene-3-carboxylic acid {(S)-2-cyclohexyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide;

3-methyl-furo[3,2-b]- pyridine-2-carboxylic acid {(S)-2-cyclohexyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide;

(2R,4aR,8aR)-octahydro-benzo[1,4]dioxine-2-carboxylic acid [(S)-1-((4S,7R)-1-methanesulfonyl-7-methy l-3-oxo-azepan-4-ylcarbamoyl)-3-methyl-butyl]-amide;

furan-2-carboxylic acid [(S)-2-cyclohexyl-1-((4S,7R)-7-methyl-3-oxo-1-propyl-azepan-4-ylcarbamoyl)-ethyl]-amide;

thiophene-3-carboxylic acid [(S)-2-cyclohexyl-1-((4S,7R)-7-methyl-3-oxo-1-propyl-azepan-4-ylcarbamoyl)-ethyl]-amide;

benzofuran-2-carboxylic acid [(S)-2-cyclohexyl-1-((4S,7R)-7-methyl-3-oxo-1-propyl-azepan-4-ylcarbamoyl)-ethyl]-amide;

1-(3-cyclohexyl-propanoylamino)-cyclohexanecarboxylic acid ((4S,7R)-1-cyclohexylmethyl-7-methyl-3-oxo-azepan-4-yl)-amide;

benzofuran-2-carboxylic acid [1-((4S,7R)-1-cyclohexylmethyl-7-methyl-3-oxo-azepan-4-ylcarbamoyl)-cyclohexyl]-amide;

benzofuran-2-carboxylic acid [(S)-3-methyl-1-((4S,7R)-7-methyl-3-oxo-1-propyl-azepan-4-ylcarbamoyl)- butyl]-amide;

(2R,5S)-5-((S)-2-tert-butoxycarbonylamino-4-methyl-pentanoylamino)-2-methyl-6-oxo-azepane-1-carboxylic acid benzyl ester;

benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-1-(1-morpholin-4-yl-methanoyl)-3-oxo- azepan-4-ylcarbamoyl]-butyl}-amide;

(S)-2-(3-cyclohexyl-propanoylamino)-4-methyl-pentanoic acid [(4S,7R)-7-methyl-1-(1-morpholin-4-yl-me thanoyl)-3-oxo-azepan-4-yl]-amide;

(2R,5S)-5-{(S)-2-[(1-benzofuran-2-yl-methanoyl)-amino]-4-methyl-pentanoylamino}-2-methyl-6-oxo-azepane-1-carboxylic acid (tetrahydro-pyran-4-yl)-amide;

(S)-2-{[1-((2R,5S)-5-{(S)-2-[(1-benzofuran-2-yl-methanoyl)-amino]-4-methyl-pentanoylamino}-2-methyl-6-oxo-azepan-1-yl)-methanoyl]-amino}-4-methyl-pentanoic acid methyl ester;

(S)-2-{[1-((2R,5S)-5-{(S)-2-[(1-benzofuran-2-yl-methanoyl)-amino]-4-methyl-pentanoylamino}-2-methyl-6-oxo-azepan-1-yl)-methanoyl]-amino}-4-methyl-pentanoic acid;

(S)-2-{[1-(4-{(S)-2-[(1-benzofuran-2-yl-methanoyl)-amino]-4-methyl-pentanoylamino}-3-oxo-azepan-1-yl)-methanoyl]-amino}-4-methyl-pentanoica cid methyl ester;

(S)-2-{[1-(4-{(S)-2-[(1-benzofuran-2-yl-methanoyl)-amino]-4-methyl-pentanoylamino}-3-oxo-azepan-1-yl)-methanoyl]-amino}-4-methyl-pentanoic acid;

(S)-4-methyl-2-{[1-((2R,5S)-2-methyl-5-{(S)-4-methyl-2-[(1-quinolin-8-yl-methanoyl)-amino]-pentanoylamino}-6-oxo-azepan-1-yl)-methanoyl]-amino}-pentanoic acid methyl ester;

(S)-4-methyl-2-{[1-((2R,5S)-2-methyl-5-{(S)-4-methyl-2-[(1-quinolin-8-yl-methanoyl)-amino]-pentanoylamino}-6-oxo-azepan-1-yl)-methanoyl]-amino}-pentanoic acid;

(R)-2-{[1-(4-{(S)-2-[(1-benzofuran-2-yl-methanoyl)-amino]-4-methyl-pentanoylamino}-3-oxo-azepan-1-yl)-methanoyl]-amino}-4-methyl-pentanoic acid methyl ester;

(R)-2-{[1-(4-{(S)-2-[(1-benzofuran-2-yl-methanoyl)-amino]-4-methyl-pentanoylamino}-3-oxo-azepan-1-yl)-methanoyl]-amino}-4-methyl-pentanoic acid;

(R)-2-biphenyl-3-yl-4-methyl-pentanoic acid [(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-yl]-amide

3-methyl-furo[3,2-b]-pyridine-2-carboxylic acid {1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-cyclohexyl}-amide; and

1-(3-cyclohexyl-propanoylamino)-cyclohexanecarboxylic acid [(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-yl]-amide.

53. A compound according to Claim 52 which is benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

54. A pharmaceutical composition comprising a compound according to Claims 1 to 53 and a pharmaceutically acceptable carrier, diluent or excipient.

55. A method of inhibiting a protease, comprising administering to a patient in need thereof an effective amount of a compound according to Claims 1 to 53.

56. A method according to Claim 55 wherein said protease is selected from the group consisting of a cysteine protease and a serine protease.

57. A method according to Claim 56 wherein said protease is a cysteine protease.

58. A method according to Claim 57 wherein said cysteine protease is cathepsin K.

59. A method according to claim 57 wherein the cysteine protease is falcipain.

60. A method of treating a disease characterized by bone loss comprising inhibiting said bone loss by administering to a patient in need thereof an effective amount of a compound according to Claims 1 to 53.

61. A method according to Claim 60 wherein said disease is osteoporosis.

62. A method according to Claim 60 wherein said disease is periodontitis.

63. A method according to Claim 60 wherein said disease is gingivitis.

64. A method of treating a disease characterized by excessive cartilage or matrix degradation comprising inhibiting said excessive cartilage or matrix degradation by administering to a patient in need thereof an effective amount of a compound according to Claims 1 to 53.

65. A method according to Claim 64 wherein said disease is osteoarthritis.

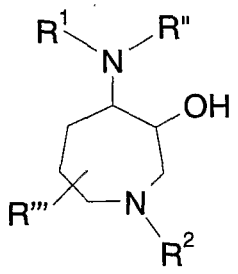
66. A method according to Claim 64 wherein said disease is rheumatoid arthritis.

67. A method of treating a disease characterized by infection by a parasite selected from the group consisting of: *Plasmodium falciparum*, *Trypanosoma cruzi*, *Trypanosoma Brucei*, *Leishmania mexicana*, *Leishmania pifanoi*, *Leishmania major*, *Schistosoma mansoni*, *Onchocerca volvulus*, *Brugia pahangi*, *Entamoeba histolytica*, *Giardia lamblia*, the helminths *Haemonchus contortus* and *Fasciola hepatica*, the helminths of the genera *Spirometra*, *Trichinella*, *Necator* and *Ascaris*, and protozoa of the genera *Cryptosporidium*, *Eimeria*, *Toxoplasma* and *Naegleria*, comprising inhibiting expression of a cysteine protease causing said disease by administering to a patient in need thereof an effective amount of a compound according to any one of Claims 1 to 53.

68. A method according to Claim 67 wherein said disease is selected from a group consisting of: malaria, trypanosomiasis (African sleeping sickness, Chagas disease), leishmaniasis, schistosomiasis, onchocerciasis (river blindness) and giardiasis.

69. A method according to Claim 68 wherein said disease is malaria.

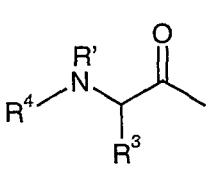
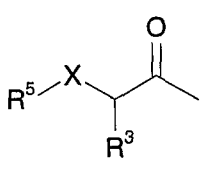
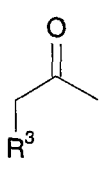
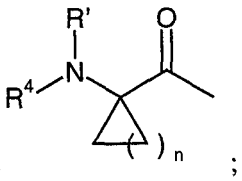
70. A compound of Formula II:

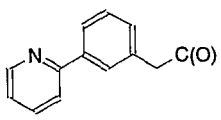
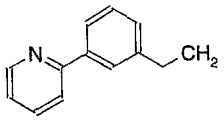
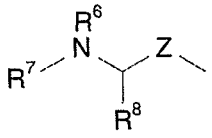


II

wherein:

R^1 is selected from the group consisting of:

 ;  ;  and  ;

R^2 is selected from the group consisting of: H, C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, $R^9C(O)$-, $R^9C(S)$-, R^9SO_2-, $R^9OC(O)$-, $R^9R^{11}NC(O)$-, $R^9R^{11}NC(S)$-, $R^9(R^{11})NSO_2$-  ,  and  ;

R^3 is selected from the group consisting of: H, C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, HetC_{0-6}alkyl, ArC_{0-6}alkyl, Ar-ArC_{0-6}alkyl, Ar-HetC_{0-6}alkyl, Het-ArC_{0-6}alkyl, and Het-HetC_{0-6}alkyl;

R^3 and R' may be connected to form a pyrrolidine, piperidine or morpholine ring;

R^4 is selected from the group consisting of: H, C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, $R^5C(O)$-, $R^5C(S)$-, R^5SO_2-, $R^5OC(O)$-, $R^5R^{12}NC(O)$-, and $R^5R^{12}NC(S)$-;

R^5 is selected from the group consisting of: H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, C_{2-6}alkanonyl, Ar-C_{0-6}alkyl and Het-C_{0-6}alkyl;

R^6 is selected from the group consisting of: H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl;

R^7 is selected from the group consisting of: H, C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, $R^{10}C(O)$-, $R^{10}C(S)$-, $R^{10}SO_2$-, $R^{10}OC(O)$-, $R^{10}R^{13}NC(O)$-, and $R^{10}R^{13}NC(S)$-;

R^8 is selected from the group consisting of: H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, HetC_{0-6}alkyl and ArC_{0-6}alkyl;

R^9 is selected from the group consisting of: C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl and Het-C_{0-6}alkyl;

R^{10} is selected from the group consisting of: C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl and Het-C_{0-6}alkyl;

R^{11} is selected from the group consisting of: H, C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, and Het-C_{0-6}alkyl;

R^{12} is selected from the group consisting of: H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, and Het-C_{0-6}alkyl;

R^{13} is selected from the group consisting of: H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, and Het-C_{0-6}alkyl;

R' is selected from the group consisting of: H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, and Het-C_{0-6}alkyl;

R" is selected from the group consisting of: H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl;

R'" is C_{1-6}alkyl;

X is selected from the group consisting of: CH_2, S, and O;

Z is selected from the group consisting of: C(O) and CH_2;

n is an integer from 1 to 5;

and pharmaceutically acceptable salts, hydrates and solvates thereof.

71. A compound according to Claim 70 wherein R'" is selected from the group consisting of: methyl, ethyl, propyl, butyl, pentyl, and hexyl.

72. A compound according to Claim 71 wherein R'" is methyl.

73. A compound according to Claim 70 wherein R'" is selected from the group consisting of: 5-, 6- and 7-C_{1-6}alkyl.

74. A compound according to Claim 73 wherein 5-, 6- and 7-C_{1-6}alkyl is selected from the group consisting of: 5-, 6- or 7-methyl, -ethyl, -propyl, -butyl, -pentyl, and -hexyl.

75. A compound according to Claim 74 wherein 5-, 6- and 7-C_{1-6}alkyl is selected from the group consisting of: 5-, 6- and 7-methyl.

76. A compound according to Claim 73 wherein R'" is selected from the group consisting of: 6- and 7-C_{1-6}alkyl.

77. A compound according to Claim 76 wherein 6- and 7-C_{1-6}alkyl is selected from the group consisting of: 6- or 7-methyl, -ethyl, -propyl, -butyl, -pentyl, and -hexyl.

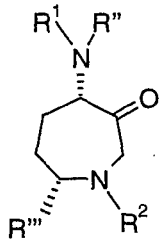
78. A compound according to Claim 77 wherein 6- and 7-C_{1-6}alkyl is selected from the group consisting of: 6- and 7-methyl.

79. A compound according to Claim 76 wherein R‴ is 7-C_{1-6}alkyl.

80. A compound according to Claim 79 wherein 7-C_{1-6}alkyl is selected from the group consisting of: 7-methyl, -ethyl, -propyl, -butyl, -pentyl, and -hexyl.

81. A compound according to Claim 80 wherein 7-C_{1-6}alkyl is 7-methyl.

82. A compound according to Claim 79 of Formula Ia:



Ia

wherein R‴ is *cis*-7-C_{1-6}alkyl.

83. A compound according to Claim 82 wherein *cis*-7-C_{1-6}alkyl is *cis*-7-methyl.

84. A compound according to Claim 70 selected from the group consisting of:

3-methyl-1-(pyridine-2-sulfonyl)-2,3,4,7-tetrahydro-1H-azepine;

5-methyl-3-(pyridine-2-sulfonyl)-8-oxa-3-aza-bicyclo[5.1.0]octane;

4-azido-5-methyl-1-(pyridine-2-sulfonyl)-azepan-3-ol;

4-amino-6-methyl-1-(pyridine-2-sulfonyl)-azepan-3-ol;

{(S)-1-[3-hydroxy-6-methyl-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-3-methyl-butyl}-carbamic acid tert-butyl ester;

5-methoxy-benzofuran-2-carboxylic acid {(S)-1-[3-hydroxy-6-methyl-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide;

allyl-(1-methyl-pent-4-enyl)-carbamic acid benzyl ester;

2-methyl-2,3,4,7-tetrahydro-azepine-1-carboxylic acid benzyl ester;

4-methyl-8-oxa-3-aza-bicyclo[5.1.0]octane-3-carboxylic acid benzyl ester;

5-azido-6-hydroxy-2-methyl-azepane-1-carboxylic acid benzyl ester;

5-amino-6-hydroxy-2-methyl-azepane-1-carboxylic acid benzyl ester;

(2R,5S,6S)-5-((S)-2- tert -butoxycarbonylamino-4-methyl-pentanoylamino)-6-hydroxy-2-methyl-azepane-1 -carboxylic acid benzyl ester;

(2S,5R,6R)-5-((S)-2- tert -butoxycarbonylamino-4-methyl-pentanoylamino)-6-hydroxy-2-methyl-azepane-1 -carboxylic acid benzyl ester;

[(S)-1-((3S,4S,7R)-3-hydroxy-7-methyl-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid tert -butyl ester;

[(S)-1-((3R,4R,7S)-3-hydroxy-7-methyl-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid tert -butyl ester;

[(S)-1-((3S,4S,7R)-1-benzenesulfonyl-3-hydroxy-7-methyl-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid tert -butyl ester;

[(S)-1-((3R,4R,7S)-1-benzenesulfonyl-3-hydroxy-7-methyl-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid tert -butyl ester;

(S)-2-amino-4-methyl-pentanoic acid ((3S,4S,7R)-1-(2-pyridine)-sulfonyl-3-hydroxy-7-methyl-azepan-4-yl)-amide;

(S)-2-amino-4-methyl-pentanoic acid ((3R,4R,7S)-1-(2-pyridine)-sulfonyl-3-hydroxy-7-methyl-azepan-4-yl)-amide;

benzofuran-2-carboxylic acid {(S)-1-[(3S,4S,7R)-3-hydroxy-7-methyl-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide;

benzofuran-2-carboxylic acid {(S)-1-[(3R,4R,7S)-3-hydroxy-7-methyl-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide;

((R)-1-methyl-pent-4-enyl)-carbamic acid benzyl ester;

allyl-((R)-1-methyl-pent-4-enyl)-carbamic acid benzyl ester;

2-methyl-2,3,4,7-tetrahydro-azepine-1-carboxylic acid benzyl ester;

(1S,4R,7R)-4-methyl-8-oxa-3-aza-bicyclo[5.1.0]octane-3-carboxylic acid benzyl ester;

(2R,5S,6S)-5-azido-6-hydroxy-2-methyl-azepane-1-carboxylic acid benzyl ester;

(2R,5S,6S)-5-amino-6-hydroxy-2-methyl-azepane-1-carboxylic acid benzyl ester;

(2R,5S,6S)-5-((S)-2- tert -butoxycarbonylamino-4-methyl-pentanoylamino)-6-hydroxy-2-methyl-azepane-1 -carboxylic acid benzyl ester;

[(S)-1-((3S,4S,7R)-3-hydroxy-7-methyl-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid tert -butyl ester;

[(S)-1-((3S,4S,7R)-2-pyridinesulfonyl-3-hydroxy-7-methyl-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid tert -butyl ester;

(S)-2-amino-4-methyl-pentanoic acid ((3S,4S,7R)-1-(2-pyridine)-sulfonyl-3-hydroxy-7-methyl-azepan-4-yl)-amide;

5-methoxy-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(3R,4R,6R)-6-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

benzo[b]thiophene-2-carboxylic acid {(S)- 1-[(3S,4S,6S)-6-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide;

benzo[b]thiophene-2-carboxylic acid {(S)- 1-[(3R,4R,6R)-6-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide;

3-methyl-benzofuran-2-carboxylic acid {(S)- 1-[(3S,4S,6S)-6-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide;

3-methyl-benzofuran-2-carboxylic acid {(S)- 1-[(3R,4R,6R)-6-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide;

thieno[3,2-b]thiophene-2-carboxylic acid {(S)- 1-[(3S,4S,6S)-6-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide;

thieno[3,2-b]thiophene-2-carboxylic acid {(S)- 1-[(3S,4R,6R)-6-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide;

benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(3S,4S,7R)-7-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(3S,4S,7S)-7-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(3R,4R,7S)-7-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(3R,4R,7R)-7-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

((R)-2-iodo-1-methyl-ethyl)-carbamic acid benzyl ester

((R)-1-methyl-pent-4-enyl)-carbamic acid benzyl ester;

allyl-((R)-1-methyl-pent-4-enyl)-carbamic acid benzyl ester;

2-methyl-2,3,4,7-tetrahydro-azepine-1-carboxylic acid benzyl ester;

(1S,4R,7R)-4-methyl-8-oxa-3-aza-bicyclo[5.1.0]octane-3-carboxylic acid benzyl ester;

(2R,5S,6S)-5-azido-6-hydroxy-2-methyl-azepane-1-carboxylic acid benzyl ester;

(2R,5S,6S)-5-amino-6-hydroxy-2-methyl-azepane-1-carboxylic acid benzyl ester;

(2R,5S,6S)-5-((S)-2- tert -butoxycarbonylamino-4-methyl-pentanoylamino)-6-hydroxy-2-methyl-azepane-1 -carboxylic acid benzyl ester;

[(S)-1-((3S,4S,7R)-3-hydroxy-7-methyl-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid tert -butyl ester;

[(S)-1-((3S,4S,7R)-2-pyridinesulfonyl-3-hydroxy-7-methyl-azepan-4-ylcarbamoyl)-3-methyl-butyl]-carbamic acid tert -butyl ester;

(S)-2-amino-4-methyl-pentanoic acid ((3S,4S,7R)-1-(2-pyridine)-sulfonyl-3-hydroxy-7-methyl-azepan-4-yl)-amide;

furo[3,2-b]pyridine-2-carboxylic acid {(S)-1-[(3S,4S,7R)-3-hydroxy-7-methyl-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide;

furo[3,2-b]pyridine-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

3-methyl-furo[3,2-b]pyridine-2-carboxylic acid {(S)-1-[(3S,4S,7R)-3-hydroxy-7-methyl-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-3-methyl-butyl}-amide;

3-methyl-furo[3,2-b]pyridine-2-carboxylic acid {(S)-3-methyl-1-[(4S,7R)-7-methyl-3-oxo-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

quinoline-6-carboxylic acid {(S)-3-methyl-1-[(3S,4S,7R)-7-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

quinoline-3-carboxylic acid {(S)-3-methyl-1-[(3S,4S,7R)-7-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

5-methoxy-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(3S,4S,7R)-7-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

3-methyl-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(3S,4S,7R)-7-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

thieno[3,2-b]thiophene-2-carboxylic acid {(S)-3-methyl-1-[(3S,4S,7R)-7-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

quinoxaline-2-carboxylic acid {(S)-3-methyl-1-[(3S,4S,7R)-7-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

thieno[3,2-b] thiophene-2-carboxylic acid {(S)-3-methyl-1-[(3S,4S,7R)-7-methyl-3-hydroxy-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

3-methyl-benzofuran-2-carboxylicacid {(S)-3-methyl-1-[(3S,4S,7R)-7-methyl-3-hydroxy-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(3S,4S,7R)-7-methyl-3-hydroxy-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

quinoline-2-carboxylic acid {(S)-3-methyl-1-[(3S,4S,7R)-7-methyl-3-hydroxy-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

5,6-difluoro-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(3S,4S,7R)-7-methyl-3-hydroxy-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

5-fluoro-3-methyl-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(3S,4S,7R)-7-methyl-3-hydroxy-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

5-fluoro-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(3S,4S,7R)-7-methyl-3-hydroxy-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

3-methyl-furo[3,2-b]]pyridine-2-carboxylic acid {(S)-3-methyl-1-[(3S,4S,7R)-7-methyl-3-hydroxy-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

cyclohexanecarboxylic acid {(S)-3-methyl-1-[(3S,4S,7R)-7-methyl-3-hydroxy-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

(S)-2-(2-cyclohexyl-ethanoylamino)-4-methyl-pentanoic acid [(3S,4S,7R)-7-methyl-3-hydroxy-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-yl]-amide;

(S)-2-(3-cyclohexyl-propanoylamino)-4-methyl-pentanoic acid [(3S,4S,7R)-7-methyl-3-hydroxy-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-yl]-amide;

(S)-2-(4-cyclohexyl-butanoylamino)-4-methyl-pentanoic acid [(3S,4S,7R)-7-methyl-3-hydroxy-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-yl]-amide;

(S)-2-(5-cyclohexyl-pentanoylamino)-4-methyl-pentanoic acid [(3S,4S,7R)-7-methyl-3-hydroxy-1-(1-oxy-pyridine-2-sulfonyl)-azepan-4-yl]-amide;

benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(3S,4S,7R)-7-methyl-3-hydroxy-1-(5-trifluoromethyl-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

5-fluoro-benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(3S,4S,7R)-7-methyl-3-hydroxy-1-(5-trifluoromethyl-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

thieno[3,2-b] thiophene-2-carboxylic acid {(S)-3-methyl-1-[(3S,4S,7R)-7-methyl-3-hydroxy-1-(5-trifluoromethyl-pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

benzofuran-2-carboxylic acid {1-[(3S,4S,7R)-7-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-cyclohexyl}-amide;

thiophene-3-carboxylic acid {(S)-3,3-dimethyl-1-[(3S,4S,7R)-7-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

furan-2-carboxylic acid {(S)-3,3-dimethyl-1-[(3S,4S,7R)-7-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

thieno[3,2-b] thiophene-2-carboxylic acid {(S)-3,3-dimethyl-1-[(3S,4S,7R)-7-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-butyl}-amide;

benzofuran-2-carboxylic acid {(S)-2-cyclohexyl-1-[(3S,4S,7R)-7-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide;

furan-2-carboxylic acid {(S)-2-cyclohexyl-1-[(3S,4S,7R)-7-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide;

thiophene-3-carboxylic acid {(S)-2-cyclohexyl-1-[(3S,4S,7R)-7-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide;

3-methyl-furo[3,2-b]- pyridine-2-carboxylic acid {(S)-2-cyclohexyl-1-[(3S,4S,7R)-7-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-ethyl}-amide;

(2R,4aR,8aR)-octahydro-benzo[1,4]dioxine-2-carboxylic acid [(S)-1-((3S,4S,7R)-1-methanesulfonyl-7-methy l-3-hydroxy-azepan-4-ylcarbamoyl)-3-methyl-butyl]-amide;

furan-2-carboxylic acid [(S)-2-cyclohexyl-1-((3S,4S,7R)-7-methyl-3-hydroxy-1-propyl-azepan-4-ylcarbamoyl)-ethyl]-amide;

thiophene-3-carboxylic acid [(S)-2-cyclohexyl-1-((3S,4S,7R)-7-methyl-3-hydroxy-1-propyl-azepan-4-ylcarbamoyl)-ethyl]-amide;

benzofuran-2-carboxylic acid [(S)-2-cyclohexyl-1-((3S,4S,7R)-7-methyl-3-hydroxy-1-propyl-azepan-4-ylcarbamoyl)-ethyl]-amide;

1-(3-cyclohexyl-propanoylamino)-cyclohexanecarboxylic acid ((3S,4S,7R)-1-cyclohexylmethyl-7-methyl-3-hydroxy-azepan-4-yl)-amide;

benzofuran-2-carboxylic acid [1-((3S,4S,7R)-1-cyclohexylmethyl-7-methyl-3-hydroxy-azepan-4-ylcarbamoyl)-cyclohexyl]-amide;

benzofuran-2-carboxylic acid [(S)-3-methyl-1-((3S,4S,7R)-7-methyl-3-hydroxy-1-propyl-azepan-4-ylcarbamoyl)- butyl]-amide;

(2R,5S)-5-((S)-2-tert-butoxycarbonylamino-4-methyl-pentanoylamino)-2-methyl-6-hydroxy-azepane-1-carboxylic acid benzyl ester;

benzofuran-2-carboxylic acid {(S)-3-methyl-1-[(3S,4S,7R)-7-methyl-1-(1-morpholin-4-yl-methanoyl)-3-hydroxy- azepan-4-ylcarbamoyl]-butyl}-amide;

(S)-2-(3-cyclohexyl-propanoylamino)-4-methyl-pentanoic acid [(3S,4S,7R)-7-methyl-1-(1-morpholin-4-yl-me thanoyl)-3-hydroxy-azepan-4-yl]-amide;

(2R,5S,6S)-5-{(S)-2-[(1-benzofuran-2-yl-methanoyl)-amino]-4-methyl-pentanoylamino}-2-methyl-6-hydroxy-azepane-1-carboxylic acid (tetrahydro-pyran-4-yl)-amide;

(S)-2-{[1-((2R,5S,6S)-5-{(S)-2-[(1-benzofuran-2-yl-methanoyl)-amino]-4-methyl-pentanoylamino}-2-methyl-6-hydroxy-azepan-1-yl)-methanoyl]-amino}-4-methyl-pentanoic acid methyl ester;

(S)-2-{[1-(4-{(S)-2-[(1-benzofuran-2-yl-methanoyl)-amino]-4-methyl-pentanoylamino}-3-hydroxy-azepan-1-yl)-methanoyl]-amino}-4-methyl-pentanoica cid methyl ester;

(S)-4-methyl-2-{[1-((2R,5S,6S)-2-methyl-5-{(S)-4-methyl-2-[(1-quinolin-8-yl-methanoyl)-amino]-pentanoylamino}-6-hydroxy-azepan-1-yl)-methanoyl]-amino}-pentanoic acid methyl ester;

(R)-2-{[1-(4-{(S)-2-[(1-benzofuran-2-yl-methanoyl)-amino]-4-methyl-pentanoylamino}-3-hydroxy-azepan-1-yl)-methanoyl]-amino}-4-methyl-pentanoic acid methyl ester;

2-biphenyl-3-yl-4-methyl-pentanoic acid [(3R, 4R,7R)-7-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-yl]-amide;

3-methyl-furo[3,2-b]-pyridine-2-carboxylic acid {1-[(4S,7R)-7-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-cyclohexyl}-amide; and

1-(3-cyclohexyl-propanoylamino)-cyclohexanecarboxylic acid [(4S,7R)-7-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-yl]-amide.

85. A process for the synthesis of a compound according to Claim 1 comprising the step of oxidizing a corresponding compound of Claim 70 with an oxidant to provide the compound of Formula (I) as a mixture of diastereomers.

86. The process of Claim 85 wherein the oxidant is sulfur dioxide-pyridine complex.

87. The process of Claim 85 further comprising the step of separating the diasteromers by separating means.

88. The process of Claim 87 wherein said separating means is high presssure liquid chromatography (HPLC).

89. The process of Claim 85 further comprising the step of deuterating said diastereomers with a deuterating agent.

90. The process of Claim 89 wherein said deuterating agent is CD_3OD: D_2O (10:1) in triethylamine.

(S)-4-methyl-2-{[1-((2R,5S,6S)-2-methyl-5-{(S)-4-methyl-2-[(1-quinolin-8-yl-methanoyl)-amino]-pentanoylamino}-6-hydroxy-azepan-1-yl)-methanoyl]-amino}-pentanoic acid methyl ester;

(R)-2-{[1-(4-{(S)-2-[(1-benzofuran-2-yl-methanoyl)-amino]-4-methyl-pentanoylamino}-3-hydroxy-azepan-1-yl)-methanoyl]-amino}-4-methyl-pentanoic acid methyl ester;

2-biphenyl-3-yl-4-methyl-pentanoic acid [(3R, 4R,7R)-7-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-yl]-amide;

3-methyl-furo[3,2-b]-pyridine-2-carboxylic acid {1-[(4S,7R)-7-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-ylcarbamoyl]-cyclohexyl}-amide; and

1-(3-cyclohexyl-propanoylamino)-cyclohexanecarboxylic acid [(4S,7R)-7-methyl-3-hydroxy-1-(pyridine-2-sulfonyl)-azepan-4-yl]-amide.

85. A process for the synthesis of a compound according to Claim 1 comprising the step of oxidizing a corresponding compound of Claim 70 with an oxidant to provide the compound of Formula (I) as a mixture of diastereomers.

86. The process of Claim 85 wherein the oxidant is sulfur dioxide-pyridine complex.

87. The process of Claim 85 further comprising the step of separating the diasteromers by separating means.

88. The process of Claim 87 wherein said separating means is high presssure liquid chromatography (HPLC).

89. The process of Claim 85 further comprising the step of deuterating said diastereomers with a deuterating agent.

90. The process of Claim 89 wherein said deuterating agent is CD_3OD: D_2O (10:1) in triethylamine.

91. Use of a compound according to any one of Claims 1 to 53 in the manufacture of a medicament for use in inhibiting a protease selected from the group consisting of a cysteine protease and a serine protease.

92. A use according to Claim 91 wherein said protease is a cysteine protease.

93. A use according to Claim 92 wherein said cysteine protease is cathepsin K.

94. A use according to claim 92 wherein the cysteine protease is falcipain.

95. Use of a compound according to any one of Claims 1 to 53 in the manufacture of a medicament for use in treating a disease characterized by bone loss.

96. A use according to Claim 95 wherein said disease is osteoporosis.

97. A use according to Claim 95 wherein said disease is periodontitis.

98. A use according to Claim 95 wherein said disease is gingivitis.

99. Use of a compound according to any one of Claims 1 to 53 in the manufacture of a medicament for use in treating a disease characterized by excessive cartilage or matrix degradation.

100. A use according to Claim 99 wherein said disease is osteoarthritis.

101. A use according to Claim 99 wherein said disease is rheumatoid arthritis.

102. Use of a compound according to any one of Claims 1 to 53 in the manufacture of a medicament for treating a disease caused by infection by a parasite selected from the group consisting of: *Plasmodium falciparum*, *Trypanosoma cruzi*, *Trypanosoma Brucei*, *Leishmania mexicana*, *Leishmania pifanoi*, *Leishmania major*, *Schistosoma mansoni*, *Onchocerca volvulus*, *Brugia pahangi*, *Entamoeba histolytica*, *Giardia lamblia*, the helminths *Haemonchus contortus* and *Fasciola hepatica*, the helminths of the genera

Spirometra, *Trichinella*, *Necator* and *Ascaris*, and protozoa of the genera *Cryptosporidium*, *Eimeria*, *Toxoplasma* and *Naegleria*.

103. A use according to Claim 102 wherein said disease is selected from a group consisting of: malaria, trypanosomiasis (African sleeping sickness, Chagas disease), leishmaniasis, schistosomiasis, onchocerciasis (river blindness) and giardiasis.

104. A use according to Claim 103 wherein said disease is malaria.