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(54) Title: NOVEL KETO-OXADIAZOLE DERIVATIVES AS CATHEPSIN INHIBITORS

(57) Abstract: Novel difluorinated amide derivatives of Formula (II) as inhibitors of cathepsin S, K, B, and L, the pharmaceutically acceptable salts and *N*-oxides thereof, their uses as therapeutic agents and the methods of their making.

NOVEL COMPOUNDS AND COMPOSITIONS AS CATHEPSIN INHIBITORS

FIELD OF THE INVENTION

This invention relates to the use of novel difluoro derivatives for treating diseases associated with cysteine protease and, particularly, diseases associated with activity of cathepsin S, K, and B. This invention also relates to processes of making such compounds.

BACKGROUND OF THE INVENTION

Cysteine proteases represent a class of peptidases characterized by the presence of a cysteine residue in the catalytic site of the enzyme. Cysteine proteases are associated with the normal degradation and processing of proteins. The aberrant activity of cysteine proteases, for example, as a result of increased expression or enhanced activation, however, may have pathological consequences. In this regard, certain cysteine proteases are associated with a number of disease states, including arthritis, atherosclerosis, emphysema, osteoporosis, muscular dystrophy, inflammation, tumor invasion, glomerulonephritis, periodontal disease, metachromatic leukodystrophy and others.

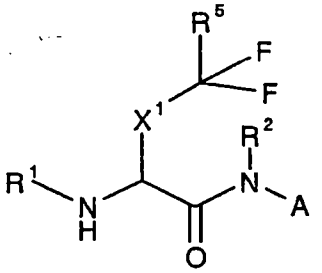
An increase in cathepsin activity such as, for example, cathepsin S, contributes to the pathology and/or symptomatology of a number of diseases such as, for example, autoimmune disorders, including, but not limited to, juvenile onset diabetes, multiple sclerosis, pemphigus vulgaris, Graves' disease, myasthenia gravis, systemic lupus erythemotasus, irritable bowel disease, rheumatoid arthritis and Hashimoto's thyroiditis, allergic disorders including but not limited to, asthma, and allogeneic immune responses, including, but not limited to, organ transplants or tissue grafts. Cathepsin S is also implicated in disorders involving excessive elastolysis, such as chronic obstructive pulmonary disease (e.g., emphysema), bronchiolitis, excessive airway elastolysis in asthma and bronchitis, pneumonities and cardiovascular disease such as plaque rupture and atheroma. Cathepsin S is implicated in fibril formation and, therefore, inhibitors of cathepsin S may be of use in treatment of systemic amyloidosis.

The activity of, for example, cathepsin B in synovial fluid is significantly elevated in osteoarthritis models (F. Mehraban Ann. Rheum. Dis. 1997; *56*, 108-115). Similarly, cathepsin K is a critical protease in synovial fibroblast-mediated collagen degradation (W.-S. Hou (et al.) Am. J. Pathol. 2001, 159, 2167-2177). Thus, inhibition of Cathepsin B and K, for example, is a useful method for the treatment of degenerative joint diseases such as, for example, osteoarthritis. Cathepsin K inhibition, for example, leads to inhibition of bone resorption (G. B. Stroup (et al.) J. Bone Mineral Res. 2001, 16, 1739-1746). Cathepsin K inhibitors are, therefore, useful for the treatment of osteoporosis.

It is known in the art that cathepsins play an important role in the degradation of connective tissues, the generation of bioactive proteins and antigen processing. They have been implicated in osteoporosis, muscular dystrophy, bronchitis, emphysema, viral infection, cancer metastasis and neurodegenerative diseases, such as Alzheimer's disease and Huntington's disease. Recently, increased interest in cathepsin inhibitors has been generated with potential therapeutic targets, such as cathepsin K or cathepsin L for osteoporosis and cathepsin S for immune modulation (W. Kim., K. Kang. Expert Opin. Ther. Pat. 2002, 12, 419-432). An increase in cathepsin K or B activity contributes to the pathology and/or symptomatology of a number of diseases. Accordingly, molecules that inhibit the activity of cathepsin protease are useful as therapeutic agents in the treatment of such diseases.

SUMMARY OF THE INVENTION

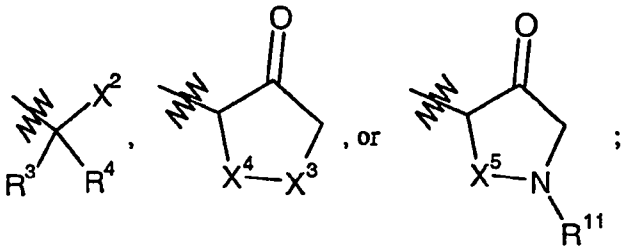
In one aspect of the present invention, compounds are provided that inhibit the enzymatic activity of cathepsin S, B, and K and have a structure of formula (I):



(I)

wherein

A is



X^1 is methylene, ethylene or a bond;

X^2 is CN, CHO, $C(O)R^6$, $C(O)C(O)NR^7R^7$, $C(O)C(O)NR^7R^8$, $C(O)C(O)R^{13}$, $C(O)C(O)OR^{13}$, $C(O)CH_2X^3R^{13}$;

X^3 is selected from the group consisting of O, $S(O)_n$, CO, CONH, NHCO, $NHSO_2$ and SO_2NH;

X^4 is $CH(R^{12})$ or $CH(R^{12})$-CH_2;

X^5 is methylene, ethylene, propylene or a bond;

X^6 is a bond or (C_{1-2})alkylene;

R^1 is H, $R^{13}C(O)$-, $R^{13}S(O)_2$-, $R^{13}OC(O)$-, $R^8R^7NC(O)$-, $R^8R^7NS(O)_2$-; $R^{13}S(O)_2NC(O)$- or $R^{13}C(O)NS(O)_2$-; or R^1 is selected from the group consisting of (C_{1-9})alkyl, (C_{3-12})cycloalkyl(C_{0-6})alkyl, hetero(C_{5-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl and hetero(C_{5-13})aryl(C_{0-6})alkyl , each of which is optionally substituted by 1 to 5 radicals independently selected from a group consisting of (C_{1-4})alkyl, cyano, halo, halo-substituted (C_{1-4})alkyl, $-X^6NR^9R^9$, $-X^6OR^9$, $-X^6SR^9$, $-X^6C(O)NR^9R^9$, $-X^6OC(O)NR^9R^9$, $-X^6C(O)OR^9$, $-X^6NC(O)OR^9$, $-X^6S(O)R^{10}$, $-X^6S(O)_2R^{10}$ and $-X^6C(O)R^{10}$;

R^2 is selected from the group consisting of hydrogen, (C_{1-6})alkyl, (C_{3-12})cycloalkyl(C_{0-6})alkyl, hetero(C_{5-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl or hetero(C_{5-12})aryl(C_{0-6})alkyl;

R^3 is selected from the group consisting of H, (C_{1-6})alkyl, (C_{3-12})cycloalkyl(C_{0-6})alkyl, hetero(C_{5-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl or hetero(C_{5-13})aryl(C_{0-6})alkyl optionally is substituted by 1 to 5 radicals independently selected from a group consisting of (C_{1-4})alkyl, cyano, halo, halo-substituted (C_{1-4})alkyl, $-X^6NR^9R^9$, $-X^6OR^9$, $-X^6SR^9$, $-X^6C(O)NR^9R^9$, $-X^6OC(O)NR^9R^9$, $-X^6C(O)OR^9$, $-X^6NC(O)OR^9$, $-X^6S(O)R^{10}$, $-X^6S(O)_2R^{10}$ and $-X^6C(O)R^{10}$;

R^4 is H or (C_{1-6})alkyl; or R^3 and R^4 taken together with the carbon atom to which both R^3 and R^4 are attached to form (C_{3-8})cycloalkylene or (C_{3-8})heterocycloalkylene;

R^5 is H, F, or R^5 is (C_{1-9})alkyl, (C_{3-12})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl, hetero(C_{5-13})aryl(C_{0-6})alkyl each optionally substituted by 1 to 5 radicals independently selected from a group consisting of (C_{1-4})alkyl,

cyano, halo, halo-substituted (C_{1-4})alkyl, $-X^6NR^9R^9$, $-X^6OR^9$, $-X^6SR^9$, $-X^6C(O)NR^9R^9$, $-X^6OC(O)NR^9R^9$, $-X^6C(O)OR^9$, $-X^6NC(O)OR^9$, $-X^6S(O)R^{10}$, $-X^6S(O)_2R^{10}$ and $-X^6C(O)R^{10}$;

R^6 is (C_{6-12})aryl, hetero(C_{5-13})aryl and halo substituted (C_{1-6}) alkyl; wherein R^6 is optionally is substituted by 1 to 5 radicals independently selected from a group consisting of (C_{1-9})alkyl, (C_{3-12})cycloalkyl(C_{0-6})alkyl, hetero(C_{5-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl, hetero(C_{5-13})aryl(C_{0-6})alkyl, cyano, halo, halo-substituted (C_{1-6})alkyl, $-X^6NR^9R^9$, $-X^6OR^9$, $-X^6SR^9$, $-X^6C(O)NR^9R^9$, $-X^6OC(O)NR^9R^9$, $-X^6C(O)OR^9$, $-X^6NC(O)OR^9$, $-X^6S(O)R^{10}$, $-X^6S(O)_2R^{10}$ and $-X^6C(O)R^{10}$;

R^7 is H, (C_{1-6})alkyl, (C_{3-12})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl, hetero(C_{5-13})aryl(C_{0-6})alkyl, and halo substituted (C_{1-6}) alkyl; wherein R^7 is optionally is substituted by 1 to 5 radicals independently selected from a group consisting of (C_{1-4})alkyl, cyano, halo, halo-substituted (C_{1-4})alkyl, $-X^6NR^9R^9$, $-X^6OR^9$, $-X^6SR^9$, $-X^6C(O)NR^9R^9$, $-X^6OC(O)NR^9R^9$, $-X^6C(O)OR^9$, $-X^6NC(O)OR^9$, $-X^6S(O)R^{10}$, $-X^6S(O)_2R^{10}$ and $-X^6C(O)R^{10}$;

R^8 is selected from the group consisting of H, (C_{1-6})alkyl, (C_{3-12})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl, and hetero(C_{5-13})aryl(C_{0-6})alkyl, or R^7 and R^8 together with the atom attached to form (C_{3-8})cycloalkylene or (C_{3-8})heterocycloalkylene;

R^9 at each occurrence independently is hydrogen, (C_{1-6})alkyl or halo-substituted (C_{1-6})alkyl;

R^{10} is (C_{1-6})alkyl or halo-substituted (C_{1-6})alkyl;

R^{11} is selected from the group consisting of hydrogen, (C_{1-9})alkyl, (C_{3-12})cycloalkyl(C_{0-6})alkyl, hetero(C_{5-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl, hetero(C_{5-13})aryl(C_{0-6})alkyl, (C_{9-12})bicycloaryl(C_{0-3})alkyl, hetero(C_{8-12})-bicycloaryl(C_{0-3})alkyl, $-C(O)R^{13}$, $-C(S)R^{13}$, $-S(O)_2R^{13}$, $-C(O)OR^{13}$, $-C(O)N(R^7)R^8$, $-C(S)N(R^7)R^8$ and $-S(O)_2N(R^7)R^8$;

R^{12} is H or C_{1-6}alkyl optionally substituted by amido, (C_{6-12})aryl, hetero(C_{5-12})aryl, hetero(C_{5-12})cycloalkyl or hydroxy;

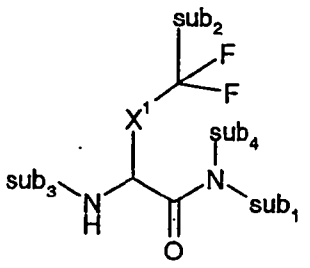
R^{13} is (C_{1-6})alkyl, (C_{3-12})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl, hetero(C_{5-13})aryl(C_{0-6})alkyl, and halo substituted (C_{1-6}) alkyl; wherein R^{13} is optionally is substituted by 1 to 5 radicals independently selected from a group consisting of (C_{1-4})alkyl, cyano, halo, halo-substituted (C_{1-4})alkyl, $-X^6NR^9R^9$, $-X^6OR^9$, $-X^6SR^9$,

$-X^6C(O)NR^9R^9$, $-X^6OC(O)NR^9R^9$, $-X^6C(O)OR^9$, $-X^6NC(O)OR^9$, $-X^6S(O)R^{10}$, $-X^6S(O)_2R^{10}$ and $-X^6C(O)R^{10}$; and

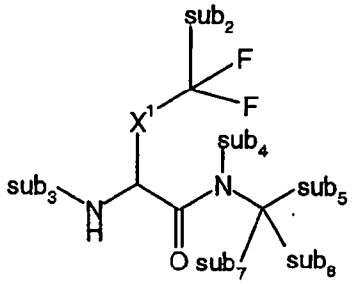
n is zero or an integer 1 or 2;

and their corresponding *N*-oxides, and their prodrugs, and their protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates (e.g. hydrates) of such compounds of Formula (Ia) and their *N*-oxides and their prodrugs, and their protected derivatives, individual isomers and mixtures of isomers thereof.

In another aspect of the present invention, the inventive subject matter is the backbone structures of Formulae II, III, IV or V, wherein sub_1-sub_8 are general substituents. The specific substituents at sub_1- sub_8 are not part of this aspect of the invention and can be any chemical groups or radicals which may be substituted at those positions (referred to as "general substituents" hereinafter), including those substitutions made possible by any conventional means or by any new technologies developed in the future. Thus, for the purpose of this application, "general substituents" do not serve as a claim element or limitation of the claim and they themselves may be novel and non-obvious, or unknown at the time of the invention.



II



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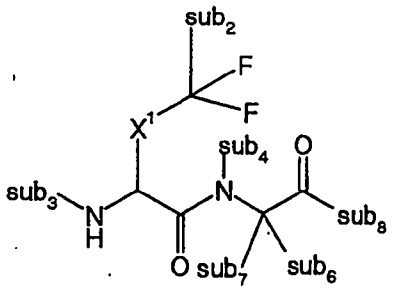
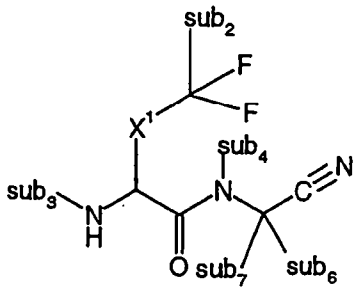


IV



V

In yet another aspect of the invention, the inventive subject matter includes the backbone structure of Formulae II, III, IV or V together with popular substituents at sub_1-sub_8. For the purpose

of this application, "a popular substituent" means a chemical group or radical which, at the time of the present invention, people of ordinary skill in the art, by using the specific substitutions disclosed hereinafter as guidance, would deem practical to substitute at sub_1-sub_8 without undue experimentation in practicing the present invention.

In still another aspect of the invention, the inventive subject matter includes the backbone structures of Formulae II, III, IV or V and specific substituents disclosed hereinafter at sub_1-sub_8. The specific substituent disclosed in the present application is refereed to as a "particular substituent." For the purpose of the present application, a particular substituent, if recited in the claims, serves as a claim limitation and may confer patentability on the claim by itself or in combination with the backbone structure along with other substituents therein.

Definitions:

Unless otherwise stated, the following terms used in the specification and claims are defined for the purposes of this Application and have the following meanings.

"A related chemical entity" of a compound, means an N-oxide derivative, a prodrug derivative, a protected derivative, an individual isomer, a mixture of isomers, or a pharmaceutically acceptable salt or solvate, of said compound, which can be prepared without undue experimentation by people with ordinary skill in the field.

"Acyl" means an H-CO- or alkyl-CO- group in which the alkyl group is as described herein.

"Acylamino" is an acyl-NH- group wherein acyl is as defined herein.

"Alkoxy" means an alkyl-O- group in which the alkyl group is as described herein. Exemplary alkoxy groups include allyloxy, difluoromethoxy, methoxy, trifluoromethoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy and heptoxy.

"Alkoxycarbonyl" means an alkyl-O-CO- group in which the alkyl group is as described herein. Exemplary alkoxycarbonyl groups include methoxy- and ethoxycarbonyl.

"Alkyl" represented by itself means a straight or branched, saturated or unsaturated, aliphatic radical having the number of carbon atoms indicated (e.g., (C_{1-6})alkyl includes methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, isobutyl, *tert*-butyl, vinyl, allyl, 1-propenyl, isopropenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methylallyl, ethynyl, 1-propynyl, 2-propynyl, and the like). Alkyl represented along with another radical (e.g., as in arylalkyl) means a straight or branched, saturated or unsaturated aliphatic divalent radical having the number of atoms indicated or when no atoms are indicated means a bond (e.g., (C_{6-12})aryl(C_{0-6})alkyl includes phenyl, benzyl, phenethyl, 1-phenylethyl 3-phenylpropyl, and the like). It will be appreciated by those skilled in the art that when alkyl represents an unsaturated aliphatic radical such radicals may not be attached directly to an oxygen, nitrogen or sulphur atom via the carbon carbon multiple bond of said unsaturated aliphatic radical.

"Alkylene", unless indicated otherwise, means a straight or branched, saturated or unsaturated, aliphatic, divalent radical having the number of carbon atoms indicated, (C_{1-2})alkylene includes methylene (-CH_2-) and ethylene (-CH_2CH_2-). It will be appreciated by those skilled in the art that when alkylene represents an unsaturated, aliphatic, divalent radical such radicals may not be attached directly to an oxygen, nitrogen or sulphur atom via the carbon carbon multiple bond of said unsaturated, aliphatic, divalent radical.

"Alkylenedioxy" means an -O-alkylene-O- group in which alkylene is as defined above. Exemplary alkylenedioxy groups include methylenedioxy and ethylenedioxy.

"Alkylsulfinyl" means an alkyl-SO- group in which the alkyl group is as previously described. Preferred alkylsulfinyl groups are those in which the alkyl group is C_{1-4}alkyl.

"Alkylsulfonyl" means an alkyl-SO_2- group in which the alkyl group is as previously described. Preferred alkylsulfonyl groups are those in which the alkyl group is C_{1-4}alkyl.

"Alkylthio" means an alkyl-S- group in which the alkyl group is as previously described. Exemplary alkylthio groups include methylthio, ethylthio, isopropylthio and heptylthio.

"Aromatic" means a moiety wherein the constituent atoms make up an unsaturated ring system, all atoms in the ring system are sp^2 hybridized and the total number of pi electrons is equal to 4n+2.

"Aroyl" means an aryl-CO- group in which the aryl group is as described herein. Exemplary aroyl groups include benzoyl and 1- and 2-naphthoyl.

"Aroylamino" is an aroyl-NH- group wherein aroyl is as previously defined.

"Aryl" as a group or part of a group denotes: (i) an optionally substituted monocyclic or multicyclic aromatic carbocyclic moiety of 6 to 12 carbon atoms, such as phenyl or naphthyl; or (ii) an optionally substituted partially saturated multicyclic aromatic carbocyclic moiety in which an aryl and a cycloalkyl or cycloalkenyl group are fused together to form a cyclic structure, such as a tetrahydronaphthyl, indenyl or indanyl ring. Except where otherwise defined, aryl groups may be substituted with one or more aryl group substituents, which may be the same or different, where "aryl group substituent" includes, for example, acyl, acylamino, alkoxy, alkoxycarbonyl, alkylenedioxy, alkylsulfinyl, alkylsulfonyl, alkylthio, aroyl, aroylamino, aryl, arylalkyloxy, arylalkyloxycarbonyl, arylalkylthio, aryloxy, aryloxycarbonyl, arylsulfinyl, arylsulfonyl, arylthio, carboxy (or an acid bioisostere), cyano, cycloalkyl, halo, heteroaroyl, heteroaryl, heteroarylalkyloxy, heteroaroylamino, heteroaryloxy, heterocycloalkyl, hydroxy, nitro, trifluoromethyl, -NY^3Y^4, -$CONY^3Y^4$, -$SO_2NY^3Y^4$, -NY^3-C(=O)alkyl, -NY^3SO_2alkyl or alkyl optionally substituted with aryl, heteroaryl, hydroxy, or -NY^3Y^4(in which Y^3 and Y^4 are independently hydrogen, alkyl, aryl, arylalkyl, cycloalkyl, heteroaryl or heteroarylalkyl; or the group -NY^3Y^4 may form a cyclic amine). Exemplary optionally substituted

(C_{6-12})aryl include, but is not limited to, biphenyl, bromophenyl, chlorophenyl, dichlorophenyl, , difluoromethoxyphenyl, dimethylphenyl, ethoxycarbonylphenyl, fluorophenyl, isopropylphenyl, methoxyphenyl, methylphenyl, methylsulfonylphenyl, naphthyl, pentafluorophenyl, phenyl, trifluoromethoxyphenyl, trifluoromethylphenyl, and the like. Optionally substituted (C_{6-12})aryl as used in this Application to define a radical substituent attached to the group R^6 includes trifluoromethoxyphenyl, difluoromethoxyphenyl, 4-fluorophenyl, and the like.

"Arylalkyloxy" means an arylalkyl-O- group in which the arylalkyl groups is as previously described. Exemplary arylalkyloxy groups include benzyloxy and 1- or 2-naphthalenemethoxy.

"Arylalkyloxycarbonyl" means an arylalkyl-O-CO- group in which the arylalkyl groups is as previously described. An exemplary arylalkyloxycarbonyl group is benzyloxycarbonyl.

"Arylalkylthio" means an arylalkyl-S- group in which the arylalkyl group is as previously described. An exemplary arylalkylthio group is benzylthio.

"Aryloxy" means an aryl-O- group in which the aryl group is as previously described. Exemplary aryloxy groups include phenoxy and naphthoxy, each optionally substituted.

"Aryloxycarbonyl" means an aryl-O-C(=O)- group in which the aryl group is as previously described. Exemplary aryloxycarbonyl groups include phenoxycarbonyl and naphthoxycarbonyl.

"Arylsulfinyl" means an aryl-SO- group in which the aryl group is as previously described.

"Arylsulfonyl" means an aryl-SO_2- group in which the aryl group is as previously described.

"Arylthio" means an aryl-S- group in which the aryl group is as previously described. Exemplary arylthio groups include phenylthio and naphthylthio.

"Cycloalkyl" means a saturated or partially unsaturated, monocyclic, fused bicyclic or bridged polycyclic ring assembly containing the number of ring carbon atoms indicated, and any carbocyclic ketone, thioketone or iminoketone derivative thereof (e.g., (C_{3-12})cycloalkyl includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, 2,5-cyclohexadienyl, bicyclo[2.2.2]octyl, adamantan-1-yl, decahydronaphthyl, oxocyclohexyl, dioxocyclohexyl, thiocyclohexyl, 2-oxobicyclo[2.2.1]hept-1-yl, and the like). It will be appreciated by those skilled in the art that when cycloalkyl represents an unsaturated cyclic ring assembly such rings may not be attached directly via the carbon carbon multiple bond to an oxygen, nitrogen or sulphur atom.

"Cycloalkylene" means a divalent saturated or partially unsaturated, monocyclic ring or bridged polycyclic ring assembly containing the number of ring carbon atoms indicated, and any carbocyclic ketone, thioketone or iminoketone derivative thereof.

"Heteroaroyl" means a heteroaryl-C(=O)- group in which the heteroaryl group is as described herein. Exemplary heteroaryl groups include pyridylcarbonyl.

"Heteroaroylamino" means a heteroaroyl-NH- group in which the heteroaryl moiety is as previously described.

"Heteroaryl" as a group or part of a group denotes: (i) an optionally substituted aromatic monocyclic or multicyclic organic moiety of about 5 to about 13 ring members in which one or more of the ring members is/are element(s) other than carbon, for example nitrogen, oxygen or sulfur (examples of such groups include benzimidazolyl, benzoxazolyl, benzothiazolyl, furyl, imidazolyl, indolyl, indolizinyl, isoxazolyl, isoquinolinyl, isothiazolyl, oxadiazolyl, oxazolyl, pyrazinyl, pyridazinyl, pyrazolyl, pyridyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl, 1,3,4-thiadiazolyl, thiazolyl, thienyl and triazolyl groups, optionally substituted by one or more aryl group substituents as defined above except where otherwise defined); (ii) an optionally substituted partially saturated multicyclic heterocarbocyclic moiety in which a heteroaryl and a cycloalkyl or cycloalkenyl group are fused together to form a cyclic structure (examples of such groups include pyrindanyl groups, optionally substituted by one or more "aryl group substituents" as defined above, except where otherwise defined). Optional substituents include one or more "aryl group substituents" as defined above, except where otherwise defined. Optionally substituted hetero(C_{5-13})aryl as used in this Application to define R^6 includes benzoxazol-2-yl, 5-tert-butyl-[1,2,4]oxadiazol-3-yl, 3-cyclopropyl-1,2,4-oxadiazol-5-yl, 5-cyclopropyl-1,2,4-oxadiazol-5-yl, 5-cyclopropyl-1,3,4-oxadiazol-2-yl , 5-ethyl-[1,3,4]oxadiazol-2-yl, 5-(4-fluoro-phenyl)-1,2,4-oxadiazol-3-yl, 5-isopropyl-isoxazol-3-yl, 5-(5-methyl-isoxazol-3-yl)-oxazol-2-yl, oxazol-2-yl, 3-phenyl-1,2,4-oxadiazol-5-yl, 5-phenyl-1,2,4-oxadiazol-3-yl, 3-(tetrahydro-pyran-4-yl)-1,2,4-oxadiazol-5-yl ,5-thiophen-2-yl-oxazol-2-yl, 5-(4-trifluoromethoxy-phenyl)-1,3,4-oxadiazol-2-yl, and the like.

"Heteroarylalkyloxy" means an heteroarylalkyl-O- group in which the heteroarylalkyl group is as previously described. Exemplary heteroaryloxy groups include optionally substituted pyridylmethoxy.

"Heteroaryloxy" means an heteroaryl-O- group in which the heteroaryl group is as previously described. Exemplary heteroaryloxy groups include optionally substituted pyridyloxy.

"Heterocycloalkyl" means cycloalkyl, as defined in this Application, provided that one or more of the ring carbon atoms indicated are replaced by a heteroatom moiety selected from -N=, -NR-, -O- or -S-, wherein R is hydrogen, (C_{1-6})alkyl, a protecting group or represents the free valence which serves as the point of attachment to a ring nitrogen, and any carbocyclic ketone, thioketone or iminoketone derivative thereof (e.g., the term hetero(C_{5-12})cycloalkyl includes imidazolidinyl, morpholinyl, piperazinyl, piperidyl, pyrrolidinyl, pyrrolinyl, quinuclidinyl, and the like). Suitable protecting groups include *tert*-butoxycarbonyl, benzyloxycarbonyl, benzyl, 4-methoxybenzyl, 2-nitrobenzyl, and the like. Both the unprotected and protected derivatives fall within the scope of the invention.

"Heterocycloalkylene" means cycloalkylene, as defined in this Application, provided that one or more of the ring member carbon atoms indicated, is replaced by heteroatom moiety selected from -N=, -NR-, -O-, -S- or -$S(O)_2$-, wherein R is hydrogen, (C_{1-6})alkyl or a protecting group.

"Isomers", as used in this disclosure, mean the compounds of the present invention having identical molecular formulae but differing in the nature or sequence of bonding of their atoms or in the arrangement of their atoms in space. Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers". Stereoisomers that are not mirror images of one another are termed "diastereomers" and stereoisomers that are nonsuperimposable mirror images are termed "enantiomers" or sometimes "optical isomers". A carbon atom bonded to four nonidentical substituents is termed a "chiral center". A compound, which has one chiral center has two enantiomeric forms of opposite chirality. A "racemic mixture" contains both enantiomers as a 1 : 1 ratio. However, in terms of this application a racemic mixture has been employed when both enantiomers were present irrespective of their ratios. A compound that has more than one chiral center has 2^{n-1} enantiomeric pairs, where n is the number of chiral centers. Compounds with more than one chiral center may exist as either an individual diastereomer or as a mixture of diastereomers, termed a "diastereomeric mixture". When one chiral center is present a stereoisomer may be characterized by the absolute configuration of that chiral center. Absolute configuration refers to the arrangement in space of the substituents attached to the chiral center. Enantiomers are characterized by the absolute configuration of their chiral centers and described by the *R*- and *S*-sequencing rules of Cahn, Ingold and Prelog. Conventions for stereochemical nomenclature, methods for the determination of stereochemistry and the separation of stereoisomers are well known in the art (e.g., see "Advanced Organic Chemistry", 4th edition, March, Jerry, John Wiley & Sons, New York, 1992). It is understood that the names and illustrations used in this disclosure to describe compounds of the present invention are meant to encompass all possible stereoisomers. Thus, for example, [the name morpholine-4-carboxylic acid {1-[1-(3-cyclopropyl-[1,2,4]oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-hexyl}-amide is meant to include morpholine-4-carboxylic acid {(S)-1-[(S)-1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-hexyl}-amide and morpholine-4-carboxylic acid {(R)-1-[(R)-1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-hexyl}-amide and any mixture, racemic or otherwise, thereof.]

"*N*-oxide derivatives" means derivatives of compounds of the present invention in which nitrogens are in an oxidized state (i.e., N-O) and which possess the desired pharmacological activity.

"Pharmaceutically acceptable" means that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary use as well as human pharmaceutical use.

"Pharmaceutically acceptable salts" means salts of compounds of present invention which are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological

activity. Such salts include acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or with organic acids such as acetic acid, propionic acid, hexanoic acid, heptanoic acid, cyclopentane propionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, *o*-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methylsulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, *p*-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, *p*-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid and the like.

Pharmaceutically acceptable salts also include base addition salts which may be formed when acidic protons present are capable of reacting with inorganic or organic bases. Acceptable inorganic bases include sodium hydroxide, sodium carbonate, potassium hydroxide, aluminum hydroxide and calcium hydroxide. Acceptable organic bases include ethanolamine, diethanolamine, triethanolamine, tromethamine, *N*-methylglucamine and the like.

"Prodrug" means a compound, which is convertible in vivo by metabolic means to a compound of present invention. For example an ester of a compound of present invention containing a hydroxy group may be convertible by hydrolysis in vivo to the parent molecule. Alternatively an ester of a compound of present invention containing a carboxy group may be convertible by hydrolysis in vivo to the parent molecule. Suitable esters of compounds of present invention containing a hydroxy group, are for example acetates, citrates, lactates, tartrates, malonates, oxalates, salicylates, propionates, succinates, fumarates, maleates, methylene-bis-b-hydroxynaphthoates, gentisates, isethionates, di-*p*-toluoyltartrates, methylsulfonates, ethanesulfonates, benzenesulfonates, p-toluenesulfonates, cyclohexylsulfamates and quinates. Suitable esters of compounds of present invention containing a carboxy group are, for example, those described by F.J.Leinweber, Drug Metab. Res., 1987, 18, page 379. An especially useful class of esters of compounds of present invention containing a hydroxy group, may be formed from acid moieties selected from those described by Bundgaard et al., J. Med. Chem., 1989, 32, page 2503-2507, and include substituted (aminomethyl)-benzoates, for example, dialkylamino-methylbenzoates in which the two alkyl groups may be joined together and/or interrupted by an oxygen atom or by an optionally substituted nitrogen atom, e.g., an alkylated nitrogen atom, more especially (morpholino-methyl)benzoates, e.g., 3- or 4-(morpholinomethyl)-benzoates, and (4-alkylpiperazin-1-yl)benzoates, e.g., 3- or 4-(4-alkylpiperazin-1-yl)benzoates.

"Protected derivatives" means derivatives of compounds of present invention in which a reactive site or sites are blocked with protecting groups. Protected derivatives of compounds of

present invention are useful in the preparation of compounds of present invention or in themselves may be active cathepsin S inhibitors. A comprehensive list of suitable protecting groups can be found in T.W. Greene, *Protecting Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons, Inc., 1999.

"Therapeutically effective amount" means that amount which, when administered to an animal for treating a disease, is sufficient to effect such treatment for the disease.

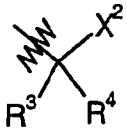
"Treatment" or "treating" means any administration of a compound of the present invention and includes:

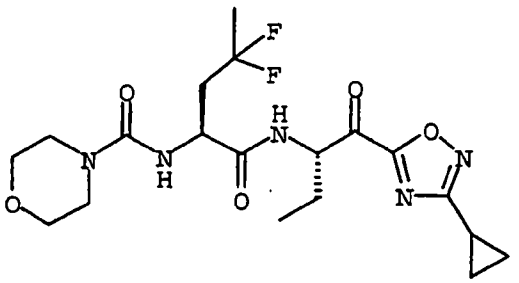
(1) preventing the disease from occurring in an animal which may be predisposed to the disease but does not yet experience or display the pathology or symptomatology of the disease,

(2) inhibiting the disease in an animal that is experiencing or displaying the pathology or symptomatology of the diseased (i.e., arresting further development of the pathology and/or symptomatology), or

(3) ameliorating the disease in an animal that is experiencing or displaying the pathology or symptomatology of the diseased (i.e., reversing the pathology and/or symptomatology).

Nomenclature:

The compounds of present invention and the intermediates and starting materials used in their preparation are named in accordance with IUPAC rules of nomenclature in which the characteristic groups have decreasing priority for citation as the principle group as follows: acids, esters, amides, etc. Alternatively, the compounds are named by AutoNom 4.0 (Beilstein Information Systems, Inc.). [For example, a compound of formula (I) wherein R^1 is morpholine-4-carbonyl, X^1 is methylene, R^5 is methyl, R^2 is H and A is  , in which R^3 is ethyl, R^4 is H and X^2 is $C(O)R^6$ where R^6 is 3-cyclopropyl-1,2,4-oxadiazol-5-yl; that is, a compound having the following structure:



is named morpholine-4-carboxylic acid {(S)-1-[(S)-1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-butyl}-amide

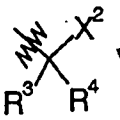
However, it is understood that, for a particular compound referred to by both a structural formula and a nomenclature name, if the structural formula and the nomenclature name are inconsistent with each other, the structural formula takes the precedence over the nomenclature name.

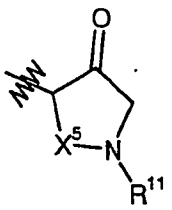
The various features of novelty which characterize the invention are pointed out with particularity in the claims annexed to and forming a part of this disclosure. For a better understanding of the invention, its operating advantages, and specific objects attained by its use, reference should be made to the following description in which there are illustrated and described preferred embodiments of the invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

With reference to formula (I) above, the following are particular groupings:

X^1 may particularly represent methylene.

A may particularly represent  wherein: R^3 is H, (C_{6-12})aryl(C_{2-6})alkyl or (C_{1-6})alkyl optionally substituted by $-X^6OR^9$ [in which X^6 is a bond and R^9 is (C_{1-6})alkyl]; R^4 is H or (C_{1-6})alkyl; and X^2 is CHO, CN or $C(O)R^6$ [in which R^6 is hetero(C_{5-13})aryl optionally substituted by (C_{1-9})alkyl, (C_{3-12})cycloalkyl, (C_{6-12})aryl or hetero(C_{5-13})aryl].

A may also particularly represent  wherein X^5 is propylene and R^{11} is $-C(O)OR^{13}$ or $-S(O)_2R^{13}$, in which R^{13} is alkyl or (C_{6-12})aryl.

R^1 may particularly represent $R^{13}C(O)-$ in which R^{13} is hetero(C_{5-12})cycloalkyl.

R^1 may also particularly represent $R^{13}OC(O)-$ in which R^{13} is (C_{6-12})aryl(C_{1-6})alkyl.

R^1 may also particularly represent (C_{1-9})alkyl.

R^1 may also particularly represent hetero(C_{5-12})cycloalkyl.

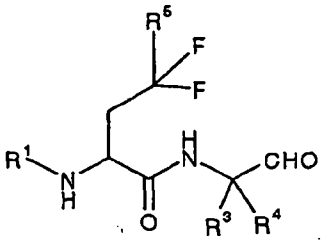
R^2 may particularly represent H.

R^5 may particularly represent (C_{1-9})alkyl.

R^5 may also particularly represent (C_{6-12})aryl(C_{1-6})alkyl.

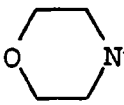
Particular Genera:

A particular group of compounds of the invention are compounds of Formula (Ia):

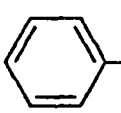


(Ia)

wherein R^1, R^3, R^4 and R^5 are as hereinbefore described, and their corresponding *N*-oxides, and their prodrugs, and their protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates (e.g. hydrates) of such compounds of Formula (Ia) and their *N*-oxides and their prodrugs, and their protected derivatives, individual isomers and mixtures of isomers thereof.

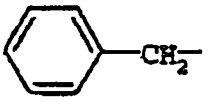
Compounds of Formula (Ia) in which R^1 is $R^{13}C(O)$- and R^{13} is hetero(C_{5-12})cycloalkyl are examples. Compounds of Formula (Ia) in which R^1 is  are particular examples.

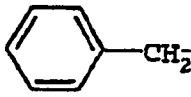
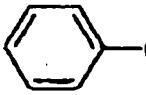
Compounds of Formula (Ia) in which R^3 is H, (C_{6-12})aryl(C_{1-6})alkyl or (C_{1-6})alkyl are examples.

Compounds of Formula (Ia) in which R^3 is H,  or $CH_3-CH_2-CH_2-$ are particular examples.

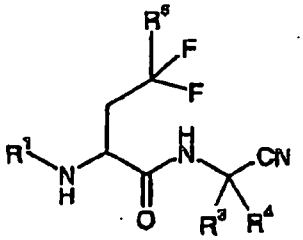
Compounds of Formula (Ia) in which R^4 is H or methyl are examples.

Compounds of Formula (Ia) in which R^5 is (C_{6-12})aryl(C_{1-6})alkyl are examples.

Compounds of Formula (Ia) in which R^5 represents  are particular examples.

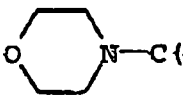
A particular group of compounds of the invention are compounds of formula (Ia) in which: R^1 is $R^{13}C(O)$- (especially ); R^3 is H, (C_{6-12})aryl(C_{1-6})alkyl (especially ) or (C_{1-6})alkyl (especially $CH_3-CH_2-CH_2-$); R^4 is H or methyl and R^5 is (C_{6-12})aryl(C_{1-6})alkyl (especially ).

A further particular group of compounds of the invention are compounds of Formula (Ib):

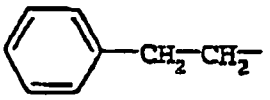


(Ib)

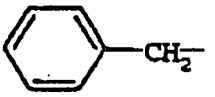
wherein R^1, R^3, R^4 and R^5 are as hereinbefore described, and their corresponding *N*-oxides, and their prodrugs, and their protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates (e.g. hydrates) of such compounds of Formula (Ib) and their *N*-oxides and their prodrugs, and their protected derivatives, individual isomers and mixtures of isomers thereof.

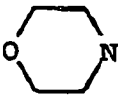
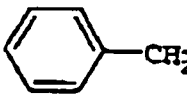
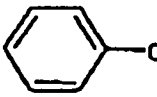
Compounds of Formula (Ib) in which R^1 is $R^{13}C(O)$- and R^{13} is hetero(C_{5-12})cycloalkyl are examples. Compounds of Formula (Ib) in which R^1 is  are particular examples.

Compounds of Formula (Ib) in which R^3 is H, (C_{6-12})aryl(C_{1-6})alkyl or (C_{1-6})alkyl are examples.

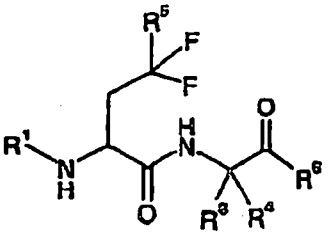
Compounds of Formula (Ib) in which R^3 is H,  or $CH_3-CH_2-CH_2-$ are particular examples.

Compounds of Formula (Ib) in which R^4 is H or methyl are examples.

Compounds of Formula (Ib) in which R^5 is (C_{6-12})aryl(C_{1-6})alkyl are examples. Compounds of Formula (Ib) in which R^5 represents  are particular examples.

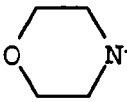
A particular group of compounds of the invention are compounds of formula (Ib) in which: R^1 is $R^{13}C(O)$- (especially ); R^3 is H, (C_{6-12})aryl(C_{1-6})alkyl (especially ) or (C_{1-6})alkyl (especially CH_3-CH_2-); R^4 is H or methyl and R^5 is (C_{6-12})aryl(C_{1-6})alkyl (especially ).

A further particular group of compounds of the invention are compounds of Formula (Ic):



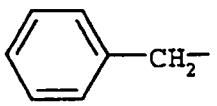
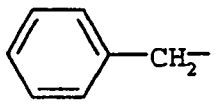
(Ic)

wherein R^1, R^3, R^4, R^5 and R^6 are as hereinbefore described, and their corresponding *N*-oxides, and their prodrugs, and their protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates (e.g. hydrates) of such compounds of Formula (Ic) and their *N*-oxides and their prodrugs, and their protected derivatives, individual isomers and mixtures of isomers thereof.

Compounds of Formula (Ic) in which R^1 is $R^{13}C(O)$- and R^{13} is hetero(C_{5-12})cycloalkyl are examples. Compounds of Formula (Ic) in which R^1 is  are particular examples.

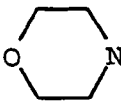
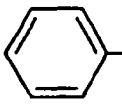
Compounds of Formula (Ic) in which R^3 is (C_{1-6})alkyl optionally substituted by $-X^6OR^9$ [in which X^6 is a bond and R^9 is (C_{1-6})alkyl] are examples. Compounds of Formula (Ic) in which R^3 is CH_3-CH_2- , $CH_3-CH_2-CH_2-$ or CH_3-O-CH_2- are particular examples.

Compounds of Formula (Ic) in which R^4 is H or methyl are examples. Compounds of Formula (Ic) in which R^4 is H are examples.

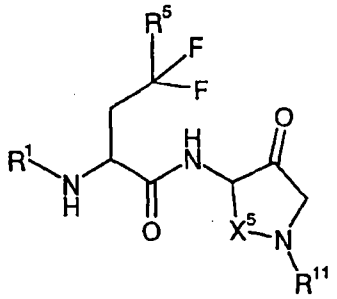
Compounds of Formula (Ic) in which R^5 is (C_{1-9})alkyl or (C_{6-12})aryl(C_{1-6})alkyl are examples. Compounds of Formula (Ic) in which R^5 represents $CH_3CH_2CH_2$ or CH_3 CH_2 or CH_3 or  are particular examples. Compounds of Formula (Ic) in which R^5 represents  are particular examples.

Compounds of Formula (Ic) in which R^6 is hetero(C_{5-13})aryl, optionally substituted by (C_{1-9})alkyl, (C_{3-12})cycloalkyl, (C_{6-12})aryl or hetero(C_{5-13})aryl, are examples. Exemplary optionally substituted hetero(C_{5-13})aryl groups include optionally substituted benzoxazolyl, oxadiazolyl, isoxazolyl, or oxazolyl. Compounds of Formula (Ic) in which R^6 is benzoxazol-2-yl, 5-tert-butyl-[1,2,4]oxadiazol-3-yl, 3-cyclopropyl-1,2,4-oxadiazol-5-yl, 5-cyclopropyl-1,2,4-oxadiazol-2-yl, 5-cyclopropyl-1,3,4-oxadiazol-2-yl , 5-ethyl-1,3,4-oxadiazol-2-yl, 5-(4-fluoro-phenyl)-1,2,4-oxadiazol-3-yl, 5-isopropyl-

isoxazol-3-yl, 5-(5-methyl-isoxazol-3-yl)-oxazol-2-yl, 5-(5-methyl-thien-2-yl)-oxazol-2-yl, oxazol-2-yl, 3-phenyl-1,2,4-oxadiazol-5-yl, 5-phenyl-1,2,4-oxadiazol-3-yl, 5-thiophen-2-yl-oxazol-2-yl, 5-(4-trifluoromethoxy-phenyl)-1,3,4-oxadiazol-2-yl and the like, are examples. Compounds of Formula (Ic) in which R^6 is benzoxazol-2-yl, 3-cyclopropyl-1,2,4-oxadiazol-5-yl, oxazol-2-yl, are particular examples.

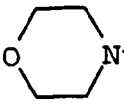
A particular group of compounds of the invention are compounds of formula (Ic) in which: R^1 is $R^{13}C(O)$- (especially ); R^3 is (C_{1-6})alkyl optionally substituted by $-X^6OR^9$ (especially CH_3-CH_2-, $CH_3-CH_2-CH_2-$ or CH_3-O-CH_2-); R^4 is H and R^5 is (C_{1-9})alkyl or (C_{6-12})aryl(C_{1-6})alkyl (especially ); R^6 is hetero(C_{5-13})aryl, optionally substituted by (C_{1-9})alkyl, (C_{3-12})cycloalkyl, hetero(C_{5-12}) cycloalkyl, (C_{6-12})aryl or hetero(C_{5-13})aryl (especially benzoxazol-2-yl, 3-cyclopropyl-1,2,4-oxadiazol-5-yl, oxazol-2-yl and 5-methyl-isoxazol-3-yl)-oxazole-2-yl).

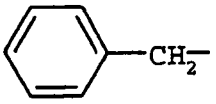
A further particular group of compounds of the invention are compounds of Formula (Id):

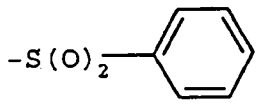


(Id)

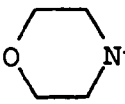
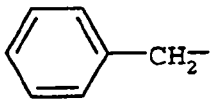
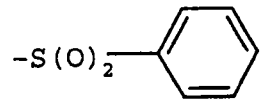
wherein R^1, R^5, R^{11} and X^5 are as hereinbefore described, and their corresponding *N*-oxides, and their prodrugs, and their protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates (e.g. hydrates) of such compounds of Formula (Id) and their *N*-oxides and their prodrugs, and their protected derivatives, individual isomers and mixtures of isomers thereof.

Compounds of Formula (Id) in which R^1 is $R^{13}C(O)$- and R^{13} is hetero(C_{5-12})cycloalkyl are examples. Compounds of Formula (Id) in which R^1 is  are particular examples.

Compounds of Formula (Id) in which R^5 is (C_{6-12})aryl(C_{1-6})alkyl are examples. Compounds of Formula (Id) in which R^5 represents  are particular examples.

Compounds of Formula (Id) in which R^{11} is $-C(O)OR^{13}$ or $-S(O)_2R^{13}$, in which R^{13} is alkyl or (C_{6-12})aryl are example. Compounds of Formula (Id) in which R^{11} represents $-C(O)OC(CH_3)_3$ or  are particular examples.

Compounds of Formula (Id) in which X^1 is propylene are examples.

A particular group of compounds of the invention are compounds of formula (Id) in which: R^1 is $R^{13}C(O)$- (especially ); R^5 is (C_{6-12})aryl(C_{1-6})alkyl (especially ); R^{11} is $-C(O)OR^{13}$ [especially $-C(O)OC(CH_3)_3$] or $-S(O)_2R^{13}$ (especially ) and X^1 is propylene are examples.

Particular compounds of the present invention include:

morpholine-4-carboxylic acid {(S)-1-[(S)-1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-hexyl}-amide;

morpholine-4-carboxylic acid {(S)-1-[(S)-1-(5-cyclopropyl-1,3,4-oxadiazole-2-carbonyl)-propylcarbamoyl]-3,3-difluoro-hexyl}-amide;

morpholine-4-carboxylic acid ((S)-3,3-difluoro-1-{(S)-1-[5-(4-trifluoromethoxy-phenyl)-1,3,4-oxadiazole-2-carbonyl]-propylcarbamoyl}-hexyl)-amide;

morpholine-4-carboxylic acid {(S)-1-[(S)-1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-4-phenyl-butyl}-amide;

morpholine-4-carboxylic acid {1-[1-(3-cyclopropyl-[1,2,4]oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-5-methyl-hexyl}-amide;

morpholine-4-carboxylic acid {(S)-1-[(S)-1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-butyl}-amide;

morpholine-4-carboxylic acid {(S)-3,3-difluoro-1-[(S)-1-(3-phenyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-butyl}-amide;

morpholine-4-carboxylic acid {(S)-3,3-difluoro-1-[(S)-1-(5-phenyl-1,2,4-oxadiazole-3-carbonyl)-propylcarbamoyl]-butyl}-amide;

morpholine-4-carboxylic acid {1-[1-(5-cyclopropyl-[1,3,4]oxadiazole-2-carbonyl)-propylcarbamoyl]-3,3-difluoro-4-phenyl-butyl}-amide;

morpholine-4-carboxylic acid {3,3-difluoro-1-[1-(5-isopropyl-isoxazole-3-carbonyl)-propylcarbamoyl]-hexyl}-amide;

morpholine-4-carboxylic acid ((S)-3,3-difluoro-1-{1-[5-(5-methyl-isoxazol-3-yl)-oxazole-2-carbonyl]-propylcarbamoyl}-hexyl)-amide;

morpholine-4-carboxylic acid {(S)-3,3-difluoro-1-[(S)-1-(oxazole-2-carbonyl)-propylcarbamoyl]-4-phenyl-butyl}-amide;

morpholine-4-carboxylic acid {(S)-3,3-difluoro-4-phenyl-1-[(S)-1-(5-thiophen-2-yl-oxazole-2-carbonyl)-propylcarbamoyl]-butyl}-amide;

morpholine-4-carboxylic acid {(S)-1-[(S)-1-(benzoxazole-2-carbonyl)-butylcarbamoyl]-3,3-difluoro-4-phenyl-butyl}-amide;

morpholine-4-carboxylic acid [1-(2-benzooxazol-2-yl-1-methoxymethyl-2-oxo-ethylcarbamoyl)-3,3-difluoro-4-phenyl-butyl]-amide;

morpholine-4-carboxylic acid {(S)-1-[(S)-1-(benzoxazole-2-carbonyl)-1-methyl-butylcarbamoyl]-3,3-difluoro-4-phenyl-butyl}-amide;

morpholine-4-carboxylic acid [(S)-1-((S)-1-cyano-3-phenyl-propylcarbamoyl)-3,3-difluoro-4-phenyl-butyl]-amide;

morpholine-4-carboxylic acid [(S)-1-(cyanomethyl-carbamoyl)-3,3-difluoro-4-phenyl-butyl]-amide;

morpholine-4-carboxylic acid [(S)-3,3-difluoro-1-((S)-1-formyl-1-methyl-butylcarbamoyl)-4-phenyl-butyl]-amide;

morpholine-4-carboxylic acid {(S)-1-[1-(5-ethyl-[1,3,4]oxadiazole-2-carbonyl)-propylcarbamoyl]-3,3-difluoro-4-phenyl-butyl}-amide;

morpholine-4-carboxylic acid {(S)-1-[1-(5-tert-butyl-[1,2,4]oxadiazole-3-carbonyl)-propylcarbamoyl]-

3,3-difluoro-4-phenyl-butyl}-amide;

morpholine-4-carboxylic acid {(S)-3,3-difluoro-4-phenyl-1-[(S)-1-(5-phenyl-[1,2,4]oxadiazol-3-yl)-propylcarbamoyl]-butyl}-amide;

[(S)-1-(cyanomethyl-carbamoyl)-3,3-difluoro-4-phenyl-butyl]-carbamic acid benzyl ester;

(S)-4,4-difluoro-5-phenyl-2-(tetrahydro-pyran-4-ylamino)-pentanoic acid cyanomethyl-amide;

(S)-4,4-difluoro-2-isobutylamino-5-phenyl-pentanoic acid cyanomethyl-amide;

morpholine-4-carboxylic acid [(S)-1-((S)-1-benzenesulfonyl-3-oxo-azepan-4-ylcarbamoyl)-3,3-difluoro-4-phenyl-butyl]-amide;

(S)-4-{(S)-4,4-difluoro-2-[(morpholine-4-carbonyl)-amino]-5-phenyl-pentanoylamino}-3-oxo-azepane-1-carboxylic acid tert-butyl ester;

morpholine-4-carboxylic acid ((S)-1-{(S)-1-[(5-ethyl-1,3,4-oxadiazol-2-yl)-hydroxy-methyl]-propylcarbamoyl}-3,3-difluoro-hexyl)-amide;

morpholine-4-carboxylic acid {(S)-1-[1-(5-cyclopropyl-1,3,4-oxadiazole-2-carbonyl)-propylcarbamoyl]-3,3-difluoro-butyl}-amide;

morpholine-4-carboxylic acid {(S)-1-[1-(5-cyclopropyl-1,2,4-oxadiazole-3-carbonyl)-propylcarbamoyl]-3,3-difluoro-hexyl}-amide;

morpholine-4-carboxylic acid ((S)-3,3-difluoro-1-{(S)-1-[5-(4-fluoro-phenyl)-1,2,4-oxadiazole-3-carbonyl]-propylcarbamoyl}-butyl)-amide;

morpholine-4-carboxylic acid ((S)-3,3-difluoro-1-{1-[5-(4-fluoro-phenyl)-1,2,4-oxadiazole-3-carbonyl]-propylcarbamoyl}-butyl)-amide;

morpholine-4-carboxylic acid ((S)-3,3-difluoro-1-{(R)-1-[5-(4-fluoro-phenyl)-1,2,4-oxadiazole-3-carbonyl]-propylcarbamoyl}-butyl)-amide;

morpholine-4-carboxylic acid {(S)-1-[(S)-1-(benzoxazole-2-carbonyl)-propylcarbamoyl]-3,3-difluoro-butyl}-amide;

morpholine-4-carboxylic acid [(S)-1-(cyanomethyl-carbamoyl)-3,3-difluoro-hexyl]-amide;

morpholine-4-carboxylic acid ((S)-3,3-difluoro-1-{(R)-1-[5-(5-methyl-thiophen-2-yl)-oxazole-2-carbonyl]-propylcarbamoyl}-hexyl)-amide;

morpholine-4-carboxylic acid ((S)-3,3-difluoro-1-{(S)-1-[5-(5-methyl-thiophen-2-yl)-oxazole-2-carbonyl]-propylcarbamoyl}-hexyl)-amide;

and their corresponding *N*-oxides, and their prodrugs, and their protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates (e.g. hydrates) of such compounds of Formula (Ia) and their *N*-oxides and their prodrugs, and their protected derivatives, individual isomers and mixtures of isomers thereof.

Pharmacology and Utility:

The compounds of the invention are inhibitors of cathepsin S and, as such, are useful for

treating diseases in which cathepsin S activity contributes to the pathology and/or symptomatology of the disease. For example, the compounds of the invention may be useful in treating autoimmune disorders, including, but not limited to, juvenile onset diabetes, multiple sclerosis, pemphigus vulgaris, Graves' disease, myasthenia gravis, systemic lupus erythemotasus, irritable bowel disease, rheumatoid arthritis and Hashimoto's thyroiditis, allergic disorders including but not limited to, asthma, and allogeneic immune responses, including, but not limited to, organ transplants or tissue grafts.

Cathepsin S is also implicated in disorders involving excessive elastolysis, such as chronic obstructive pulmonary disease (e.g., emphysema), bronchiolitis, excessive airway elastolysis in asthma and bronchitis, pneumonities and cardiovascular disease such as plaque rupture and atheroma. Cathepsin S is implicated in fibril formation and, therefore, inhibitors of cathepsin S may be of use in treatment of systemic amyloidosis.

The cysteine protease inhibitory activities of the compounds of the invention can be determined by methods known to those of ordinary skill in the art. Suitable *in vitro* assays for measuring protease activity and the inhibition thereof by test compounds are known. Typically, the assay measures protease-induced hydrolysis of a peptide-based substrate. Details of assays for measuring protease inhibitory activity are set forth in Examples 31, 32, 33, 34, *infra*.

The compounds of the invention are also inhibitors of cathepsin K and B and, as such, are useful for treating diseases in which cathepsin K and B activity contributes to the pathology and/or symptomatology of the disease. For example, the compounds of the invention may be useful in treating osteoarthritis, osteoporosis or cancer such as lung cancer, leukemia (B- and T-cell, acute), ovarian cancer, sarcomas, kaposi's sarkoma, bowel cancer, lymph node cancer, brain tumor, breast cancer, pancreas cancer, prostate cancer or skin cancer.

Administration and Pharmaceutical Compositions:

In general, compounds of the present invention will be administered in therapeutically effective amounts via any of the usual and acceptable modes known in the art, either singly or in combination with one or more therapeutic agents. A therapeutically effective amount may vary widely depending on the severity of the disease, the age and relative health of the subject, the potency of the compound used and other factors. For example, therapeutically effective amounts of a compound of the invention may range from about 1 micrograms per kilogram body weight (µg/kg) per day to about 60 milligram per kilogram body weight (mg/kg) per day, typically from about 1 µg/kg/day to about 20 mg/kg/day. Therefore, a therapeutically effective amount for a 80 kg human patient may range from about 80 µg /day to about 4.8 g/day, typically from about 80 µg /day to about 1.6 g/day. In general, one of ordinary skill in the art, acting in reliance upon personal knowledge and the disclosure of this

Application, will be able to ascertain a therapeutically effective amount of a compound of the invention for treating a given disease.

The compounds of the invention can be administered as pharmaceutical compositions by one of the following routes: oral, systemic (e.g., transdermal, intranasal or by suppository) or parenteral (e.g., intramuscular, intravenous or subcutaneous). Compositions can take the form of tablets, pills, capsules, semisolids, powders, sustained release formulations, solutions, suspensions, elixirs, aerosols, or any other appropriate composition and are comprised of, in general, a compound of the invention in combination with at least one pharmaceutically acceptable excipient. Acceptable excipients are non-toxic, aid administration, and do not adversely affect the therapeutic benefit of the active ingredient. Such excipient may be any solid, liquid, semisolid or, in the case of an aerosol composition, gaseous excipient that is generally available to one of skill in the art.

Solid pharmaceutical excipients include starch, cellulose, talc, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, magnesium stearate, sodium stearate, glycerol monostearate, sodium chloride, dried skim milk, and the like. Liquid and semisolid excipients may be selected from water, ethanol, glycerol, propylene glycol and various oils, including those of petroleum, animal, vegetable or synthetic origin (e.g., peanut oil, soybean oil, mineral oil, sesame oil, and the like). Preferred liquid carriers, particularly for injectable solutions, include water, saline, aqueous dextrose and glycols.

The amount of a compound of the invention in the composition may vary widely depending upon the type of formulation, size of a unit dosage, kind of excipients and other factors known to those of skill in the art of pharmaceutical sciences. In general, a composition of a compound of the invention for treating a given disease will comprise from 0.01%w to 10%w, preferably 0.3%w to 1%w, of active ingredient with the remainder being the excipient or excipients. Preferably the pharmaceutical composition is administered in a single unit dosage form for continuous treatment or in a single unit dosage form ad libitum when relief of symptoms is specifically required. Representative pharmaceutical formulations containing a compound of the invention are described in Example 35.

Chemistry:

Processes for Making Compounds of the invention:

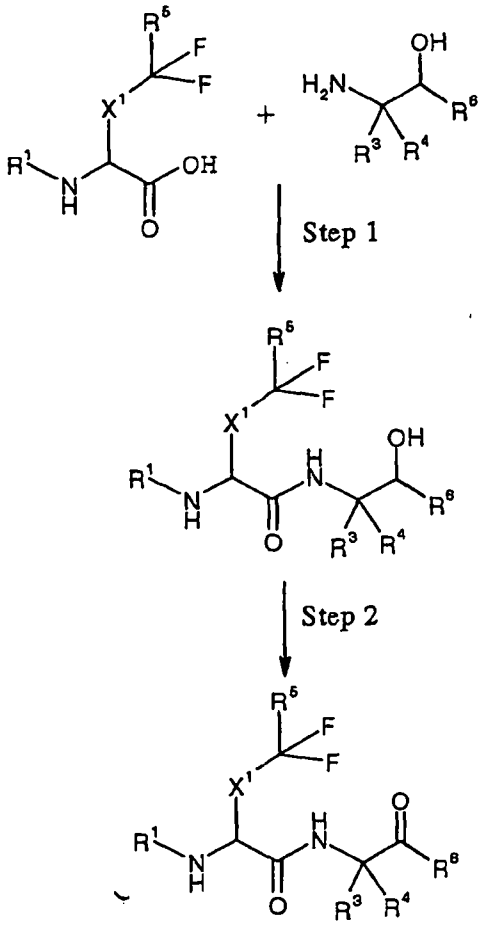
Compounds of the invention may be prepared by the application or adaptation of known methods, by which is meant methods used heretofore or described in the literature, for example those described by R.C. Larock in Comprehensive Organic Transformations, VCH publishers, 1989.

In the reactions described hereinafter it may be necessary to protect reactive functional groups, for example hydroxy, amino, imino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice, for examples see T.W. Greene and P. G. M. Wuts in

"Protective Groups in Organic Chemistry" John Wiley and Sons, 1991.

Compounds of the invention can be prepared by proceeding according to Reaction Scheme 1:

Reaction Scheme 1



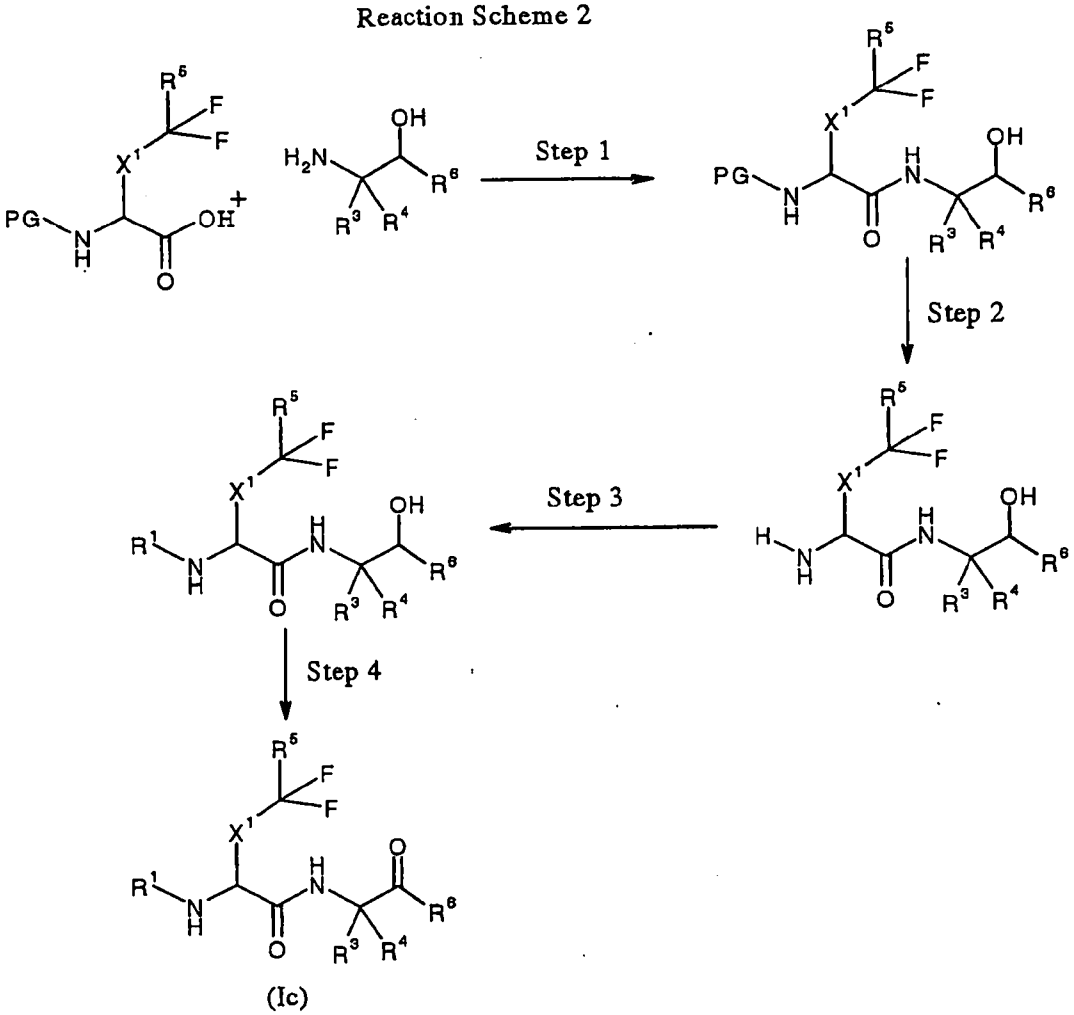
(Ic)

in which each X^1, R^1, R^3, R^4, R^5, and R^6 are as defined in the Summary of the Invention. Thus, in step 1, an acid may be condensed with an amino compound of formula to give a β-hydroxy amide. The condensation reaction can be effected with an appropriate coupling agent (e.g., benzotriazol-1-yloxytrispyrrolidinophosphonium hexafluorophosphate (PyBOP®), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI), *O*-benzotriazol-1-yl-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate (HBTU), 1,3-dicyclohexylcarbodiimide (DCC), or the like) and optionally an appropriate catalyst (e.g., 1-hydroxybenzotriazole (HOBt), 1-hydroxy-7-azabenzotriazole (HOAt), *O*-(7-azabenzotrizol-1-yl)-1,1,3,3, tetra-methyluroniumhexafluorophosphate (HATU), or the like) and non-nucleophilic base (e.g., triethylamine, *N*-methylmorpholine, and the like, or any suitable combination thereof) at ambient temperature and requires 2 to 10 hours to complete. The β-hydroxy amide may then be oxidized, in step 2, to give a compound of formula (Ic). The oxidation reaction may conveniently be carried out

using Dess-Martin periodinane in an inert solvent, such as dichloromethane, and at a temperature from about 0°C to about room temperature.

Alternatively the compounds of this invention can be prepared by proceeding according to Reaction Scheme 2:

Reaction Scheme 2



(Ic)

in which each X^1, R^1, R^3, R^4, R^5, and R^6 are as defined in the Summary of the Invention and PG is a suitable protecting group. Thus, in step 1, an acid may be condensed with an amino compound of formula to give a β-hydroxy amide. Removal of the protecting group (Step 2) followed by introduction of R^1 group (Step 3) and oxidation (Step 4) to give a compound of formula (Ic).

Examples:

The present invention is further exemplified, but not limited by, the following examples that illustrate the preparation of compounds of Formula (I) (Examples) and intermediates (References) according to the invention.

^1H nuclear magnetic resonance spectra (NMR) were recorded on Varian Mercury-300 or Unity-400 or UnityPlus-500 or Inova-500machines. In the nuclear magnetic resonance spectra (NMR) the chemical shifts (δ) are expressed in ppm relative to tetramethylsilane. Abbreviations have the following significances: s = singlet; d = doublet; t = triplet; m = multiplet; q = quartet; dd = doublet of doublets; ddd = doublet of double doublets.

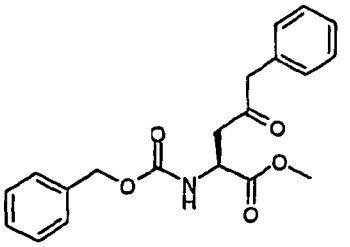
The high pressure liquid chromatography (HPLC) was run on Kromasil 10 micron, 100A Silica, 4.6mmID x 250 mm column using mixture of Heptane/THF/1,2-Dichloroethane as Mobile Phase.
Mass spectra were run on Agilent 1100 series or MICROMASS LCT-TOF MS.
The thin layer chromatography (TLC) R_F values were determined using Merck silica plates.

Abbreviations

CBZ- Benzyloxy carbonyl
DAST- (Diethylamino)sulfur trifluoride
DCM- Dichloromethane
DMF- Dimethyl formamide
DMSO - Dimethyl sulfoxide
DTT - Dithiothreitol
EDCI - N-(3-Dimethylaminopropyl)-N¢-ethylcarbodiimide hydrochloride
EDTA - Ethylenediaminetetraacetic acid
EtOAc – Ethyl acetate
HOBT - 1-Hydroxybenzotriazole hydrate
MeOH - Methanol
MES - 2-Morpholinoethanesulfonic acid
PyBOP - (Benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate
THF - Tetrahydrofuran

REFERENCE 1

(S)-2-Benzyloxycarbonylamino-4-oxo-5-phenyl-pentanoic acid methyl ester:

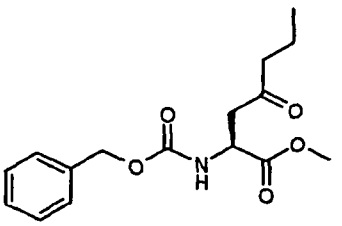


To a suspension of copper (I) bromide (4.26 mmol, 611.1 mg) in 3 mL of dry THF under N_2 was added a solution of lithium bromide (8.52 mmol, 740 mg) in 5 mL of dry THF. The mixture was stirred at room temperature for 20 min, and then cooled to -78°C. A solution of benzyl magnesium chloride (20 wt. % in THF, 4.26 mmol, 3.25 mL) followed by a solution of (S)-2-benzyloxycarbonylamino-3-chlorocarbonyl-propionic acid methyl ester [Ref: Synth. Comm 1993, 23(18), 2511-2526] (3.59 mmol) in 7 mL of dry THF was added. The mixture was stirred at -78 °C for 30 min and then quenched with saturated NH_4Cl (50 mL). The mixture was extracted twice with ethyl acetate (30 mL). The organic layers were dried over magnesium sulfate and then concentrated in vacuum. The residue was purified over 35 g silica gel, eluting with EtOAc:Heptane (1:1) to afford (S)-2-benzyloxycarbonyl-amino-4-oxo-5-phenyl-pentanoic acid methyl ester (1.07 g, 84%).

^1H NMR ($CDCl_3$): δ 7.4-7.17 (m, 10H), 5.73 (d, J = 8.2 Hz, 1H), 5.11 (s, 2H), 4.57 (m, 1H), 3.7 (2xs, 5H), 3.24 (dd, J = 18.5, 4.4 Hz, 1H), 3.0 (dd, J = 18.2, 4.1 Hz, 1H); LC/MS: 100% 378 (M+Na).

REFERENCE 2

(S)-2-Benzyloxycarbonylamino-4-oxo-heptanoic acid methyl ester

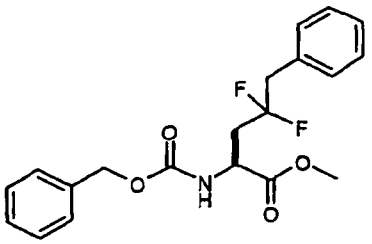


By proceeding in a similar manner to Reference Example 1 above but using propyl magnesium chloride instead of benzyl magnesium chloride there was prepared (S)-2-benzyloxycarbonylamino-4-oxo-heptanoic acid methyl ester.

^1H NMR ($CDCl_3$): δ 7.35 (m, 5H), 5.78 (d, J = 8.5 Hz, 1H), 5.13 (s, 2H), 4.58 (m, 1H), 3.75 (s, 3H), 3.2 (dd, J = 18.3, 4.2 Hz, 1H), 2.96 (dd, J = 18.3, 4.1 Hz, 1H), 2.4 (m, 2H), 1.6 (m, 2H), 0.92 (t, J = 7.4 Hz, 3H); LC/MS: 330 (M+Na).

REFERENCE 3

(S)-2-Benzyloxycarbonylamino-4,4-difluoro-5-phenyl-pentanoic acid methyl ester:

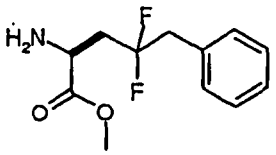


A mixture of 2-benzyloxycarbonylamino-4-oxo-5-phenyl-pentanoic acid methyl ester (3.310g, 9.31 mmol) and DAST (7 mL) was stirred at room temperature over 3 days. The mixture was diluted with dichloromethane (100 mL) and carefully added to 0.5N NaOH solution (150 mL). The aqueous layer was extracted with dichloromethane (50 mL). The organic layers were dried over magnesium sulfate and then concentrated in vacuum. The residue was purified over 110 g silica gel, eluting with EtOAc:Heptane (1:4 then 1:3) to afford (S)-2-benzyloxycarbonylamino-4,4-difluoro-5-phenyl-pentanoic acid methyl ester (1.797g, 51.1%).

^{1}H NMR ($CDCl_3$) δ 7.3 (m, 10H), 5.43 (d, J = 7.6 Hz, 1H), 5.14 (s, 2H), 4.65 (m, 1H), 3.74 (s, 3H), 3.2 (t, J = 16.5 Hz, 2H), 2.4 (m, 2H); LC/MS: 97% 400 (M+Na).

REFERENCE 4

(S)-2-Amino-4,4-difluoro-5-phenyl-pentanoic acid methyl ester hydrochloride:

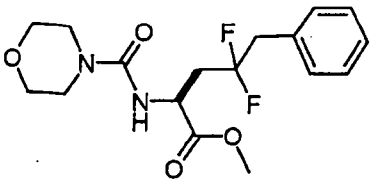


A solution of (S)-2-benzyloxycarbonylamino-4,4-difluoro-5-phenyl-pentanoic acid methyl ester (7.806g, 20.68 mmol) in 120 mL of methanol and 4 M HCl in dioxane (41.4 mmol, 10.3 mL) was hydrogenated over 10% Pd/C (1.0g) at 50 psi. After 8 hr, another portion of 10% Pd/C (1.0g) was added. After 24 hr, the catalyst was removed by filtration over a pad of Celite, and the filtrate was concentrated in vacuum. The resulting light yellow solid was dissolved in a minimum amount of methanol and slowly added to ether (150 mL). The resulting slurry was aged for 30 min and then filtered. The white solid was dried under suction to afford (S)-2-amino-4,4-difluoro-5-phenyl-pentanoic acid methyl ester hydrochloride (4.950g, 85.5%).

^{1}H NMR (DMSO-D_6): δ 8.6 (b, 3H), 7.3 (m, 5H), 4.26 (t, J = 6 Hz, 1H), 3.73 (s, 3H), 3.3 (t, J = 17.5 Hz, 2H), 2.55 (m, 2H); LC/MS: 100% 244 (M+1).

REFERENCE 5

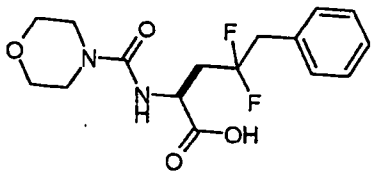
(S)-4,4-Difluoro-2-[(morpholine-4-carbonyl)-amino]-5-phenyl-pentanoic acid methyl ester:



To a mixture of (S)-2-amino-4,4-difluoro-5-phenyl-pentanoic acid methyl ester hydrochloride (2.50g, 8.94 mmol) and diisopropyl amine (22.3 mmol, 2.89 g) in dry dichloromethane (40 mL) under N_2 was added drop wise morpholine carbonyl chloride (13.4 mmol, 2.0 g). The mixture was stirred at room temperature for 15 hours, and then diluted with water (50 mL). The aqueous layer was extracted with dichloromethane (30 mL). The organic layers were dried over magnesium sulfate and then concentrated in vacuum. Purification over 110 g silica gel, eluting with EtOAc:Heptane (1:1, then 2:1) afforded (S)-4,4-difluoro-2-[(morpholine-4-carbonyl)-amino]-5-phenyl-pentanoic acid methyl ester (2.82g, 88.5%). ^{1}H NMR ($CDCl_3$): δ 7.3 (m, 5H), 5.16 (d, J = 7.5 Hz, 1H), 4.75 (dd, J = 13, 6 Hz, 1H), 3.73 (s, 3H), 3.7 (m, 4H), 3.4 (m, 4H), 3.2 (t, J = 16.7 Hz, 2H), 2.4 (m, 2H). LC/MS: 100% 357 (M+1).

REFERENCE 6

(S)-4,4-Difluoro-2-[(morpholine-4-carbonyl)-amino]-5-phenyl-pentanoic acid:

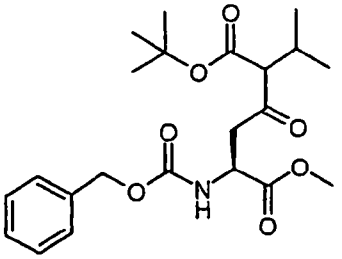


To a solution of (S)-4,4-difluoro-2-[(morpholine-4-carbonyl)-amino]-5-phenyl-pentanoic acid methyl ester (2.81 g, 7.88 mmol) in MeOH:H_2O (2:1 vol, 40 mL) was added LiOH mono hydrate (662 mg, 15.76 mmol). The mixture was stirred at room temperature for 2.5h, and then diluted with water (30 mL). Methanol was removed in vacuum. The pH was adjusted to pH 1 with 6N HCl and the aqueous layer was extracted with dichloromethane (2x30 mL). The organic layers were dried over magnesium sulfate and concentrated in vacuum to afford (S)-4,4-Difluoro-2-[(morpholine-4-carbonyl)-amino]-5-phenyl-pentanoic acid (2.509g, 93%).

^{1}H NMR ($CDCl_3$): δ 8.2 (b, 1H), 7.3 (m, 5H), 5.3 (m, 1H), 4.6 (m, 1H), 3.65 (m, 4H), 3.4 (m, 4H), 3.2 (t, J = 16.5 Hz, 2H), 2.4 (m, 2H); LC/MS: 94% 343 (MH^+)

REFERENCE 7

(S)-5-Benzyloxycarbonylamino-2-isopropyl-3-oxo-hexanedioic acid 1-tert-butyl ester 6-methyl ester:

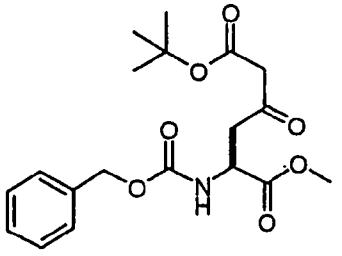


To a cooled to –78 °C solution of diisopropyl amine (3.53g, 34.88 mmol) in dry THF (20 mL) under N_2 was added drop wise a solution of n-butyl lithium (2.5 M in hexane, 34.88 mmol, 13.95 mL). The mixture was stirred at –78°C for 30 min then a solution of 3-Methyl-butyric acid tert-butyl ester (34.88 mmol, 5.52 g) in THF (40 mL) was added. The mixture was stirred at –78 °C for 30 min then a solution of (S)-2-Benzyloxycarbonylamino-3-chlorocarbonyl-propionic acid methyl (Ref: Synth. Comm 1993, 23(18), 2511-2526) (16.6 mmol) in 30 mL of dry THF was added drop wise. After stirring for another 2 hr at –78 °C, the reaction was quenched with 50 mL of 1N HCl and warmed to room temperature. The pH was adjusted to pH 3 with 1N NaOH and the THF was removed in vacuum. The organic layer was extracted with EtOAc (2x60 mL). The organic layers were dried over magnesium sulfate and then concentrated in vacuum. The residue was purified over 90 g silica gel, eluting with EtOAc:Heptane (1:3 then 1:2) afforded (S)-5-Benzyloxycarbonylamino-2-isopropyl-3-oxo-hexanedioic acid 1-tert-butyl ester 6-methyl ester (2.417 g, 34.5%).

^{1}H NMR ($CDCl_3$): δ 7.4 (m, 5H), 5.73 (d, J = 8.4 Hz, 1H), 5.12 (s, 2H); 4.6 (m, 1H), 3.74 (s, 3H), 3.39-3.06 (m, 3H), 2.4 (m, 1H), 1.45 (2s, 9H), 0.98 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.7 Hz, 3H); LC/MS: 100% 422 (M+1).

REFERENCE 8

(S)-2-Benzyloxycarbonylamino-4-oxo-hexanedioic acid 6-tert-butyl ester 1-methyl ester:

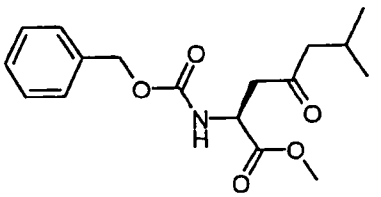


To a solution of N-CBZ L-aspartic acid 1-methyl ester (1.00 g, 3.55 mmol) in dry tetrahydrofuran (17 mL) was added carbonyl diimidazole (634.1 mg, 3.91 mmol). The mixture was stirred at room temperature for 6 hr then the magnesium salt of mono-tert butyl malonate (1.339 g, 3.91 mmol) (prepared according to Angew. Chem. Int. Ed. Engl. 1979, 18(1), 72-74) was added. The mixture was stirred at room temperature for another 20 h, then concentrated in vacuum. The residue was

partitioned between ether (60 mL) and 0.5 N HCl (60 mL). The organic layer was washed with saturated $NaHCO_3$ solution (50 mL) then dried over magnesium sulfate and concentrated in vacuum. The residue was purified over 35 g of silica gel, eluted with EtOAc:Heptane (1:1) to afford (S)-2-Benzyloxycarbonylamino-4-oxo-hexanedioic acid 6-tert-butyl ester 1-methyl ester (1.17 g, 87%). ^1H NMR ($CDCl_3$): δ 7.4 (m, 5H), 5.73 (d, J = 8.3 Hz, 1H), 5.1 (s, 2H), 4.6 (m, 1H), 3.75 (s, 3H), 3.37 (s, 2H), 3.32 (dd, J = 18.7, 4.3 Hz, 1H), 3.13 (dd, J = 18.5, 4.1 Hz, 1H), 1.47 (s, 9H); LC/MS: 93% 402 (M+Na).

REFERENCE 9

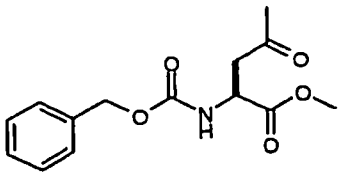
(S)-2-Benzyloxycarbonylamino-6-methyl-4-oxo-heptanoic acid methyl ester:



A solution of 5-Benzyloxycarbonylamino-2-isopropyl-3-oxo-hexanedioic acid 1-tert-butyl ester 6-methyl ester (1.06 g, 2.51 mmol) and p-toluenesulfonic acid monohydrate (35.8 mg, 0.19 mmol) in toluene (20 mL) was heated to reflux under N_2 for 6.5 hr. The mixture was cooled to room temperature, and concentrated in vacuum. The residue was purified over 35 g silica gel, eluting with EtOAc:Heptane (1:4) to afford (S)-2-Benzyloxycarbonylamino-6-methyl-4-oxo-heptanoic acid methyl ester (727 mg, 90%). ^1H NMR ($CDCl_3$): δ 7.4 (m, 5H), 5.78 (d, J = 9.1 Hz, 1H), 5.13 (s, 2H), 4.6 (m, 1H), 3.74 (s, 3H), 3.2 (dd, J = 18.3, 4.4 Hz, 1H), 2.95 (dd, J = 18.2, 4.0 Hz, 1H), 2.3 (m, 2H), 2.1 (m, 1H), 0.92 (d, J = 6.7 Hz, 6H); LC/MS: 77% 322 (MH^+).

REFERENCE 10

(S)-2-Benzyloxycarbonylamino-4-oxo-pentanoic acid methyl ester:



By proceeding in a similar manner to Reference Example 9 above but using 2-benzyloxycarbonylamino-4-oxo-hexanedioic acid 6-tert-butyl ester 1-methyl ester there was prepared (S)-2-benzyloxycarbonylamino-4-oxo-pentanoic acid methyl ester

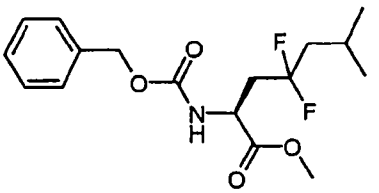
^1H NMR ($CDCl_3$): δ 7.4 (m, 5H), 5.76 (d, J = 8.1 Hz, 1H), 5.14 (s, 2H), 4.57 (m, 1H), 3.75 (s, 3H), 3.23 (dd, J = 18.4, 4.3 Hz, 1H), 3.0 (dd, J = 18.4, 4.3 Hz, 1H), 2.18 (s, 3H); LC/MS: >85% 280 (MH^+).

Alternate Method

To a cooled to 0°C suspension of copper (I) iodide in ether (20 mL) under N_2 was slowly added methyl lithium (1.6 M solution in ether, 21.3 mmol, 13.3 mL). The mixture was stirred at 0°C for 10 min then cooled to -78°C. A solution of 3.55 mmol of (S)-2-Benzyloxycarbonylamino-3-chlorocarbonyl-propionic acid methyl ester (Ref: Synth. Comm 1993, 23(18), 2511-2526) in 12 mL of dry THF was added drop wise. The mixture was stirred at -78 °C for 30 min then quenched by adding methanol (2 mL). The mixture was poured into saturated NH_4Cl (80 mL) and extracted with ether (2x40 mL). The organic layers were dried over magnesium sulfate and concentrated in vacuum. The residue was purified over 35 g silica gel, eluted with EtOAc:Heptane (1:1) to afford (S)-2-benzyloxycarbonylamino-4-oxo-pentanoic acid methyl ester (261 mg, 26%).

REFERENCE 11

(S)-2-Benzyloxycarbonylamino-4,4-difluoro-6-methyl-heptanoic acid methyl ester:

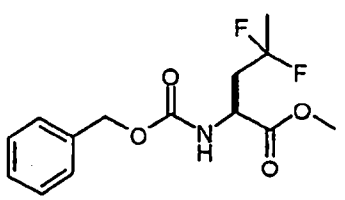


A mixture of (S)-2-benzyloxycarbonylamino-6-methyl-4-oxo-heptanoic acid methyl ester (915 mg, 2.85 mmol) and DAST (3 mL, XS) was stirred at 35°C for 47h. The mixture was diluted with dichloromethane (50 mL) and carefully added to saturated $NaHCO_3$ solution (150 mL). The aqueous layer was extracted with dichloromethane (30 mL). The organic layers were dried over magnesium sulfate and concentrated in vacuum. The residue was purified over 35 g silica gel, eluting with EtOAc:Heptane (1:4) to afford (S)-2-Benzyloxycarbonylamino-4,4-difluoro-6-methyl-heptanoic acid methyl ester (156 mg, 16%).

^1H NMR ($CDCl_3$): δ 7.4 (m, 5H), 5.48 (d, J = 7.9 Hz, 1H), 5.15 (s, 2H), 4.61 (q, J = 5.9 Hz, 1H), 3.78 (s, 3H), 2.4 (m, 2H), 1.95 (m, 1H), 1.8 (m, 2H), 0.98 (d, J = 6.6 Hz, 6H); LC/MS: 98% 366 (M+Na).

REFERENCE 12

(S)-2-Benzyloxycarbonylamino-4,4-difluoro-pentanoic acid methyl ester

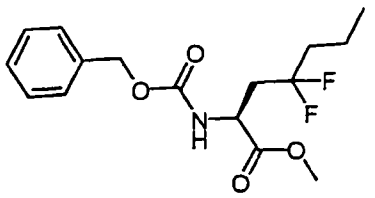


By proceeding in a similar manner to Reference Example 11 above but using (S)-2-benzyloxycarbonylamino-4-oxo-pentanoic acid methyl ester there was prepared (S)-2-benzyloxycarbonylamino-4,4-difluoro-pentanoic acid methyl ester

^{1}H NMR ($CDCl_3$): δ 7.4 (m, 5H), 5.46 (d, J = 7.1 Hz, 1H), 5.15 (s, 2H), 4.61 (q, J = 7.3 Hz, 1H), 3.78 (s, 3H), 2.45 (m, 2H), 1.67 (t, J = 18.8 Hz, 3H); LC/MS: 94% 324 (M+Na).

REFERENCE 13

(S)-2-Benzyloxycarbonylamino-4,4-difluoro-heptanoic acid methyl ester

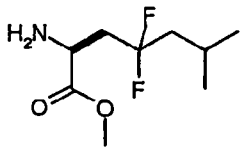


By proceeding in a similar manner to Reference Example 11 above but using (S)-2-benzyloxycarbonylamino-4-oxo-heptanoic acid methyl ester there was prepared (S)-2-benzyloxycarbonylamino-4,4-difluoro-heptanoic acid methyl ester.

LC/MS: 96% 330 (MH^+), 352 (M+Na).

REFERENCE 14

(S)-2-Amino-4,4-difluoro-6-methyl-heptanoic acid methyl ester hydrochloride:

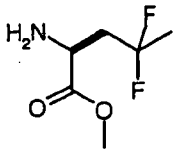


A solution of (S)-2-benzyloxycarbonylamino-4,4-difluoro-6-methyl-heptanoic acid methyl ester: (333 mg, 0.97 mmol) in methanol (10 mL) and 4 M HCl in dioxane (4 mmol, 1 mL) was hydrogenated over 10% Pd/C (150 mg) at 55 psi. After 7 hr, another portion of 10% Pd/C (200 mg) was added and the hydrogenation resumed. After 5.5 hr, the reaction did not progress. Catalyst was filtered and the filtrate was concentrated in vacuum and subjected to the hydrogenation conditions. After 6.5 hr, the catalyst was removed by filtration over a pad of Celite, and the filtrate was concentrated in vacuum to afford (S)-2-amino-4,4-difluoro-6-methyl-heptanoic acid methyl ester hydrochloride as a yellow sticky solid (240 mg, quant.).

^{1}H NMR ($CDCl_3$): δ 4.8 (b, 3H), 4.35 (b, 1H), 3.84 (s, 3H), 2.6 (m, 2H), 1.9 (m, 3H), 0.99 (d, J = 6.2 Hz, 6H); LC/MS: 90% 210 (M+1).

REFERENCE 15

(S)-2-Amino-4,4-difluoro-pentanoic acid methyl ester hydrochloride:

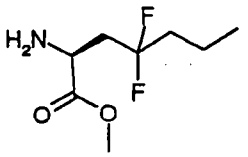


By proceeding in a similar manner to Reference Example 14 above but using (S)-2-benzyloxycarbonylamino-4,4-difluoro-pentanoic acid methyl ester there was prepared (S)-2-amino-4,4-difluoro-pentanoic acid methyl ester hydrochloride.

^{1}H NMR ($CDCl_3$): δ 4.8 (s, 3H), 4.37 (m, 1H), 3.86 (s, 3H), 2.4-2.8 (m, 2H), 1.73 (t, J = 18.9 Hz, 3H); LC/MS: 100% 168 (M+1).

REFERENCE 16

(S)-2-Amino-4,4-difluoro-heptanoic acid methyl ester hydrochloride

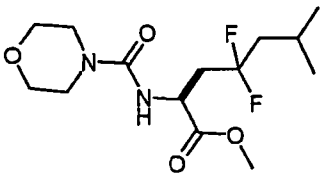


By proceeding in a similar manner to Reference Example 14 above but using (S)-2-benzyloxycarbonylamino-4,4-difluoro-heptanoic acid methyl ester there was prepared (S)-2-amino-4,4-difluoro-heptanoic acid methyl ester hydrochloride

LC/MS: 100% 196 (MH^+).

REFERENCE 17

(S)-4,4-Difluoro-6-methyl-2-[(morpholine-4-carbonyl)-amino]-heptanoic acid methyl ester:

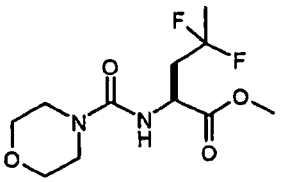


To a mixture of (S)-2-amino-4,4-difluoro-6-methyl-heptanoic acid methyl ester hydrochloride (238 mg, 0.97 mmol) and diisopropyl amine (2.42 mmol, 313 mg) in dry dichloromethane (5 mL) under N_2 was added drop wise morpholine carbonyl chloride (1.45 mmol, 218 mg). The mixture was stirred at room temperature for 23 h, then diluted with dichloromethane (25 mL) and washed with dilute HCl (30 mL), and saturated $NaHCO_3$ (30 mL). The organic layers were dried over magnesium sulfate and concentrated in vacuum. Purification over 12 g silica gel, eluting with EtOAc:Heptane (1:1, then 2:1) afforded (S)-4,4-Difluoro-6-methyl-2-[(morpholine-4-carbonyl)-amino]-heptanoic acid methyl ester (206 mg, 66%).

^{1}H NMR ($CDCl_3$): δ 5.2 (d, J = 7.4 Hz, 1H), 4.72 (dd, J = 13, 6 Hz, 1H), 3.78 (s, 3H), 3.7 (m, 4H), 3.4 (m, 4H), 2.4 (m, 2H), 1.95 (m, 1H), 1.8 (m, 2H), 0.99 (d, J = 6.4 Hz, 6H);LC/MS: 90% 345 (M+Na).

REFERENCE 18

(S)-4,4-Difluoro-2-[(morpholine-4-carbonyl)-amino]-pentanoic acid methyl ester:

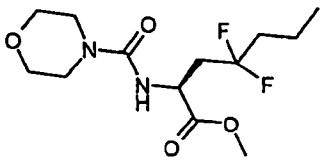


By proceeding in a similar manner to Reference Example 17 above but using (S)-2-amino-4,4-difluoro-pentanoic acid methyl ester hydrochloride there was prepared (S)-4,4-Difluoro-2-[(morpholine-4-carbonyl)-amino]-pentanoic acid methyl ester.

^{1}H NMR ($CDCl_3$): δ 5.18 (d, J = 7.5 Hz, 1H), 4.71 (q, J = 7 Hz, 1H), 3.78 (s, 3H), 3.71 (m, 4H), 3.4 (m, 4H), 2.37-2.55 (m, 2H), 1.67 (t, J = 18.7 Hz, 3H); LC/MS: 100% 303 (M+ Na).

REFERENCE 19

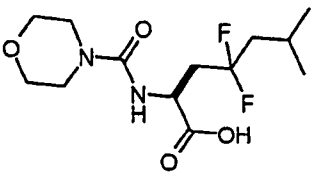
(S)-4,4-Difluoro-2-[(morpholine-4-carbonyl)-amino]-heptanoic acid methyl ester



By proceeding in a similar manner to Reference Example 17 above but using (S)-2-amino-4,4-difluoro-heptanoic acid methyl ester hydrochloride there was prepared (S)-4,4-difluoro-2-[(morpholine-4-carbonyl)-amino]-heptanoic acid methyl ester LC/MS: 100% 309 (MH^+).

REFERENCE 20

(S)-4,4-Difluoro-6-methyl-2-[(morpholine-4-carbonyl)-amino]-heptanoic acid:



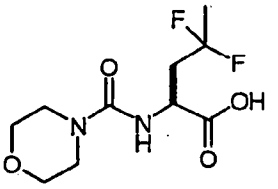
To a solution of methyl ester (205mg, 0.63 mmol) in MeOH: H2O (2:1 vol, 4 mL) was added LiOH-mono hydrate (80 mg, 1.9 mmol). The mixture was stirred at room temperature for 21h, then diluted with water (15 mL) and extracted with ether (20 mL). The pH of the aqueous layer was adjusted to pH 1 with 1N HCl and it was extracted with dichloromethane (2x20 mL). The organic layers were

dried over magnesium sulfate and concentrated in vacuum to afford (S)-4,4-dDifluoro-6-methyl-2-[(morpholine-4-carbonyl)-amino]-heptanoic acid (168 mg, 86%).

^{1}H NMR ($CDCl_3$): δ 6.4 (b, 1H), 5.3 (d, J = 6.2 Hz, 1H), 4.6 (m, 1H), 3.7 (m, 4H), 3.4 (m, 4H), 2.5 (m, 2H), 2.0 (m, 1H), 1.8 (m, 2H), 1.0 (d, J = 6.6 Hz, 6H); LC/MS: 90% 309 (M+1).

REFERENCE 21

(S)-4,4-Difluoro-2-[(morpholine-4-carbonyl)-amino]-pentanoic acid:

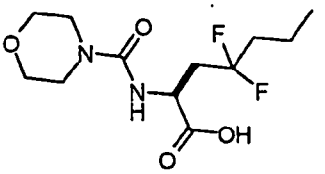


By proceeding in a similar manner to Reference Example 20 above but using (S)-4,4-Difluoro-2-[(morpholine-4-carbonyl)-amino]-pentanoic acid methyl ester there was prepared (S)-4,4-Difluoro-2-[(morpholine-4-carbonyl)-amino]-pentanoic acid

^{1}H NMR ($CDCl_3$): δ 5.9 (b, 1H), 5.29 (d, J = 6.3 Hz, 1H), 4.6 (m, 1H), 3.71 (m, 4H), 3.4 (m, 4H), 2.38-2.65 (m, 2H), 1.70 (t, J = 18.9 Hz, 3H); LC/MS: 100% 267 (M+ 1).

REFERENCE 22

(S)-4,4-Difluoro-2-[(morpholine-4-carbonyl)-amino]-heptanoic acid

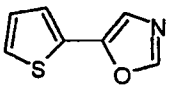


By proceeding in a similar manner to Reference Example 20 above but using (S)-4,4-difluoro-2-[(morpholine-4-carbonyl)-amino]-heptanoic acid methyl ester there was prepared (S)-4,4-difluoro-2-[(morpholine-4-carbonyl)-amino]-heptanoic acid

^{1}H NMR ($CDCl_3$): δ 5.3 (b, 1H), 5.25 (d, J = 5.4 Hz, 1H), 4.6 (m, 1H), 3.71 (m, 4H), 3.4 (m, 4H), 2.6-2.3 (m, 2H), 1.9 (m, 2H), 1.55 (m, 2H), 1.0 (t, J = 7.3 Hz, 3H); LC/MS: 83% 295 (M+1).

REFERENCE 23

5-Thiophen-2-yl-oxazole



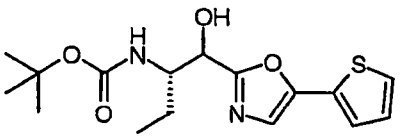
To a solution of p-toluenesulfonylmethyl isocyanide (3.0 g, 15.36 mmol) and Thiophene-2-carboxaldehyde (1.72 g, 15.36 mmol) in methanol (45 mL) under N_2 was added potassium carbonate

(2.12 g, 15.36 mmol). The mixture was heated to reflux for 5 hr, then cooled and concentrated in vacuum (cold water bath). The residue was partitioned between ether (100 mL) and water (100 mL). The organic layer was washed with water (100 mL), dried over magnesium sulfate and then concentrated in vacuum. The residue was purified over 35 g silica gel, eluted with ethyl acetate: heptane (1:5) to afford 5-thiophen-2-yl-oxazole (0.852 g, 37%).

^{1}H NMR ($CDCl_3$): δ 7.9 (s, 1H), 7.3 (m, 2H), 7.2 (s, 1H), 7.1 (dd, J = 5, 3.8 Hz, 1H); LC/MS: 100% 152 (M+1).

REFERENCE 24

{(S)-1-[Hydroxy-(5-thiophen-2-yl-oxazol-2-yl)-methyl]-propyl}-carbamic acid tert-butyl ester

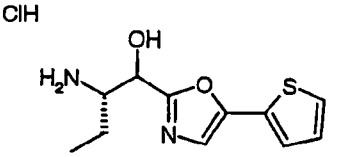


To a solution of 5-thiophen-2-yl-oxazole (0.85 g, 5.62 mmol) in dry THF (4 mL) was added triethylborane (1.0 M in THF, 5.62 mmol, 5.62 mL). The mixture was stirred at room temperature for 45 min, then cooled to –78°C and n-butyl lithium (1.6 M in hexane, 5.62 mmol, 3.51 mL) was added drop wise. The mixture was stirred at –78°C for 45 min then a solution of (1-Formyl-propyl)-carbamic acid tert-butyl ester (2.81 mmol, 0.526 g) in dry THF (3 mL) was added slowly. The mixture was stirred at –78°C for 4 h, then warmed to 0°C and quenched by adding 30 mL of 10% (vol) HOAc in ethanol. The mixture was stirred at room temperature for 18 hr and then concentrated in vacuum. The residue was purified over 90 g of silica gel, eluted with ethyl acetate: heptane (1:2 then 1:1) to afford {(S)-1-[hydroxy-(5-thiophen-2-yl-oxazol-2-yl)-methyl]-propyl}-carbamic acid tert-butyl ester (363 mg, 38%) as yellow oil.

^{1}H NMR ($CDCl_3$): δ (mixture of isomers) 7.35 (m, 2H), 7.1 (m, 2H), 4.9 (m, 2H), 4.0 (b, 1H), 3.6 (m, 1H), 1.8-1.55 (m, 2H), 1.4 and 1.3 (2s, 9H), 1.0 and 0.9 (2t, J = 7.4 Hz, 3H); LC/MS: 100 339 (M+1).

REFERENCE 25

(S)-2-Amino-1-(5-thiophen-2-yl-oxazol-2-yl)-butan-1-ol hydrochloride



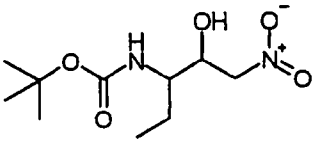
To a solution of {(S)-1-[hydroxy-(5-thiophen-2-yl-oxazol-2-yl)-methyl]-propyl}-carbamic acid tert-butyl ester (361 mg, 1.07 mmol) in dry dichloromethane (3 mL) was added 4N HCl in dioxane (3.0

mL, XS). The mixture was stirred at room temperature for 16 h, then concentrated in vacuum to afford (S)-2-Amino-1-(5-thiophen-2-yl-oxazol-2-yl)-butan-1-ol hydrochloride as a tan solid (quant.).

^{1}H NMR ($CDCl_3$): δ 7.5 (dd, J = 5.2, 1.2 Hz, 1H), 7.4 (dd, J = 3.6, 1.1 Hz, 1H), 7.3 (s, 1H), 7.1 (dd, J = 5, 3.6 Hz, 1H), 4.8 (m, 3H), 3.6 (m, 2H), 3.3 (b, 1H), 1.75 (m, 2H), 1.0 (t, J = 7.5 Hz, 3H); LC/MS: 100% 239 (M+1).

REFERENCE 26

1-Ethyl-2-hydroxy-3-nitro-propyl)-carbamic acid tert-butyl ester

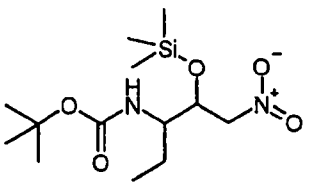


To a solution of (1-formyl-propyl)-carbamic acid tert-butyl ester (1.0 g, 5.34 mmol) in dry THF (10 mL) and ethanol was added nitromethane (3.91 g, 64.09 mmol) followed by triethylamine (2.70 g, 26.7 mmol). The mixture was stirred at room temperature for 22 h, and then concentrated in vacuum. The residue was diluted with ether (50 mL) and washed with concentrated NH_4Cl (60 mL). The ether layer was dried over magnesium sulfate and concentrated in vacuum. The residue was purified over 35 g silica gel, eluted with ethyl acetate: heptane (1:3) to afford the desired alcohol (1.09 g, 82%) as a light yellow oily solid.

^{1}H NMR ($CDCl_3$): δ 4.2-4.8 (m, 4H), 3.15-3.8 (m, 2H), 1.69-1.6 (m, 2H), 1.47 (2xs, 9H), 1.02 and 1.0 (2xt, J = 7.1 Hz, 3H) LC/MS: 2 isomers, total 100% 149 (M-BOC+1).

REFERENCE 27

(1-Ethyl-3-nitro-2-trimethylsilanyloxy-propyl)-carbamic acid tert-butyl ester

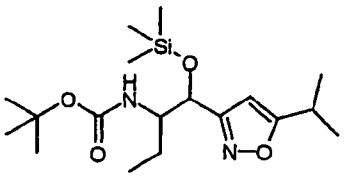


To a mixture of (1-ethyl-2-hydroxy-3-nitro-propyl)-carbamic acid tert-butyl ester (1.83 g, 7.37 mmol) and triethylamine (1.49 g, 14.75 mmol) in dry dichloromethane (25 mL) under N_2 was added trimethylsilyl chloride (1.20 g, 11.05 mmol). The mixture was stirred at room temperature for 24 h, then diluted with 40 mL of dichloromethane and washed with water (40 mL). The organic layer was dried over magnesium sulfate and concentrated in vacuum. The residue was purified over 110 g silica gel, eluted with ethyl acetate: heptane (1:4) to afford (1-ethyl-3-nitro-2-trimethylsilanyloxy-propyl)-carbamic acid tert-butyl ester (1.505 g, 86%) as a colorless oil.

^{1}H NMR ($CDCl_3$): δ 4.4-4.65 (m, 4H); 3.55 (m, 1H), 1.2-1.7 (m, 11H), 0.98 (2xt, J = 7.4 Hz, 3H), 0.13 (2s, 9H); LC/MS: 2 isomers, total 100% 221 (M-BOC+1).

REFERENCE 28

{1-[(5-Isopropyl-isoxazol-3-yl)-trimethylsilanyloxy-methyl]-propyl}-carbamic acid tert-butyl ester

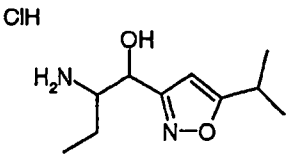


To a solution of (1-Ethyl-3-nitro-2-trimethylsilanyloxy-propyl)-carbamic acid tert-butyl ester (918 mg, 2.86 mmol), 1,4-Phenylene diisocyanate (1.38 g, 8.5 mmol) and 3-methyl-1-butyne (586 mg, 8.5 mmol) in dry toluene (15 mL) under N_2 was added triethylamine (10 drops). The mixture was heated to 50°C in a sealed vial for 28 h, and then cooled to room temperature Water (1 mL) was added and the mixture was stirred for an additional 2 h, then filtered. The filtrate was concentrated in vacuum and the residue was purified over 35 g silica gel, eluted with ethyl acetate: heptane (1:5) to afford {1-[(5-Isopropyl-isoxazol-3-yl)-trimethylsilanyloxy-methyl]-propyl}-carbamic acid tert-butyl ester (764 mg, 72%) as a colorless oil.

^{1}H NMR ($CDCl_3$): δ 6.0 (2s 1H), 4.4-4.9 (m, 2H), 3.7 (m, 1H), 3.0 (m, 1H), 1.2-1.6 (m, 17H), 1.0 (m, 3H), 0.11 and 0.1 (2xs, 9H); LC/MS: 2 isomers, total 67% 271 (M-BOC+1).

REFERENCE 29

2-Amino-1-(5-isopropyl-isoxazol-3-yl)-butan-1-ol hydrochloride

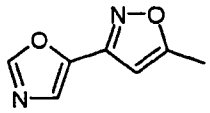


To a solution of {1-[(5-Isopropyl-isoxazol-3-yl)-trimethylsilanyloxy-methyl]-propyl}-carbamic acid tert-butyl ester in dry dichloromethane (5 mL) under N_2 was added a 4M solution of HCl in dioxane (5.0 mL, XS). The mixture was stirred at room temperature for 22 h, then concentrated in vacuum to afford the amine salt (475 mg, 99%) as a tan solid.

^{1}H NMR ($CDCl_3$): δ 6.25 (2xs, 1H), 5.0 (d, J = 3.9 Hz, 1H), 4.8 (d, J = 6.8 Hz, 1H), 3.4 (m, 1H), 3.1 (m, 1H), 1.5-1.7 (m, 2H), 1.3 (d, J = 6.8 Hz, 6H); 1.0 (t, J = 6.7 Hz, 3H); LC/MS: 100% 199 (M+1).

REFERENCE 30

5-Methyl-3-oxazol-5-yl-isoxazole

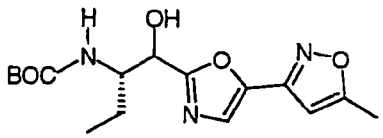


Diisobutylaluminum hydride (1.0M in DCM, 25.5ml, 25.5 mmol) was added drop wise over 20 minutes to a solution of methyl-5-methylisoxazole-3-carboxylate (3.0 gm, 21.3 mmol) in 35 ml of dry methylene chloride, with stirring at -78°C, and the reaction mixture was stirred at -78°C for 5.5 hours. The reaction was warmed to -40°C and quenched with ice (60 gm). After the biphasic mixture was allowed to warm to room temperature, potassium sodium tartrate tetrahydrate (100 ml saturated aqueous solution) was added. The bilayer were separated, the aqueous was extracted with methylene chloride. The organic extracts were dried over sodium sulfate and concentrated under reduced pressure to give 5-Methyl-isoxazole-3-carbaldehyde as white solid (1.3 gm).

P--Toluenesulfonyl methyl isocyanide (1.75 gm, 8.97 mmol) and Potassium carbonate (1.24 gm, 8.97 mmol) were added to a solution of 5-Methyl-isoxazole-3-carbaldehyde (1.0 gm, 8.97 mmol) in 35 ml of dry methanol and the reaction mixture was refluxed (90°C) for 5 hours. The reaction was cooled to room temperature and concentrated under reduce pressure. The residue was partitioned in diethyl ether (100 ml) and water (200 ml). The organic layer was separated and the aqueous extracted with diethyl ether. The organic extracts were washed with brine and water, dried over sodium sulfate and concentrated under reduced pressure to give the title compound as yellowish solid (1.25gm).
LC/MS: 87%, 238 (M+1)

REFERENCE 31

((S)-1-{Hydroxy-[5-(5-methyl-isoxazol-3-yl)-oxazol-2-yl]-methyl}-propyl)-carbamic acid tert-butyl ester



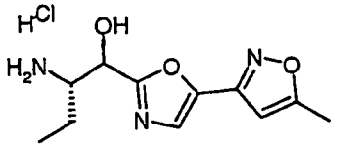
Triethylborane (1M in THF, 12 ml, 12 mmol) was added to a solution of 5-Methyl-3-oxazol-5-yl-isoxazole (1.8 gm, 12 mmol) in 40 ml of dry Tetrahydrofuran and the mixture was stirred at room temperature for 15 minutes. The mixture was cooled to -78°C, nBuLi (2.5M in Hexanes, 4.8 ml, 12 mmol) was added drop wise and the mixture was stirred at -78°C for 15 minutes. A solution of (S)-1-Formyl-propyl)-carbamic acid tert-butyl ester (898.7 mg, 4.8 mmol) in 15 ml of dry tetrahydrofuran was added drop wise and the reaction mixture was stirred at -78°C for 3 hours, then let warm to -30°C and quenched with acetic acid in ethanol (4%, 250 ml), stirring continued for 2 hours, while warming to room temperature. The reaction was concentrated under reduced pressure; the residue was dissolved in diethyl ether (250 ml) and stirred for 1.5 hours at room temperature. The precipitate was filtered; the

filtrate was concentrated under reduced pressure. Column chromatography on silica eluting with a mixture of methylene chloride and ethyl acetate gave the title compound as pale yellow solid (830 mg).

LC/MS 100%, 338 (M+1)

REFERENCE 32

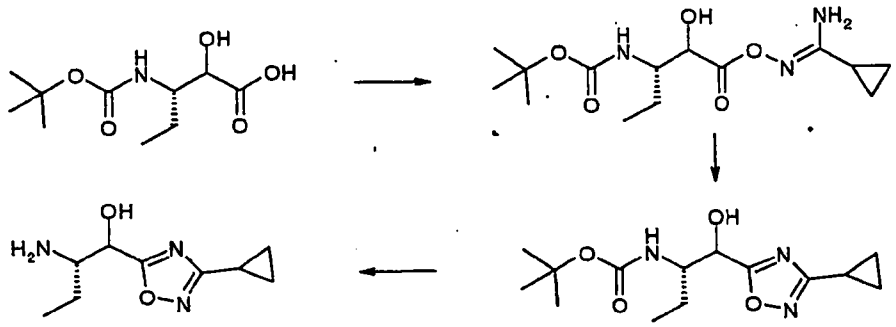
(S)-2-Amino-1-[5-(5-methyl-isoxazol-3-yl)-oxazol-2-yl]-butan-1-ol; hydrochloride



Hydrogen chloride (4M in 1,4-dioxane, 3.3 ml) was added dropwise to a solution of ((S)-1-{Hydroxy-[5-(5-methyl-isoxazol-3-yl)-oxazol-2-yl]-methyl}-propyl)-carbamic acid tert-butyl ester (0.75 gm, 2.22 mmol) in 10 ml of methylene chloride an the reaction mixture was stirred at room temperature for 2.5 hours. The reaction was diluted with diethyl ether (50 ml) and stirred for another hour at room temperature, concentrated in reduced pressure to give the title compound as yellowish solid (0.75 gm). ^{1}H NMR [$(CD)_3SO$]: δ 8.18 (m, 3H), 7.84 (s, 1H), 6.70 (s, 1H), 4.90 (m, 1H), 3.58 (m, 2H), 2.50 (s, 3H), 1.60 (m, 2H), 0.90 (t, 3H), LC/MS 100%, 238 (M+1)

REFERENCE 33

(S)-2-Amino-1-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-butan-1-ol



A solution of (S)-3-tert-Butoxycarbonylamino-2-hydroxy-pentanoic acid (2.00g, 8.57mmol) and N-hydroxy-cyclopropanecarboxamidine (1.03g, 10.29mmol) in dichloromethane (20mL) was stirred at 0°C and 1.25 equivalents of N-cyclohexylcarbodiimide-N'-methyl polystyrene (1.70mmol/g, 6.30g, 10.72mmol) was added in portions. The reaction mixture stirred under nitrogen for three hours while warming to 15°C. The reaction mixture was filtered, the resin washed with dichloromethane and the filtrate evaporated under vacuum to dryness. [LC/MS m/z=338 (M+H+Na)].

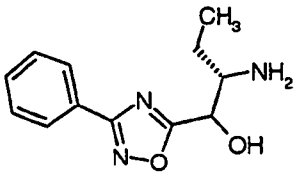
The residue was dissolved in tetrahydrofuran (20mL) and heated in a microwave reactor (Smith Creator) at 160°C for three minutes, cooled to room temperature and evaporated under vacuum to dryness. [LC/MS m/z=320 (M+H+Na)]. The residue was dissolved in dichloromethane (50mL) and

stirred at room temperature as a 50mL solution of 50% trifluoroacetic acid in dichloromethane was added drop wise. After three hours the reaction was evaporated under vacuum to dryness and dissolved in 50mL of dichloromethane again. Three equivalents of Silicycle triamine-3 was added and the mixture stirred at room temperature overnight. The mixture was filtered and washed with dichloromethane. Evaporate under vacuum to give 1.04g (61% overall). [LC/MS m/z=198 (M+H)]

Alternatively, deprotection of the BOC protecting group was carried out with HCl in dioxane to give (S) -2- amino-1-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-butan-1-ol hydrochloride.

REFERENCE 34

(S)-2-Amino-1-(3-phenyl-1,2,4-oxadiazol-5-yl)-butan-1-ol



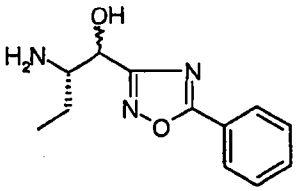
A solution of (S)-3-tert-Butoxycarbonylamino-2-hydroxy-pentanoic acid (2.00g, 8.57mmol) and N-hydroxy-benzamidine (1.3g, 9.5mmol) in dichloromethane (40mL) was stirred at 0°C. N-cyclohexylcarbodiimide-N'-methyl polystyrene (1.90mmol/g, 6g, 11.4mmol) was added in portions. The reaction mixture was stirred under nitrogen for one hour. The reaction mixture was filtered, the resin washed with dichloromethane and the filtrate evaporated under vacuum to dryness. [LC/MS m/z=352 ($M+H^+$), 296($M+H^+$-isobutene)]. The residue was dissolved in tetrahydrofuran (20mL) and heated in a microwave reactor (Smith Creator) at 180°C for three minutes, cooled to room temperature and evaporated under vacuum to dryness. The residue was purified via flash chromatography (eluted with a gradient from 5% to 65% ethyl acetate in heptane) to give the product as a white solid [LC/MS m/z=356 ($M+Na^+$), 234 ($M+H^+$-Boc)].

The product was dissolved in dichloromethane (45mL) and trifluoroacetic acid (5mL) was added. After two hours the reaction was evaporated under vacuum to dryness. The residue was re-dissolved in 50mL of dichloromethane. Silicycle triamine-3 (9.9g, 39mmol) was added and the mixture stirred at room temperature overnight. The mixture was filtered and washed with dichloromethane. The filtrate was concentrated under vacuum to give (S)-2-Amino-1-(3-phenyl-1,2,4-oxadiazol-5-yl)-butan-1-ol (775mg, 38%) as a white solid.

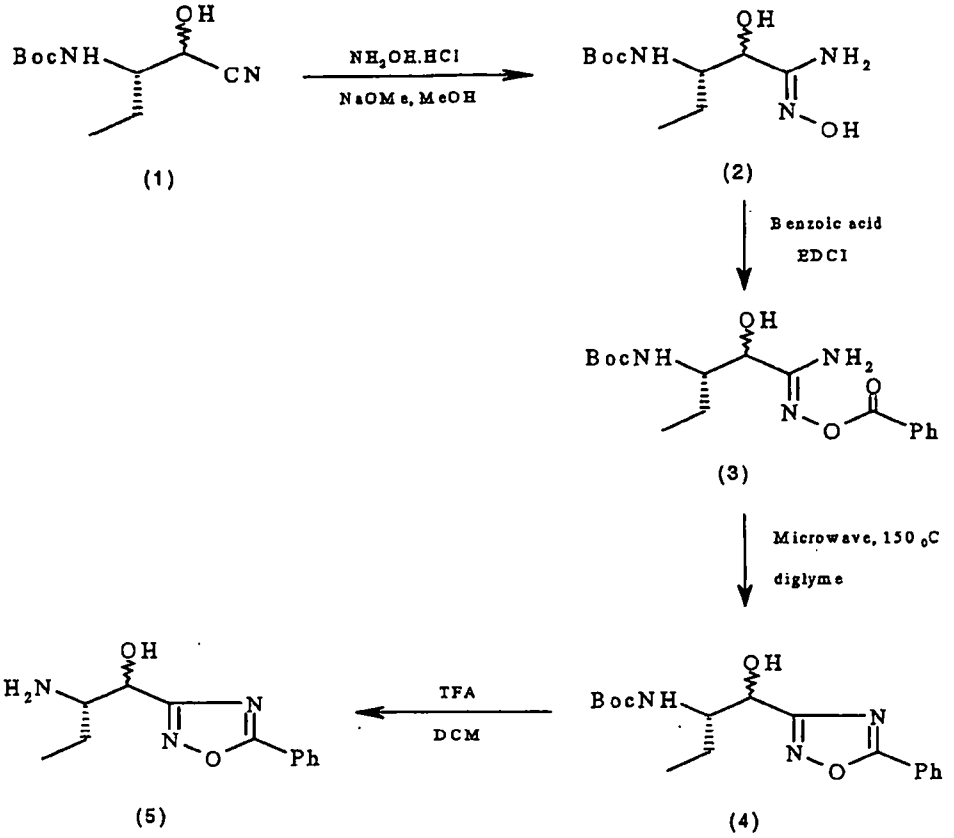
^1H NMR ($CDCl_3$):δ 8.12-8.06 (m, 2H), 7.54-7.45 (m, 3H), 4.93 & 4.75 (2xd, J= 5Hz & 3.5Hz, 1H), 3.25 &3.11 (2xm, 1H), 1.78-1.42 (2xm, 2H), 1.04 & 1.01 (2x t, J= 7.5Hz, 3H). [LC/MS m/z=234 (M+H)].

REFERENCE 35

(S)-2-Amino-1-(5-phenyl-[1,2,4]oxadiazol-3-yl)-butan-1-ol



Synthesized as described in the following reaction scheme:



{(S)-1-[Hydroxy-(N-hydroxycarbamimidoyl)-methyl]-propyl}-carbamic acid tert-butyl ester (2)

A solution of (2-cyano-1-ethyl-2-hydroxy-ethyl)-carbamic acid tert-butyl ester (9.53g, 44mmol) in methanol (80ml) was cooled to 0°C and treated successively with hydroxylamine hydrochloride (3.05g, 44mmol) in methanol (80ml) and 25% sodium methoxide solution in methanol (10.2ml). After stirring at 0°C for 5 minutes the reaction mixture stirred at room temperature for 5 hours and then evaporated. The residue was partitioned between ethyl acetate and water. The organic layer was separated, dried over magnesium sulfate and then evaporated under reduced pressure. The residual yellow oil was subjected to mplc, eluting with a mixture of ethyl acetate and heptane to give {(S)-1-[hydroxy-(N-hydroxycarbamimidoyl)-methyl]-propyl}-carbamic acid tert-butyl ester (3.5g) as white solid. MS: MH^+ 248.

{1-[Hydroxy-(N-benzoyloxycarbamimidoyl)-methyl]-propyl}-carbamicacid tert-butyl ester (3)

A solution of {1-[hydroxy-(*N*-hydroxycarbamimidoyl)-methyl]-propyl}-carbamic acid tert-butyl ester (2) (2.5g, 10mmol) in dichloromethane (125ml) was treated with benzoic acid (1.36g, 11mmol), EDCI

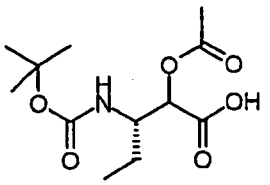
(2.14 g, 11mmol), HOBT (1.37g, 10mmol) and triethylamine (1.35mL, 11mmol) and stirred at room temperature overnight. The reaction mixture was washed with saturated sodium bicarbonate solution, then water, then dried over Na_2SO_4 and then evaporated under reduced pressure. The residue was subjected to mplc eluting with 1% triethylamine in 2:3 v/v ethyl acetate and heptane mixture to give {1-[hydroxy-(N-benzoyloxycarbamimidoyl)-methyl]-propyl}-carbamicacid tert-butyl ester (850mg) as a yellow solid. MS: MH^+ 352.

2-Amino-1-(5-phenyl-[1,2,4]oxadiazol-3-yl)-butan-1-ol (5)

A solution of (3) (1.5g, 4.3mmol) in diglyme was heated at 150°C in a microwave reactor (Smith Creator, S00219) for 40 minutes. Solvent evaporated under vacuum in Genevac Evaporator at 80°C for 3hours to give a brown solid. This was taken in dichloromethane (40ml) and treated with trifluoroacetic acid at room temperature for 2 hours. Solvent evaporated to dryness under reduced pressure, crude taken in water, washed with DCM, aqueous layer basified with 1M NaOH solution and extracted with dichloromethane. Organic layer dried over Na_2SO_4 and evaporated under reduced pressure to give 2-amino-1-(5-phenyl-[1,2,4]oxadiazol-3-yl)-butan-1-ol (300mg) as a pale brown solid. ^{1}HNMR ($CDCl_3$): δ 8.14-8.10 (m, 2H), 7.59-7.47 (m, 3H), 4.83 & 4.65 (d, J= 5Hz, 1H), 3.18-3.05 (2m, 1H), 1.71-1.20(m, 2H), 1.05-0.97 (2xt, J= 7.2Hz, 3H).

REFERENCE 36

(S)-2-Acetoxy-3-tert-butoxycarbonylamino-pentanoic acid



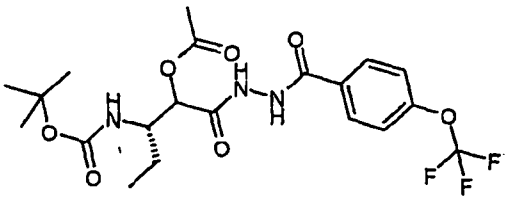
Pyridine (5 ml), 4-(dimethylamino)pyridine (0.01 g) and acetic anhydride (11 mmol, 1.12 g) were dissolved in dichloromethane (150 ml) and the resulting solution cooled to 0°C. (S)-3-tert-Butoxycarbonylamino-2-hydroxy-pentanoic acid (10 mmol, 2.33 g, A) was added at once and the resulting reaction mixture was stirred for 5 hours.

1M hydrochloric acid (250 ml) was added and the mixture transferred into a separating funnel. The phases were separated and the aqueous phase extracted three times with ethyl acetate (200 ml). The combined organic phases were washed twice with water (200 ml) and with brine (100 ml). The organic phase was dried with magnesium sulfate and the solvents evaporated under reduced pressure to give (S)-2-acetoxy-3-tert-butoxycarbonylamino-pentanoic acid (2.535 g, 92 %)..

MS: m/z=298 ($M+Na^+$), 276 ($M+H^+$)

REFERENCE 37

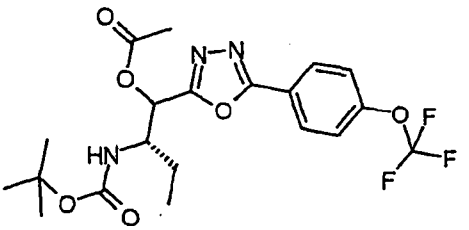
Acetic acid (S)-2-tert-butoxycarbonylamino-1-[N'-(4-trifluoromethoxy-benzoyl)hydrazinocarbonyl]-butyl ester



(S)-2-acetoxy-3-tert-butoxycarbonylamino-pentanoic acid (1.82 mmol, 0.5 g, A) was dissolved in 30 ml dichloromethane. N-Cyclohexylcarbodiimide-N'-methylpolystyrene (3.64 mmol, 1.92 g, B) was added and the resulting reaction mixture stirred for 2 min. 4-(trifluoromethoxy)benzoic acid hydrazide (1.65 mmol, 0.363 g, C) was added and the reaction mixture stirred over night. After 16 hours LC/MS analysis still showed hydrazide. Polystyrene methyl isocyanate (1.65 mmol, 1.15 g) was added and stirring continued for eight hours. The reaction mixture was filtered under suction and the filtrate concentrated under reduced pressure. To give acetic acid (S)-2-tert-butoxycarbonylamino-1-[N'-(4-trifluoromethoxy-benzoyl)hydrazinocarbonyl]-butyl ester as yellow foam (0.5 g, 64 %). According to LC/MS still some hydrazide present. MS: m/z= 500 ($M+Na^+$), 478 ($M+H^+$)

REFERENCE 38

Acetic acid (S)-2-tert-butoxycarbonylamino-1-[5-(4-trifluoromethoxy-phenyl)-1,3,4-oxadiazol-2-yl]-butyl ester



The acetic acid (S)-2-tert-butoxycarbonylamino-1-[N'-(4-trifluoromethoxy-benzoyl)-hydrazinocarbonyl]-butyl ester obtained above was split into 5 portions, which were separately reacted as follows:

acetic acid (S)-2-tert-butoxycarbonylamino-1-[N'-(4-trifluoromethoxy-benzoyl)-hydrazinocarbonyl]-butyl ester (0.21 mmol, 0.1 g) was dissolved in THF (5 ml) and the solution filled into a Smith Microwave synthesizer reaction vessel. 2-tert-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,2,3-diazaphosphorine on polystyrene (1.05 mmol, 0.456 g, 2.3 mmol/g loading) and the p-Toluenesulfonic chloride (0.25 mmol, 0.048 g) were added and the reaction mixture heated at 150°C for 10 min (fixed hold time) in the microwave synthesizer.

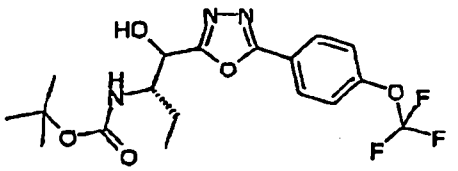
The combined reaction mixtures were filtered under suction and the resin washed with 300 ml ethyl acetate. The combined filtrates were concentrated under reduced pressure.

The crude product purified via flash chromatography (Biotage Horizon, 25M column, crude product loaded on caplet, 17 ml/min flow rate, 12 ml/fraction, 120 ml gradient from 0% ethyl acetate in heptane to 30 % ethyl acetate in heptane, 240 ml 30 % ethyl acetate in heptane, 60 ml gradient 30-50 % ethyl acetate in heptane, 300 ml 50 % ethyl acetate in heptane) to give acetic acid (S)-2-tert-butoxycarbonylamino-1-[5-(4-trifluoromethoxy-phenyl)-1,3,4-oxadiazol-2-yl]-butyl ester (0.28 g, 58 %)

MS: m/z= 460 ($M+H^+$)

REFERENCE 39

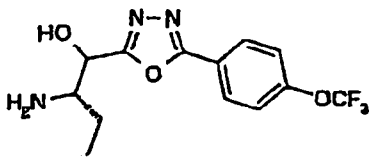
((S)-1-{Hydroxy-[5-(4-trifluoromethoxy-phenyl)-1,3,4-oxadiazol-2-yl]-methyl}-propyl)-carbamic acid tert-butyl ester



Acetic acid (S)-2-tert-butoxycarbonylamino-1-[5-(4-trifluoromethoxy-phenyl)-1,3,4-oxadiazol-2-yl]-butyl ester (0.61 mmol, 0.28 g) was dissolved in a mixture of THF (10 ml) and water (10 ml). Lithium hydroxide hydrate (1.22 mmol, 0.051 g) was added and the reaction mixture stirred for 2 h. The solvents were evaporated under reduced pressure and the residue transferred into a separating funnel with 300 ml ethyl acetate and 50 ml water. The phases were separated and the organic phase washed with brine (100 ml). The organic phase was then dried with magnesium sulfate. The solvent was evaporated under reduced pressure and dried under high vacuum to yield ((S)-1-{hydroxy-[5-(4-trifluoromethoxy-phenyl)-1,3,4-oxadiazol-2-yl]-methyl}-propyl)-carbamic acid tert-butyl ester as yellow oil (0.225 g , 89 %) MS: m/z= 440 ($M+Na^+$), 418 ($M+H^+$)

REFERENCE 40

(S)-2-Amino-1-[5-(4-trifluoromethoxy-phenyl)-1,3,4-oxadiazol-2-yl]-butan-1-ol

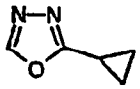


((S)-1-{hydroxy-[5-(4-trifluoromethoxy-phenyl)-1,3,4-oxadiazol-2-yl]-methyl}-propyl)-carbamic acid tert-butyl ester (0.54 mmol, 0.225 g) was dissolved in dichloromethane (9 ml) and treated with trifluoroacetic acid (1 ml). The reaction mixture was stirred for four hours. The solvents were

evaporated under reduced pressure. The residue was re-dissolved in dichloromethane (20 ml) and Silicycle Triamine (5.4 mmol, 1.47 g) was added. The reaction mixture was stirred for 60 h (over the weekend). The reaction mixtures were filtered under suction and the solvents evaporated to give (S)-2-Amino-1-[5-(4-trifluoromethoxy-phenyl)-1,3,4-oxadiazol-2-yl]-butan-1-ol (0.164 g, 96 %). MS: m/z= 318 ($M+H^+$)

REFERENCE 41

2-Cyclopropyl-[1,3,4]oxadiazole



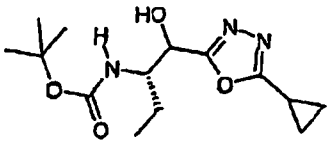
A mixture of cyclopropanecarboxylic acid methyl ester (10g, 0.1 mol) and hydrazine hydrate (7.3 mL, 0.15 mol) was refluxed for 28 hr and cooled to room temperature. The mixture was evaporated under reduced pressure and then dried by azeotropic removal of the solvent with toluene. The residue was dissolved in dichloromethane and washed with saturated NaCl. The organic phase was dried over anhydrous $MgSO_4$, solvent evaporated under reduced pressure to give cyclopropanecarboxylic acid hydrazide (4.36g, 44%)

A mixture of the Cyclopropanecarboxylic acid hydrazide (31.35g, 0.31 mol), trimethyl orthoformate (300 mL) and p-toluenesulfonic acid monohydrate (200 mg) was heated under reflux overnight. Excess trimethyl orthoformate and methanol were removed by distillation. Vacuum distillation of the residue afforded 2-Cyclopropyl-[1,3,4]oxadiazole (22g, 64%).

^1H NMR ($CDCl_3$): δ 8.24(s, 1H), 2.2 (m, 1H), 1.15 (m, 4H). LCMS: 100%, 111 (MH^+).

REFERENCE 42

{1-[(5-Cyclopropyl-[1,3,4]oxadiazol-2-yl)-hydroxy-methyl]-propyl}-carbamic acid tert-butyl ester



A solution of 2-cyclopropyl-[1,3,4]oxadiazole (2.16g, 19.6 mmol) in dry THF (100 mL) was cooled to –78°C. ^nBuLi (1.6M in hexanes, 12.3 mL, 19.6 mmol) was added dropwise. The reaction mixture was stirred at –78°C for 40 min. $MgBr_2.OEt_2$ (5.0692g, 19.6 mmol) was added. The reaction mixture was allowed to warm up to –45°C and stirred at that temperature for 1.5 hr. A solution of (1-formyl-propyl)-carbamic acid tert-butyl ester (3.7g, 19.6 mmol) in THF (40 mL) was added. The reaction mixture was allowed to warm up to –20°C and stirred at that temperature for 3.5 hrs. The reaction mixture was quenched with a solution of saturated NH_4Cl solution and extracted with ethyl acetate. Combined organic extracts was washed with saturated NaCl solution and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the crude was purified by column chromatography

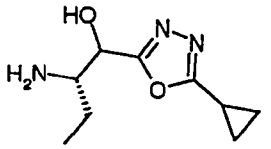
eluting with ethyl acetate and heptane mixture to give {1-[(5-cyclopropyl-[1,3,4]oxadiazol-2-yl)-hydroxy-methyl]-propyl}-carbamic acid tert-butyl ester (2.83g, 49%).

LCMS: 298 (MH^+).

REFERENCE 43

(S)-2-Amino-1-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)-butan-1-ol; compound with trifluoro-acetic acid

TFA

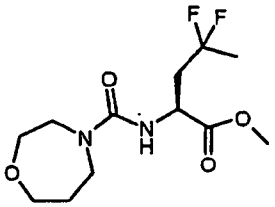


A mixture of {1-[(5-cyclopropyl-[1,3,4]oxadiazol-2-yl)-hydroxy-methyl]-propyl}-carbamic acid tert-butyl ester (2.83g, 9.95 mmol), trifluoro acetic acid (5 mL) in dichloromethane (20 mL) was stirred at room temperature for 2 hrs and concentrated to dryness under reduced pressure to give (S)-2-amino-1-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)-butan-1-ol; compound with trifluoro-acetic acid.

LCMS: 100% 198 (MH^+).

REFERENCE 44

(S)-4,4-Difluoro-2-[(perhydro-1,4-oxazepine-4-carbonyl)-amino]-pentanoic acid methyl ester.



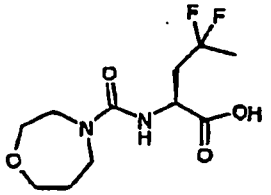
Triphosgene was dissolved in dichloromethane (10 mL) and to this was added, via syringe pump, a mixture of S-2-Amino-4, 4-difluoro-pentanoic acid hydrochloride (1.00g, 4.90 mmol) (see reference example 15), diisopropylethyl amine (1.88 mL, 10.80 mmol) dissolved in dichloromethane (10 mL) over the period of 1h. After stirring for an additional 15 minutes a solution of homomorpholine hydrochloride (0.67g, 4.90 mmol) and diisopropylethyl amine (1.90 mL, 10.90 mmol) in dichloromethane (10 mL) was added to the solution. The resulting solution was stirred at RT for 2h. The solvent was evaporated and the residue diluted with ethyl acetate (100 mL) then washed with 1M $KHSO_3$ (2x 10 mL), saturated $NaHCO_3$, and brine. The organics were dried (Na_2SO_4), filtered and concentrated to yield a pale yellow oil. The crude material was purified on 20 g silica gel eluting with ethyl acetate:heptane gradient 50-100%. (S)-4,4-Difluoro-2- [(perhydro-1, 4-oxazepine-4-carbonyl)-amino]-pentanoic acid methyl ester was obtained as a white solid (0.40g, 28%).

^1H NMR ($CDCl_3$) δ 5.12 (d, J=7.5Hz, 1H), 4.72 (dd, J = 12.0, 7.2 Hz, 1H), 3.75 (m, 7H), 3.55 (m, 4H), 2.45 (m, 2H), 1.98 (m, 2H), 1.66 (t, J = 18.7 Hz, 3H).

LC/MS: 295, 100%, (M+H), 317 (M+Na)

REFERENCE 45

(S)-4,4-Difluoro-2- [(perhydro-1,4-oxazepine-4-carbonyl)-amino]-pentanoic acid

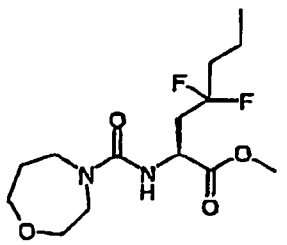


(S)-4,4-Difluoro-2- [(perhydro-1,4-oxazepine-4-carbonyl)-amino]-pentanoic acid methyl ester (0.38g, 1.29mmol) was dissolved in tetrahydrofuran/methanol (15mL/10mL) and lithium hydroxide (35mg, 1.40mmol) dissolved in water (5mL) added. The reaction was stirred at RT for 18h, and then the methanol/tetrahydrofuran was removed in vacuo. The residue was acidified with 6M hydrochloric acid (0.25mL) and extracted with dichloromethane (3x 20 mL), dried (Na_2SO_4), and concentrated to yield (S)-4,4-Difluoro-2- [(perhydro-1,4-oxazepine-4-carbonyl)-amino]-pentanoic acid as a white solid (0.36g, 99%).

^{1}H NMR (DMSO-d6) δ 12.6 (bs, 1H), 6.60 (d, 8.3 Hz, 1H), 4.30 (dd, J = 14.5, 7.0 Hz, 1H), 3.57 (m, 4H), 3.43 (m, 4H), 2.38 (m, 2H), 1.77 (m, 2H), 1.61 (t, J = 19.2Hz, 3H).
LC/MS: 100% 281 (M+H)

REFERENCE 46

(S)-4,4-Difluoro-2-[(perhydro-1,4-oxazepine-4-carbonyl)-amino]-heptanoic acid methyl ester



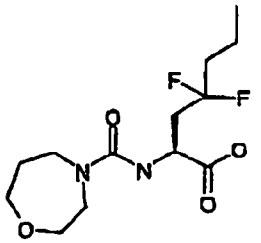
To a mixture of Sodium bicarbonate (5.25g), p-nitro chloroformate (5.03g, 25 mmol) in acetonitrile (130 ml) under nitrogen was added (S)-2-Amino-4,4-difluoro-heptanoic acid methyl ester hydrochloride (5.79g, 0.025 mol) and stirred at room temperature for 5hr. Homomorpholine hydrochloride (3.61g, 26.25 mmol) and triethyl amine (12.5 ml) were added and the reaction stirred overnight at room temperature. Solvent evaporated off under reduced pressure, crude partitioned

between water (150 ml) and ethyl acetate (200 ml). Organic layer separated, washed with K_2CO_3 solution (150 ml), HCl (150 ml) and brine (150 ml). Organic layer separated, dried ($MgSO_4$) and evaporated under reduced pressure. Crude purified by column chromatography eluting with v/v 1:1 to 8:2 ethyl acetate heptane followed by ethyl acetate to give (S)-4,4-Difluoro-2-[(perhydro-1,4-oxazepine-4-carbonyl)-amino]-heptanoic acid methyl ester (4.8g) as pale yellow oil.

LC/MS: 323 (M+H)

REFERENCE 47

(S)-4,4-Difluoro-2-[(perhydro-1,4-oxazepine-4-carbonyl)-amino]-heptanoic acid

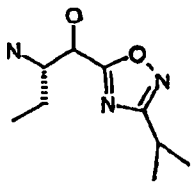


By proceeding in a similar manner to Reference Example 45 above but using (S)-4,4-Difluoro-2-[(perhydro-1,4-oxazepine-4-carbonyl)-amino]-heptanoic acid methyl ester there was prepared (S)-4,4-Difluoro-2-[(perhydro-1,4-oxazepine-4-carbonyl)-amino]-heptanoic acid.

LC/MS: 309 (M+H)

REFERENCE 48

(S)-2-Amino-1-(3-isopropyl-[1,2,4]oxadiazol-5-yl)-butan-1-ol

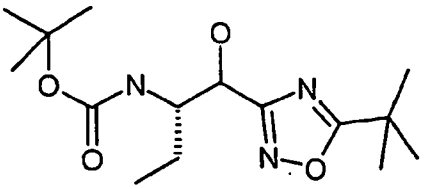


Similarly prepared according to the procedure for Reference Example 33.

LCMS: 200 (M+H)

REFERENCE 49

{(S)-1-[(5-tert-Butyl-1,2,4-oxadiazol-3-yl)-hydroxy-methyl]-propyl}-carbamic acid tert butyl ester



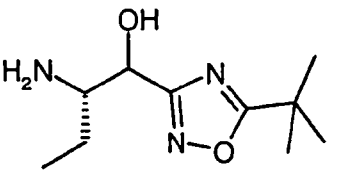
{(S)-1-[Hydroxy-(N-hydroxycarbamimidoyl)-methyl]-propyl}-carbamic acid tert-butyl ester (235mg, 0.95 mmol) in diglyme (2 ml) was treated with trimethyl acetic anhydride (0.212 ml, 1.04 mmol) and the reaction mixture heated at 170 °C for 5 minutes in a Emrys Optimizer microwave from Personal Chemistry. The solvent was evaporated under high vacuum. The crude obtained was purified by flash chromatography eluting with a mixture of ethyl acetate and heptane (1:4) to give {(S)-1-[(5-tert-Butyl-1,2,4-oxadiazol-3-yl)-hydroxy-methyl]-propyl}-carbamic acid tert butyl ester as a brown oil (100 mg) (mixture of diastereoisomers).

^{1}H NMR ($CDCl_3$) δ: 4.92-4.69 (m, 2H), 4.05-3.85 (m, 1H), 3.57-3.41 & 3.32-3.15 (2xbs, 1H), 1.73-1.48 (m, 2H), 1.45 & 1.44 (2xs, 9H), 1.43 & 1.39 (2xs, 9H), 0.99 & 0.96 (2xt, J=7.5Hz, 3H).

MS : 314 (M+H).

REFERENCE 50

(S)-2-Amino-1-(5-tert-butyl-1,2,4-oxadiazol-3-yl)-butan-1-ol



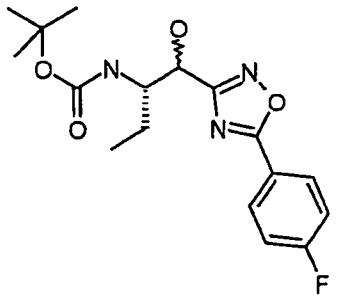
A solution of {(S)-1-[(5-tert-Butyl-1,2,4-oxadiazol-3-yl)-hydroxy-methyl]-propyl}-carbamic acid tert butyl ester (2.11 g, 6.72 mmol) in methylene chloride (20 ml) was treated with trifluoroacetic acid (5.18 ml, 67.25 mmol) and stirred at room temperature for 3h. The solvent was evaporated under reduced pressure. The residue was dissolved in methylene chloride (100 ml) and treated with PS-trisamine from Argonaut Technologies (5.38g, 20.18 mmol, 3.75 mmol/g loading) and the reaction stirred at room temperature for 4h, filtered and the filtrate evaporated to give (S)-2-Amino-1-(5-tert-butyl-1,2,4-oxadiazol-3-yl)-butan-1-ol as an orange oil (975 mg) (mixture of diastereoisomers).

^{1}H NMR ($CDCl_3$) δ : 4.73 & 4.58 (2xd, J=5Hz, 1H), 3.12-3.00 (m, 1H), 2.64-2.31 (bs, 3H), 1.69-1.44 (m, 2H), 1.43 (s, 9H), 0.99 & 0.97 (2xt, J=7.5Hz, 3H).

MS : 214 (M+H).

REFERENCE 51

(S)-1-{[5-(4-Fluoro-phenyl)-1,2,4-oxadiazol-3-yl]-hydroxy-methyl}-propyl)-carbamic acid tert-butyl ester



A suspention of 4-fluoro benzoic acid (1.70g, 0.012mol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.12g, 0.011mol) in methylene chloride (80ml) was treated with (S)-1-[Hydroxy-(N-hydroxycarbamimidoyl)-methyl]-propyl}-carbamic acid tert-butyl ester (3g, 0.012mol) and triethylamine (1.54ml, 0.011mol). The reaction was stirred at room temperature overnight. Then, it was diluted with 40ml of methylene chloride, washed with saturated aqueous bicarbonate solution (30ml), water (30ml), brine (30ml), dried over Na_2SO_4 and the solvent evaporated under reduced pressure. The residue was purified by flash chromatography eluting with a mixture of ethyl acetate and heptane (2:1) to give an off white solid (2.20g)

^{1}H NMR ($CDCl_3$) δ : 8.10-7.95 (m, 2H), 7.16-7.00 (m, 2H), 5.43-5.24 (m, 2H), 5.22-5.05 (m, 1H), 5.01-4.85 (m, 1H), 4.50-4.39 (m, 1H), 3.80-3.60 (m, 1H), 1.90-1.78 (m, 2H), 1.40 (s, 9H), 0.98 (t, J=7.5Hz, 3H).

MS : 370 (M+H).

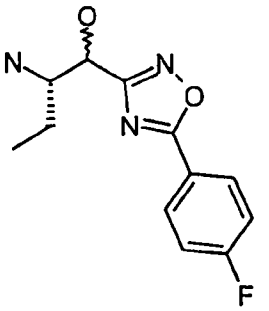
240 mg of the solid (0.65 mmol) compound obtained above was taken in diglyme (5ml) and heated at 160 ^{0}C in a microwave (Smith Creator, S00219) for 18 minutes. The solvent was evaporated under high vacuum. The crude obtained was purified by flash chromatography eluting with a mixture of ethyl acetate and heptane (1:4) to give (S)-1-{[5-(4-Fluoro-phenyl)-1,2,4-oxadiazol-3-yl]-hydroxy-methyl}-propyl)-carbamic acid tert-butyl ester as a white solid (148mg).

^{1}H NMR ($CDCl_3$) δ: 8.16-8.09 (m, 2H), 7.25-7.12 (m, 2H), 4.98-4.73 (m, 2H), 4.13-3.87 (m, 1H), 3.82-3.35 (m, 1H), 1.80-1.52 (m, 2H), 1.46 & 1.34 (2xs, 9H), 1.02 & 0.99 (2xt, J=7.5Hz, 3H).

MS : 352 (M+H).

REFERENCE 52

(S)-2-Amino-1-[5-(4-fluoro-phenyl)-1,2,4-oxadiazol-3-yl]-butan-1-ol



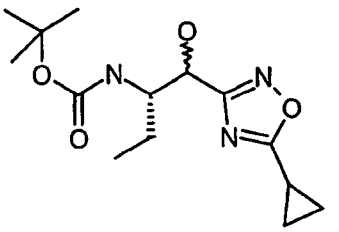
Similarly prepared according to Reference Example 50 above but using (S)-1-{[5-(4-Fluoro-phenyl)-1,2,4-oxadiazol-3-yl]-hydroxy-methyl}-propyl)-carbamic acid tert-butyl ester.

^{1}H NMR ($CDCl_3$) δ : 8.18-8.05 (m, 2H), 7.26-7.12 (m, 2H), 4.92 & 4.73 (2xd, J=5Hz, 1H), 3.27-3.05 (m, 1H), 1.75-1.62 (m, 1H), 1.59-1.41 (m, 1H), 1.02 & 1.00 (2xt, J=7.5Hz, 3H).

MS : 252 (M+H).

REFEENCE 53

{(S)-1-[(5-Cyclopropyl-1,2,4-oxadiazol-3-yl)-hydroxy-methyl]-propyl}-carbamic acid tert-butyl ester



A suspention of (S)-1-[Hydroxy-(N-hydroxycarbamimidoyl)-methyl]-propyl}-carbamic acid tert-butyl ester (6.12g, 24.78mmol) in methylene chloride (150ml) was treated with triethylamine (3.46ml, 24.82mmol) and then cooled to 0 ^{0}C. Then cyclopropyl carbonyl chloride (2.25ml, 24.79mmol) was added dropwise. The reaction was stirred at room temperature for 1h 45min. and diluted with 150ml of methylene chloride, washed with water (40ml), saturated aqueous bicarbonate (20ml), water (20ml), dried over Na_2SO_4 and solvent evaporated under reduced pressure to give a white solid (7.16g).

MS : 338 (M+Na).

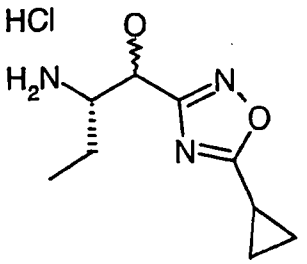
A solution of the compound obtained above (7.45g, 0.024mol) in dioxane (150ml) was heated at reflux for 15h. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography eluting with a mixture of ethyl acetate and heptane to give (S)-1-[(5-Cyclopropyl-1,2,4-oxadiazol-3-yl)-hydroxy-methyl]-propyl}-carbamic acid tert-butyl ester as a pale yellow solid (5g).

^{1}H NMR ($CDCl_3$) δ : 4.94-4.74 (m, 2H), 3.97 & 3.85 (2xm, 1H), 3.62 & 3.48 (2xbs, 1H), 2.19 (m, 1H), 1.72-1.42 (m, 2H), 1.44 & 1.39 (2xs, 9H), 1.26-1.18 (m, 4H), 0.98 & 0.95 (2xt, J=7.4Hz, 3H).

MS : 298 (M+H).

REFERENCE 54

(S)-2-Amino-1-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-butan-1-ol HCl salt



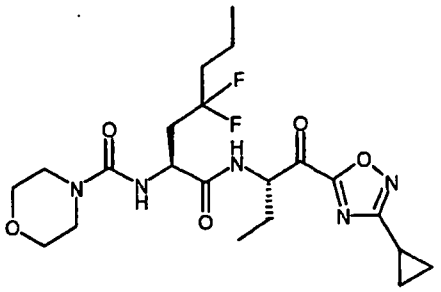
A solution of {(S)-1-[(5-Cyclopropyl-1,2,4-oxadiazol-3-yl)-hydroxy-methyl]-propyl}-carbamic acid tert-butyl ester (3.41g, 0.011mmol) in 4N HCl in dioxane (43ml, 0.172mmol) was stirred at room temperature for 2h. Solvent evaporated under reduced pressure. Residue triturated with a mixture of ethyl acetate and ether. It was then filtered to give (S)-2-Amino-1-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-butan-1-ol HCl salt as a brown solid (2.47g).

^{1}H NMR ($CDCl_3$) δ: 8.21 (bs, 2H), 5.37 & 5.14 (2xd, 1H), 3.88 & 3.73 (2xm, 1H), 2.21 (m, 1H), 1.92-1.50 (m, 2H), 1.24 (m, 4H), 1.08 & 1.06 (2xt, J=7.4Hz, 3H).

MS : 198 (M+H).

EXAMPLE 1

Morpholine-4-carboxylic acid {(S)-1-[(S)-1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-hexyl}-amide



To a mixture of (S)-4,4-difluoro-2-[(morpholine-4-carbonyl)-amino]-heptanoic acid (104 mg, 0.35 mmol), (S)-2-amino-1-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-butan-1-ol hydrochloride (86.7 mg, 0.37 mmol) and diisopropyl amine (219 mg, 0.42 mmol) in dry dichloromethane (5 mL) was added PyBOP (113 mg, 0.87 mmol). The mixture was stirred at room temperature for 16 hr and the evaporated in vacuum. The residue was diluted with ethyl acetate (25 mL) and washed with saturated $NaHCO_3$ (30 mL), dilute HCl (30 mL), then saturated $NaHCO_3$ (30 mL). The organic layer was dried over magnesium sulfate and concentrated in vacuum. The residue was purified over 12 g silica gel, eluting with ethyl acetate: heptane (2:1 then 1:0) to afford morpholine-4-carboxylic acid (1-{1-[(3-

cyclopropyl-[1,2,4]oxadiazol-5-yl)-hydroxy-methyl]-propylcarbamoyl}-3,3-difluoro-hexyl)-amide (146 mg, 88%) as a white solid. LC/MS shows 2 isomers, total 100% M+1 474.

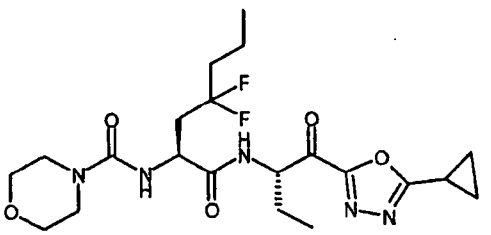
To a solution of morpholine-4-carboxylic acid (1-{1-[(3-cyclopropyl-[1,2,4]oxadiazol-5-yl)-hydroxy-methyl]-propylcarbamoyl}-3,3-difluoro-hexyl)-amide (145 mg, 0.31 mmol) in dry dichloromethane (3 mL) under N2 was added Dess-Martin periodinane (15% wt solution in dichloromethane, 1.73 g, .061 mmol). The reaction was stirred at room temperature for 2 hr, then quenched with a solution of $Na_2S_2O_3$ 193 mg, 1.22 mmol) in saturated $NaHCO_3$ (30 mL). The aqueous layer was extracted with dichloromethane (2x30 mL). The organic layers were dried over magnesium sulfate and concentrated in vacuum. The residue was purified over 12 g silica gel, eluted with ethyl acetate: heptane (1:1 then 2:1) to afford the desired ketone (119 mg, 81%) as a tan solid.

^1H NMR ($CDCl_3$): δ 7.4 (d, 7.0 Hz, 1H), 5.27 (m, 1H), 5.13 (d, J = 6.9 Hz, 1H), 4.65 (dd, J = 13.1, 6.9 Hz, 1H), 3.7 (m, 4H), 3.4 (m, 4H), 2.4 (m, 2H), 2.2 (m, 1H), 2.05 (m, 1H), 1.8 (m, 3H), 1.55 (m, 2H), 1.15 (m, 4H), 0.98 (t, J = 7.4 Hz, 6H);

LC/MS: 28% 512 ($M+H_2O+Na$) and 68% 494 (M+Na).

EXAMPLE 2

Morpholine-4-carboxylic acid {(S)-1-[(S)-1-(5-cyclopropyl-1,3,4-oxadiazole-2-carbonyl)-propylcarbamoyl]-3,3-difluoro-hexyl}-amide



PyBOP (171.73 mg, 0.33 mmol), diisopropylethylamine (0.0575 ml, 0.33mmol) and (S)-2-amino-1-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)-butan-1-ol; compound with trifluoro-acetic acid (0.30 mmol) were added to a solution of (S)-4,4-Difluoro-2-[(morpholine-4-carbonyl)-amino]-heptanoic acid (88.29 mg, 0.30 mmol) in dry methylene chloride (4 ml) and the reaction mixture was stirred overnight at room temperature. The reaction was quenched with aqueous sodium bicarbonate, extracted twice with methylene chloride, the organic extracts were dried over sodium sulfate and evaporated under reduced pressure. Column chromatography on silica eluting with a mixture of methylene chloride and ethyl acetate gave morpholine-4-carboxylic acid ((S)-1-{(S)-1-[(5-cyclopropyl-1,3,4-oxadiazol-2-yl)-hydroxy-methyl]-propylcarbamoyl}-3,3-difluoro-hexyl)-amide as white solid (87 mg). LC/MS 97%, 474 (M+1).

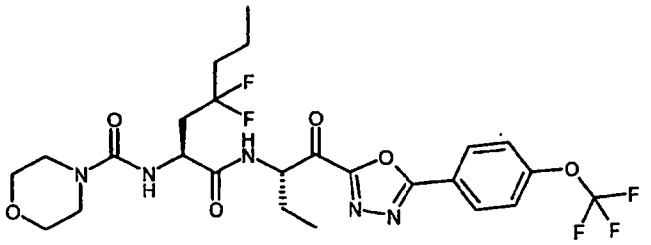
Dess-Martin Periodinane (15wt% in DCM, 0.79 gm, 0.28 mmol) was added to a solution of morpholine-4-carboxylic acid ((S)-1-{(S)-1-[(5-cyclopropyl-1,3,4-oxadiazol-2-yl)-hydroxy-methyl]-propylcarbamoyl}-3,3-difluoro-hexyl)-amide (67 mg, 0.14 mmol) in dry methylene chloride (10 ml) and stirred at room temperature for 2.5 hours. The reaction was quenched with a solution of $Na_2S_2O_3$ (110.68 mg, 0.70 mmol) in aqueous $NaHCO_3$. The organic layer was separated and the aqueous extracted with dichloromethane. The organic extracts were dried over sodium sulfate and concentrated under reduced pressure. Column chromatography on silica eluting with a mixture of methylene chloride and ethyl acetate gave morpholine-4-carboxylic acid {(S)-1-[(S)-1-(5-cyclopropyl-1,3,4-oxadiazole-2-carbonyl)-propylcarbamoyl]-3,3-difluoro-hexyl}-amide as white powder (48 mg).

^1H NMR ($CDCl_3$): δ 7.52 (d, J=7.5Hz, 1H), 5.34 (m, 1H), 5.18 (d, J=7.5Hz, 1H), 4.65 (m, 1H), 3.72 (m, 4H), 3.40 (m, 4H), 2.50-2.22 (m, 3H), 2.18-2.08 (m, 1H), 1.96-1.78 (m, 3H), 1.60-1.45 (m, 2H), 1.30 (m, 4H), 0.98 (t+t, 6H).

LC/MS 95%, 472 (M+1).

EXAMPLE 3

Morpholine-4-carboxylic acid ((S)-3,3-difluoro-1-{(S)-1-[5-(4-trifluoromethoxy-phenyl)-1,3,4-oxadiazole-2-carbonyl]-propylcarbamoyl}-hexyl)-amide.



PyBOP (68.69 mg, 0.13 mmol), diisopropylethylamine (0.023 ml, 0.13mmol) and (S)-2-Amino-1-[5-(4-trifluoromethoxy-phenyl)-1,3,4-oxadiazol-2-yl]-butan-1-ol (38.0 mg, 0.12 mmol) were added to a solution of (S)-4,4-Difluoro-2-[(morpholine-4-carbonyl)-amino]-heptanoic acid (34 mg, 0.12 mmol) in dry methylene chloride (4 ml) and the reaction mixture was stirred overnight at room temperature. The reaction was quenched with aqueous $NaHCO_3$, extracted twice with methylene chloride, the organic extracts were dried over $Na2SO_4$ and evaporated under reduced pressure. Column chromatography on silica eluting with a mixture of methylene chloride and ethyl acetate gave morpholine-4-carboxylic acid [(S)-3,3-difluoro-1-((S)-1-{hydroxy-[5-(4-trifluoromethoxy-phenyl)-1,3,4-oxadiazol-2-yl]-methyl}-propylcarbamoyl)-hexyl]-amide as white solid (61 mg). LC/MS 71%, M+1= 594

Dess-Martin Periodinane (15wt% in DCM, 0.58 gm, 0.21 mmol) was added to a solution of morpholine-4-carboxylic acid [(S)-3,3-difluoro-1-((S)-1-{hydroxy-[5-(4-trifluoromethoxy-phenyl)-

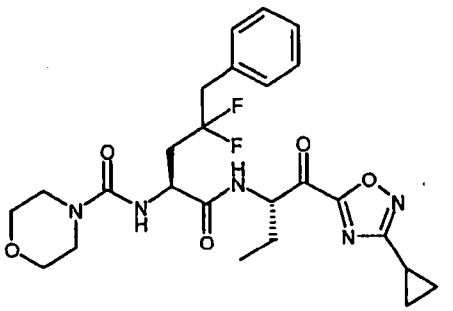
1,3,4-oxadiazol-2-yl]-methyl}-propylcarbamoyl)-hexyl]-amide (61 mg, 0.10 mmol) in dry methylene chloride (8 ml) and stirred at room temperature for 3 hrs. The reaction was quenched with a solution of $Na_2S_2O_3$ (81.43 mg, 0.50 mmol) in aqueous $NaHCO_3$. The organic layer was separated and the aqueous extracted with dichloromethane. The organic extracts were dried over sodium sulfate and concentrated under reduced pressure. Column chromatography on silica eluting with a mixture of methylene chloride and ethyl acetate gave morpholine-4-carboxylic acid ((S)-3,3-difluoro-1-{(S)-1-[5-(4-trifluoromethoxy-phenyl)-1,3,4-oxadiazole-2-carbonyl]-propylcarbamoyl}-hexyl)-amide as white powder (39 mg).

^1H NMR ($CDCl_3$): δ 8.25 (d, J=7.5Hz, 2H), 7.60 (d, J=7.5Hz, 1H), 7.42 (d, J=7.5Hz, 2H), 5.36 (m, 1H), 5.16 (d, J=7.5Hz, 1H), 4.70 (m, 1H), 3.74 (m, 4H), 3.42 (m, 4H), 2.54-2.32 (m, 2H), 2.28-2.14 (m, 1H), 2.02-1.80 (m, 3H), 1.60-1.45 (m, 2H), 1.06 (t, J=7Hz, 3H), 0.96 (t, J=7Hz, 3H).

LC/MS: 96%, 592 (M+1).

EXAMPLE 4

Morpholine-4-carboxylic acid {(S)-1-[(S)-1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-4-phenyl-butyl}-amide



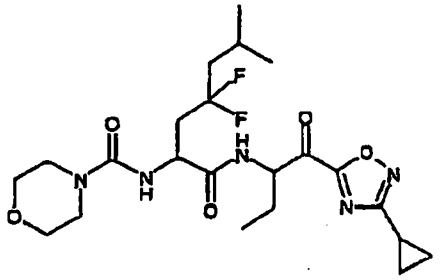
By proceeding in a similar manner to Example 1 above but using (S)-4,4-difluoro-2-[(morpholine-4-carbonyl)-amino]-5-phenyl-pentanoic acid and (S)-2-amino-1-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-butan-1-ol there was prepared morpholine-4-carboxylic acid {(S)-1-[(S)-1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-4-phenyl-butyl}-amide.

^1H NMR ($CDCl_3$): δ 7.3 (m, 6H), 5.25 (m, 1H), 5.08 (d, J = 6.9 Hz, 1H), 4.7 (dd, J = 12.8, 7.4 Hz, 1H), 3.7 (m, 4H), 3.4 (m, 4H), 3.2 (t, 16.8 Hz, 2H), 2.4-2.1 (m, 3H), 2.05 (m, 1H), 1.8 (m, 1H), 1.1 (m, 4H), 0.95 (t, J = 7.5 Hz, 3H);

LC/MS: 35% 560 ($M+H_2O+Na$) and 65% 542 (M+Na).

EXAMPLE 5

Morpholine-4-carboxylic acid {1-[1-(3-cyclopropyl-[1,2,4]oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-5-methyl-hexyl}-amide



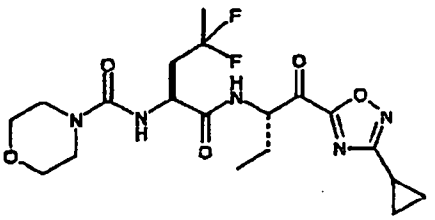
By proceeding in a similar manner to Example 1 above but using (S)-4,4-difluoro-6-methyl-2-[(morpholine-4-carbonyl)-amino]-heptanoic acid and (S)-2-amino-1-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-butan-1-ol there was prepared morpholine-4-carboxylic acid {1-[1-(3-cyclopropyl-[1,2,4]oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-5-methyl-hexyl}-amide

^{1}H NMR ($CDCl_3$): δ 7.6 (d, J = 6.8 Hz, 1H), 5.2 (m, 2H), 4.66 (dd, J = 13, 7.2 Hz, 1H), 3.7 (m, 4H), 3.4 (m, 4H), 2.3 (m, 2H), 2.2 (m, 1H), 2.05 (m, 1H), 1.95 (m, 1H), 1.8 (m, 3H), 1.1 (m, 4H), 0.97 (d, J = 6.6 Hz, 6H), 0.96 (t, J = 7.4 Hz, 3H);

LC/MS: 26%, 526 ($M+H_2O+Na$) and 74%, 508 ($M+Na$).

EXAMPLE 6

Morpholine-4-carboxylic acid {(S)-1-[(S)-1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-butyl}-amide



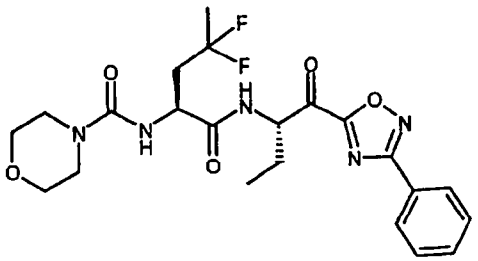
By proceeding in a similar manner to Example 1 above but using (S)-4,4-Difluoro-2-[(morpholine-4-carbonyl)-amino]-pentanoic acid and (S)-2-Amino-1-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-butan-1-ol there was prepared Morpholine-4-carboxylic acid {(S)-1-[(S)-1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-butyl}-amide

^{1}H NMR ($CDCl_3$): δ 7.47 (d, J = 6.8 Hz, 1H), 5.3 (m, 1H), 5.16 (d, J = 6.9 Hz, 1H), 4.65 (dd, J = 13, 7.4 Hz, 1H), 3.7 (m, 4H), 3.4 (m, 4H), 2.4 (m, 2H), 2.2 (m, 1H), 2.05 (m, 1H), 1.8 (m, 1H), 1.67 (t, 18.7 Hz, 3H), 1.1 (m, 4H), 0.97 (t, J = 7.5 Hz, 3H);

LC/MS: 37% 484 ($M+H_2O+Na$) and 63% 484 ($M+CH_3CN$).

EXAMPLE 7

Morpholine-4-carboxylic acid {(S)-3,3-difluoro-1-[(S)-1-(3-phenyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-butyl}-amide



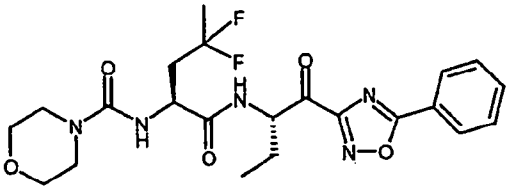
By proceeding in a similar manner to Example 1 above but using (S)-4,4-Difluoro-2-[(morpholine-4-carbonyl)-amino]-pentanoic acid and (S)-2-Amino-1-(3-phenyl-1,2,4-oxadiazol-5-yl)-butan-1-ol there was prepared Morpholine-4-carboxylic acid {(S)-3,3-difluoro-1-[(S)-1-(3-phenyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-butyl}-amide as light tan solid.

^{1}H NMR ($CDCl_3$): δ 8.15 (dd, J = 7.7, 1.5 Hz, 2H), 7.61 (d, J = 6.4 Hz, 1H), 7.5 (m, 3H), 5.35 (m, 1H), 5.2 (d, J = 6.9 Hz, 1H), 4.68 (dd, J = 13.2, 7.8 Hz, 1H), 3.7 (m, 4H), 3.4 (m, 4H), 2.4 (m, 2H), 2.2 (m, 1H), 1.95 (m, 1H), 1.66 (t, 18.7 Hz, 3H), 1.03 (t, J = 7.5 Hz, 3H);

LC/MS: 37% 520 (M+H_2O+Na) and 63% 502 (M+Na).

EXAMPLE 8

Morpholine-4-carboxylic acid {(S)-3,3-difluoro-1-[(S)-1-(5-phenyl-1,2,4-oxadiazole-3-carbonyl)-propylcarbamoyl]-butyl}-amide



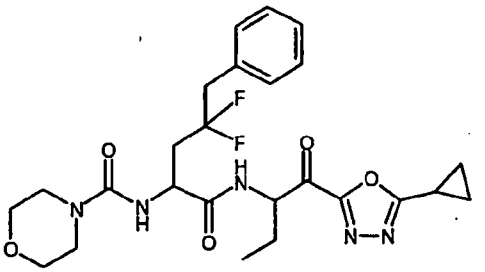
By proceeding in a similar manner to Example 1 above but using (S)-4,4-Difluoro-2-[(morpholine-4-carbonyl)-amino]-pentanoic acid and (S)-2-Amino-1-(5-phenyl-[1,2,4]oxadiazol-3-yl)-butan-1-ol there was prepared Morpholine-4-carboxylic acid {(S)-3,3-difluoro-1-[(S)-1-(5-phenyl-1,2,4-oxadiazole-3-carbonyl)-propylcarbamoyl]-butyl}-amide

^{1}H NMR ($CDCl_3$): δ 8.2 (d, J = 7.1 Hz, 2H), 7.65 (d, J = 7.4 Hz, 1H), 7.55 (m, 3H), 5.4 (dd, J = 12.2, 7 Hz, 1H), 5.3 (d, J = 7.4 Hz, 1H), 4.7 (dd, J = 13, 7.3 Hz, 1H), 3.7 (m, 4H), 3.4 (m, 4H), 2.4 (m, 2H), 2.1 (m, 1H), 1.9 (m, 1H), 1.67 (t, 18.7 Hz, 3H), 1.0 (t, J = 7.4 Hz, 3H);

LC/MS: 6% 520 (M+H_2O+Na) and 94% 502 (M+Na).

EXAMPLE 9

Morpholine-4-carboxylic acid {1-[1-(5-cyclopropyl-[1,3,4]oxadiazole-2-carbonyl)-propylcarbamoyl]-3,3-difluoro-4-phenyl-butyl}-amide:



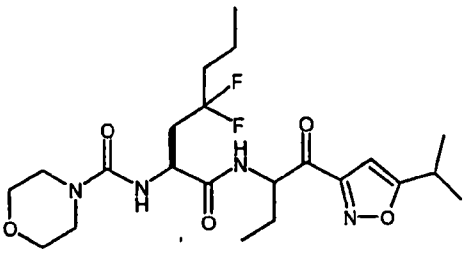
By proceeding in a similar manner to Example 1 above but using (S)-4,4-difluoro-2-[(morpholine-4-carbonyl)-amino]-5-phenyl-pentanoic acid and (S)-2-amino-1-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)-butan-1-ol Trifluoro acetic acid salt, there was prepared morpholine-4-carboxylic acid {1-[1-(5-cyclopropyl-[1,3,4]oxadiazole-2-carbonyl)-propylcarbamoyl]-3,3-difluoro-4-phenyl-butyl}-amide.

^{1}H NMR ($CDCl_3$): δ 7.3 (m, 6H), 5.27 (m, 1H), 5.0 (d, J = 7.0 Hz, 1H major), 4.95 (d, J = 7.3 Hz, 1H minor), 4.7 (m, 1H), 3.7 (m, 4H), 3.4 (m, 4H), 3.2 (t, 16.3 Hz, 2H), 2.4-2.2 (m, 3H), 2.05 (m, 1H), 1.8 (m, 1H), 1.2 (m, 4H), 0.95 (t, J = 7.5 Hz, 3H);

LC/MS: 12% 560 (M+H_2O+Na) and 83% 542 (M+Na).

EXAMPLE 10

Morpholine-4-carboxylic acid {3,3-difluoro-1-[1-(5-isopropyl-isoxazole-3-carbonyl)-propylcarbamoyl]-hexyl}-amide:



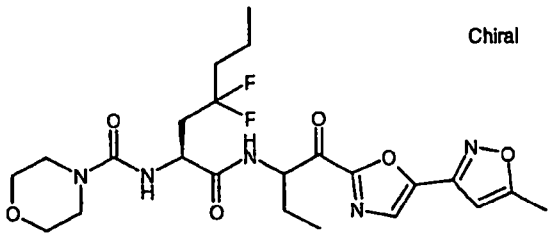
By proceeding in a similar manner to Example 1 above but using 2-amino-1-(5-isopropyl-isoxazol-3-yl)-butan-1-ol hydrochloride instead of (S)-2-amino-1-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-butan-1-ol hydrochloride there was prepared morpholine-4-carboxylic acid {3,3-difluoro-1-[1-(5-isopropyl-isoxazole-3-carbonyl)-propylcarbamoyl]-hexyl}-amide as white solid.

^{1}H NMR ($CDCl_3$): δ ca 2:1 mixture of isomers 7.4 (b, 1H), 6.37 (s, 1H), 5.4 (m, 1H), 5.26 (d, J = 6.9 Hz, 1H major), 5.2 (d, J = 7.2 Hz, 1H minor), 4.7 (m, 1H), 3.7 (m, 4H), 3.4 (m, 4H), 3.15 (m, 1H), 2.4 (m, 2H), 2.1 (m, 1H), 1.8 (m, 4H), 1.5 (m, 1H), 1.35 (d, J = 7.0 Hz, 6H), 0.95 (m, 6H);

LC/MS: 100% 473 (M+1).

EXAMPLE 11

Morpholine-4-carboxylic acid ((S)-3,3-difluoro-1-{1-[5-(5-methyl-isoxazol-3-yl)-oxazole-2-carbonyl]-propylcarbamoyl}-hexyl)-amide



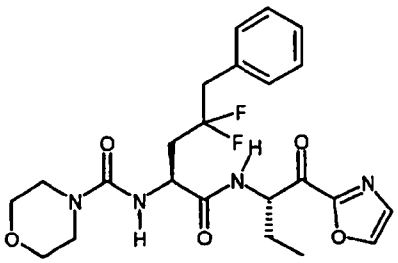
By proceeding in a similar manner to Example 3 above but using (S)-4,4-difluoro-2-[(morpholine-4-carbonyl)-amino]-heptanoic acid and (S)-2-amino-1-[5-(5-methyl-isoxazol-3-yl)-oxazol-2-yl]-butan-1-ol; hydrochloride there was prepared Morpholine-4-carboxylic acid ((S)-3,3-difluoro-1-{1-[5-(5-methyl-isoxazol-3-yl)-oxazole-2-carbonyl]-propylcarbamoyl}-hexyl)-amide as white solid.

^{1}H NMR ($CDCl_3$): δ 7.78 (s, 1H), 7.40 (m, 1H), 6.44 (s, 1H), 5.48 (m, 1H), 5.22-5.10 (m, 1H), 4.68 (m, 1H), 3.72 (m, 4H), 3.40 (m, 4H), 2.54 (s, 3H), 2.50-2.30 (m, 2H), 2.22-2.08 (m, 1H), 1.94-1.78 (m, 3H), 1.60-1.46 (m, 2H), 1.08-0.94 (2xt, 6H).

LC/MS: 99%, 512 (M+1).

EXAMPLE 12

Morpholine-4-carboxylic acid {(S)-3,3-difluoro-1-[(S)-1-(oxazole-2-carbonyl)-propylcarbamoyl]-4-phenyl-butyl}-amide

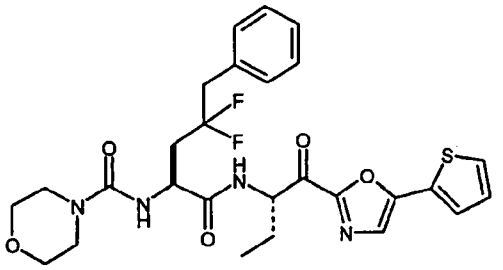


By proceeding in a similar manner to Example 2 above but using (S)-4,4-difluoro-2-[(morpholine-4-carbonyl)-amino]-5-phenyl-pentanoic acid and (S)-2-amino-1-oxazol-2-yl-butan-1-ol hydrochloride there was prepared morpholine-4-carboxylic acid {(S)-3,3-difluoro-1-[(S)-1-(oxazole-2-carbonyl)-propylcarbamoyl]-4-phenyl-butyl}-amide

^{1}H NMR ($CDCl_3$): δ 7.86 (s, 1H), 7.37 (s, 1H), 7.30 (m, 5H), 7.24 (m, 1H), 5.45 (m, 1H), 5.08 (d, J = 9Hz, 1H), 4.70 (m, 1H), 3.72 (m, 4H), 3.38 (m, 4H), 3.22 (t, J= 17Hz, 2H), 2.35 (m, 2H), 2.12 (m, 1H), 1.85 (m, 1H), 0.95 (t, J= 9Hz, 3H);
LC/MS: 97%, 479 (M+1).

EXAMPLE 13

Morpholine-4-carboxylic acid {(S)-3,3-difluoro-4-phenyl-1-[(S)-1-(5-thiophen-2-yl-oxazole-2-carbonyl)-propylcarbamoyl]-butyl}-amide

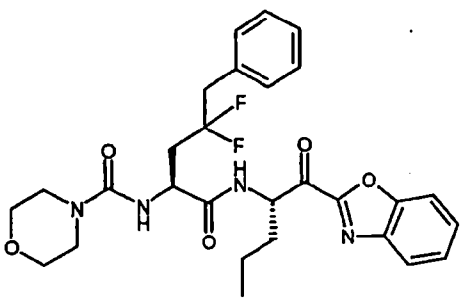


By proceeding in a similar manner to Example 1 above but using (S)-4,4-difluoro-2-[(morpholine-4-carbonyl)-amino]-5-phenyl-pentanoic acid and (S)-2-amino-1-(5-thiophen-2-yl-oxazol-2-yl)-butan-1-ol hydrochloride there was prepared morpholine-4-carboxylic acid {(S)-3,3-difluoro-4-phenyl-1-[(S)-1-(5-thiophen-2-yl-oxazole-2-carbonyl)-propylcarbamoyl]-butyl}-amide

^{1}H NMR ($CDCl_3$): δ 7.53 (dd, J = 3.6, 1 Hz, 1H), 7.48 (dd, J = 5, 1 Hz, 1H), 7.4 (s, 1H), 7.3 (m, 6H), 7.15 (dd, J = 5, 3.6 Hz, 1H), 5.4 (m, 1H), 5.15 (d, J = 7.1 Hz, 1H), 4.7 (dd, J = 13, 7.4 Hz, 1H), 3.7 (m, 4H), 3.4 (m, 4H), 3.2 (t, 16.7 Hz, 2H), 2.4 (m, 2H), 2.1 (m, 1H), 1.8 (m, 1H), 0.96 (t, J = 7.5 Hz, 3H);
LC/MS: 100% 561 (M+1).

EXAMPLE 14

Morpholine-4-carboxylic acid {(S)-1-[(S)-1-(benzoxazole-2-carbonyl)-butylcarbamoyl]-3,3-difluoro-4-phenyl-butyl}-amide



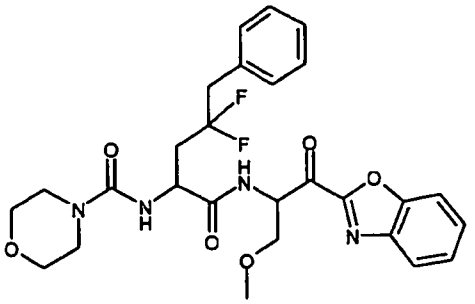
By proceeding in a similar manner to Example 1 above but using (S)-4,4-difluoro-2-[(morpholine-4-carbonyl)-amino]-5-phenyl-pentanoic acid and (S)-2-amino-1-benzoxazol-2-yl-pentan-1-ol there was prepared morpholine-4-carboxylic acid {(S)-1-[(S)-1-(benzoxazole-2-carbonyl)-butylcarbamoyl]-3,3-difluoro-4-phenyl-butyl}-amide.

^{1}H NMR ($CDCl_3$): δ 7.9 (d, J = 8.0 Hz, 1H), 7.66 (d, J = 8 Hz, 1H), 7.56 (t, J = 7.2 Hz, 1H), 7.47 (t, J = 8 Hz, 1H), 7.2 (m, 6H), 5.6 (m, 1H), 5.05 (d, J = 7Hz, 1H), 4.71 (dd, J = 12.8, 7.4 Hz, 1H), 3.7 (m, 4H), 3.35 (m, 4H), 3.18 (t, J= 16.8 Hz, 2H), 2.3 (m, 2H), 2.1 (m, 1H), 1.8 (m, 1H), 1.4 (m, 2H), 0.94 (t, J= 7.3 Hz, 3H);

LC/MS: 100% 543 (M+1).

EXAMPLE 15

Morpholine-4-carboxylic acid [1-(2-benzooxazol-2-yl-1-methoxymethyl-2-oxo-ethylcarbamoyl)-3,3-difluoro-4-phenyl-butyl]-amide



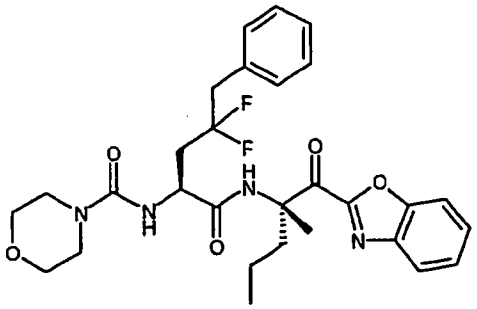
By proceeding in a similar manner to Example 1 above but using (S)-4,4-difluoro-2-[(morpholine-4-carbonyl)-amino]-5-phenyl-pentanoic acid and (S)-2-amino-1-benzooxazol-2-yl-3-methoxy-propan-1-ol there was prepared morpholine-4-carboxylic acid [1-(2-benzooxazol-2-yl-1-methoxymethyl-2-oxo-ethylcarbamoyl)-3,3-difluoro-4-phenyl-butyl]-amide.

^{1}H NMR ($CDCl_3$): δ 7.9 (d, J = 7.7 Hz, 1H), 7.67 (d, J = 8 Hz, 1H), 7.56 (t, J = 8 Hz, 1H), 7.48 (t, J = 8 Hz, 1H), 7.2 (m, 6H), 5.7 (m, 1H), 5.1 (d, J = 7 Hz, 1H major), 5.05 (d, J = 7.3 Hz, 1H minor), 4.8 (m, 1H), 4.26 (dd, J = 9.7, 3.5 Hz, 1H), 3.8 (m, 1H), 3.7 (m, 4H), 3.35 (m, 4H), 3.27 (s, 3H), 3.22 (t, J= 16.2 Hz, 2H), 2.4 (m, 2H);

LC/MS: 94% 545 (M+1).

EXAMPLE 16

Morpholine-4-carboxylic acid {(S)-1-[(S)-1-(benzoxazole-2-carbonyl)-1-methyl-butylcarbamoyl]-3,3-difluoro-4-phenyl-butyl}-amide



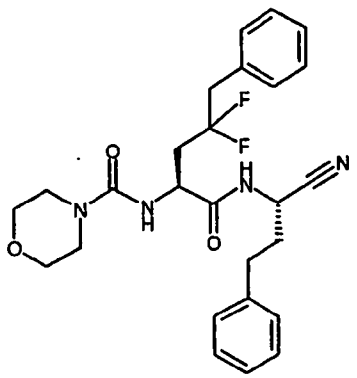
A mixture of (S)-2-amino-1-benzoxazol-2-yl-2-methyl-pentan-1-one hydrochloride (80.6 mg, 0.3 mmol), (S)-4,4-difluoro-2-[(morpholine-4-carbonyl)-amino]-5-phenyl-pentanoic acid (0.102 mg, 0.3 mmol), EDCI (69 mg, 0.36 mmol), HOBT (48.6 mg, 0.36 mmol) and Diisopropyl ethylamine (0.2 mL) in DMF was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate, washed with cold 1N HCl, saturated $NaHCO_3$ and then saturated NaCl solution. The organic phase was dried over magnesium sulfate and solvent evaporated under reduced pressure to give the crude product. Purification by Silica gel column chromatography, eluting with ethyl acetate and heptane mixture gave morpholine-4-carboxylic acid {(S)-1-[(S)-1-(benzoxazole-2-carbonyl)-1-methyl-butylcarbamoyl]-3,3-difluoro-4-phenyl-butyl}-amide (82%).

^1H NMR ($CDCl_3$): δ 7.8 (d, J = 7.8.0 Hz, 1H), 7.64 (d, J =7.8 Hz, 1H), 7.53 (dt, J = 7.2, 1.2 Hz, 1H), 7.43 (dt, J = 8, 1.2 Hz, 1H), 7.2 (m, 6H), 4.9 (d, J = 7.3 Hz, 1H), 4.65 (m, 1H), 3.7 (m, 4H), 3.3 (m, 4H), 3.1 (t, J= 16.8 Hz, 2H), 2.2 (m, 3H), 2.1 (m, 1H), 1.74 (s, 3H), 1.25 (m, 2H), 0.9 (t, J= 7.3 Hz, 3H);

LC/MS: 100% 557 (M+1).

EXAMPLE 17

Morpholine-4-carboxylic acid [(S)-1-((S)-1-cyano-3-phenyl-propylcarbamoyl)-3,3-difluoro-4-phenyl-butyl]-amide



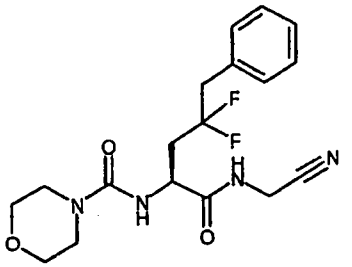
Proceeding according to the PyBOP coupling method given for example 1, but using (S)-4,4-difluoro-2-[(morpholine-4-carbonyl)-amino]-5-phenyl-pentanoic acid and (S)-2-amino-4-phenyl-butyronitrile

hydrochloride, there was prepared, morpholine-4-carboxylic acid [(S)-1-((S)-1-cyano-3-phenyl-propylcarbamoyl)-3,3-difluoro-4-phenyl-butyl]-amide.

^{1}H NMR ($CDCl_3$): δ 7.9 (d, J = 7.6 Hz, 1H), 7.2 (m, 10H), 5.1 (d, J = 7.3 Hz, 1H), 4.6 (m, 2H), 3.6 (m, 4H), 3.3 (m, 4H), 3.2 (t, J = 16.5 Hz, 2H), 2.74 (t, J = 7.2 H, 2H), 2.3 (m, 2H), 2.1 (m, 2H); LC/MS: 100 % 485 (M+1).

EXAMPLE 18

Morpholine-4-carboxylic acid [(S)-1-(cyanomethyl-carbamoyl)-3,3-difluoro-4-phenyl-butyl]-amide

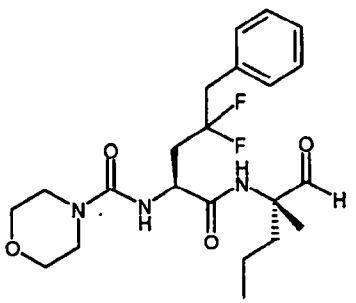


Proceeding according to the PyBOP coupling method given for Example 1, but using (S)-4,4-difluoro-2-[(morpholine-4-carbonyl)-amino]-5-phenyl-pentanoic acid and amino-acetonitrile hydrochloride, there was prepared, morpholine-4-carboxylic acid [(S)-1-(cyanomethyl-carbamoyl)-3,3-difluoro-4-phenyl-butyl]-amide.

^{1}H NMR ($CDCl_3$): δ 7.95 (b, 1H), 7.3 (m, 5H), 5.25 (d, J = 7.0 Hz, 1H), 4.7 (dd, J = 12.7, 7.2 Hz, 1H), 4.1 (m, 2H), 3.7 (m, 4H), 3.35 (m, 4H), 3.2 (t, J = 16.3 Hz, 2H), 2.4 (m, 2H); LC/MS: 83 % 403 (M+Na).

EXAMPLE 19

Morpholine-4-carboxylic acid [(S)-3,3-difluoro-1-((S)-1-formyl-1-methyl-butylcarbamoyl)-4-phenyl-butyl]-amide



A mixture of (S)-2-amino-2-methyl-pentan-1-ol hydrochloride (104.4 mg, 0.67 mmol), (S)-4,4-difluoro-2-[(morpholine-4-carbonyl)-amino]-5-phenyl-pentanoic acid (231 mg, 0.67 mmol), EDCI (154 mg, 0.8 mmol), HOBT (108 mg, 0.8 mmol) and Diisopropyl ethylamine (0.23 mL) in DMF (2mL) was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate, washed with cold 1N HCl, saturated $NaHCO_3$ and then saturated NaCl solution. The organic phase was

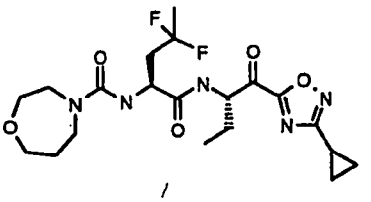
dried over $MgSO_4$ and solvent evaporated under reduced pressure to give the crude product. Purification by Silica gel column chromatography, eluting with ethyl acetate and heptane mixture gave morpholine-4-carboxylic acid [(S)-3,3-difluoro-1-((S)-1-hydroxymethyl-1-methyl-butylcarbamoyl)-4-phenyl-butyl]-amide (223 mg, 75%).

A mixture of Morpholine-4-carboxylic acid [(S)-3,3-difluoro-1-((S)-1-hydroxymethyl-1-methyl-butylcarbamoyl)-4-phenyl-butyl]-amide (217 mg) and Dess-Martin Periodinane (15% in DCM, 2 eq.) in DCM (5 mL) was stirred at room temperature for 3hrs and quenched with a solution of sodium thiosulfate in saturated $NaHCO_3$. The product was extracted with ethyl acetate and washed with saturated NaCl solution. Organic phase was dried over anhydrous $MgSO_4$, solvent evaporated under reduced pressure. Purification by silica gel chromatography eluting with ethyl acetate-heptane mixture gave Morpholine-4-carboxylic acid [(S)-3,3-difluoro-1-((S)-1-formyl-1-methyl-butylcarbamoyl)-4-phenyl-butyl]-amide (83 mg, 38%).

^1H NMR ($CDCl_3$): δ 9.3 (s, 1H), 7.2 (m, 5H), 7.0 (s, 1H), 5.0 (d, J = 7 Hz, 1H), 4.64 (dd, J = 13, 7.3 Hz, 1H), 3.7 (m, 4H), 3.4 (m, 4H), 3.2 (t, J= 16.5 Hz, 2H), 2.3 (m, 2H), 1.9 (m, 1H), 1.65 (m, 1H), 1.35 (s, 3H), 1.2 (m, 2H), 0.9 (t, J= 7.3 Hz, 3H);
LC/MS: 100% 440. (M+1)

EXAMPLE 20

Perhydro-1,4-oxazepine-4-carboxylic acid {(S)-1-[(S)-1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-butyl}-amide



I

To a mixture of (S)-4,4-Difluoro-2- [(perhydro-1,4-oxazepine-4-carbonyl)-amino]-pentanoic acid (97 mg, 0.35 mmol), (S)-2-Amino-1- (3-cyclopropyl-1,2,4-oxadiazol-5-yl)-butan-1-ol hydrochloride (83 mg, 0.36 mmol) and diisopropylethyl amine (121 µL, 0.70 mmol) in dry dichloromethane (12 mL) was added 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (66 mg, 0.35 mmol) and 1-hydroxybenzotriazole hydrate (47 mg, 0.35 mmol). The mixture was stirred at room temperature for 16 hr then was diluted with dichloromethane (20 mL) and washed with dilute HCl (30 mL), then saturated $NaHCO_3$ (30 mL). The organic layer was dried (Na_2SO_4) and concentrated in vacuum. The residue was purified over 12 g silica gel, eluting with ethyl acetate: heptane (gradient 50 - 100 %) to afford Perhydro-1, 4-oxazepine-4-carboxylic acid ((S)-1-{(S)-1-[(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-

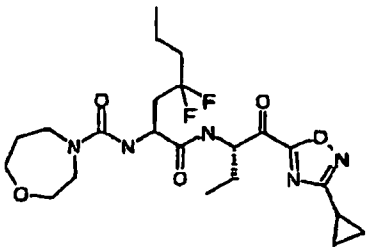
hydroxy-methyl]-propylcarbamoyl}-3,3-difluoro-butyl)-amide (120 mg, 75 %) as a colorless glassy solid. LC/MS 100% 460 (M+H).

To a solution of Perhydro-1, 4-oxazepine-4-carboxylic acid ((S)-1-{(S)-1-[(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-hydroxy-methyl]-propylcarbamoyl}-3,3-difluoro-butyl)-amide (110 mg, 0.24 mmol) in dry dichloromethane (20 mL) under N_2 was added Dess-Martin periodinane (143 mg, 0.34 mmol). The reaction was stirred at RT for 2 hr, and then dichloromethane (20 mL) was added. The reaction was quenched with a solution of $Na_2S_2O_3$ (0.26M, 2 mL) and washed with saturated $NaHCO_3$ (20 mL). The aqueous layer was extracted with dichloromethane (2 x 30 mL). The organic layers were dried (Na_2SO_4) and concentrated in vacuum. The residue was purified over 12 g silica gel, eluted with ethyl acetate: heptane (gradient 50-100%) to afford Perhydro-1,4-oxazepine-4-carboxylic acid {(S)-1-[(S)-1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-butyl}-amide (82 mg, 75%) as a white solid.

^{1}H NMR ($CDCl_3$) δ 7.52 (d, 6.2H), 5.28 (m, 1H), 5.05 (d, J = 7 Hz, 1H), 4.66 (m, 1H), 3.78 (m, 4H), 3.59 (m, 4H), 2.42 (m, 2H), 2.23 (m, 1H), 2.07 (m, 1H), 1.98 (m, 1H0, 1.85 (m, 1H), 1.69 (t, J = 18.8 Hz, 3H), 1.15 (m, 4H), 0.98 (t, J = 7.5Hz, 3H); LC/MS: 97% 458 (M+H).

EXAMPLE 21

Perhydro-1,4-oxazepine-4-carboxylic acid {(S)-1-[(S)-1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-hexyl}-amide



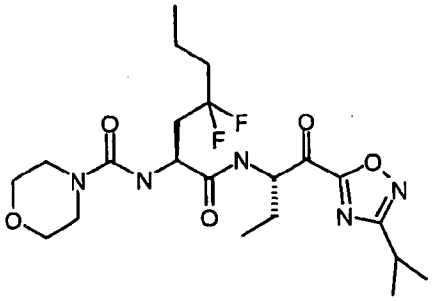
By proceeding in a similar manner Example 20 above but using (S)-4,4-Difluoro-2-[(perhydro-1,4-oxazepine-4-carbonyl)-amino]-heptanoic acid and (S) -2- amino-1-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-butan-1-ol hydrochloride there was prepared Perhydro-1,4-oxazepine-4-carboxylic acid {(S)-1-[(S)-1-(3-cyclopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-hexyl}-amide (98mg, 65%) as a white solid.

^{1}H NMR (CDCl3) δ 7.6 (d, J=7.5 Hz, 1H), 5.25 (m, 1H), 5.10 (d, J=7.5 Hz, 1H), 4.65 (dd, J=14, J=7.5 Hz, 1H), 3.75 (m, 6H), 3.55 (m, 4H), 2.4 (m, 2H), 2.2 (m, 2H), 1.95 (m, 1H), 1.8 (m, 3H), 1.55 (m, 2H), 1.10 (m, 4H), 0.95 (t, J=7.5 Hz, 6H);

LC/MS: 70% 486 (M+1) and 30% 504 (M+1+H2O).

EXAMPLE 22

Morpholine-4-carboxylic acid {(S)-1-[(S)-1-(3-isopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-hexyl}-amide

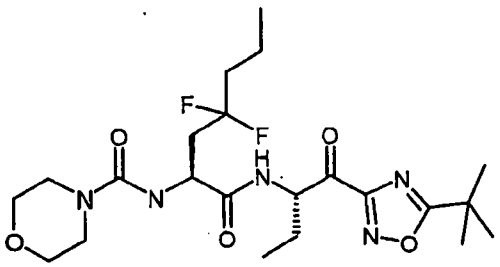


By proceeding in a similar manner to Example 20 above but using (S)-4,4-Difluoro-2-[(morpholine-4-carbonyl)-amino]-heptanoic acid and (S)-2-amino-1-(3-isopropyl-1,2,4-oxadiazol-5-yl)-butan-1-ol there was prepared, Morpholine-4-carboxylic acid {(S)-1-[(S)-1-(3-isopropyl-1,2,4-oxadiazole-5-carbonyl)-propylcarbamoyl]-3,3-difluoro-hexyl}-amide (122mg, 71%) as white solid.

1H NMR (CDCl3) δ 7.5 (d, J=7.0 Hz, 1H), 5.3 (m,1H), 5.25 (d, J=7.0 Hz, 1H), 4.65 (dd, J=13, 7.0 Hz, 1H), 3.7 (m, 4H), 3.4 (m, 4H), 3.2 (m, 1H), 2.35 (m, 2H), 2.1 (m, 1H), 1.8 (m, 3H), 1.55 (m, 2H), 1.40 (d, J=7 Hz, 6H), 0.9 (t, J=7.0 Hz, 6H);
LC/MS: 72% 474 (M+1) and 28% 492 (M+1+H2O).

EXAMPLE 23

Morpholine-4-carboxylic acid {(S)-1-[(S)-1-(5-tert-butyl-1,2,4-oxadiazole-3-carbonyl)-propylcarbamoyl]-3,3-difluoro-hexyl}-amide



A solution of (S)-4,4-Difluoro-2-[(morpholine-4-carbonyl)-amino]-heptanoic acid (175 mg, 0.60 mmol) in dimethylformamide (6 ml) was treated successively with (S)-2-Amino-1-(5-tert-butyl-1,2,4-oxadiazol-3-yl)-butan-1-ol (240 mg, 1.13 mmol), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (226 mg, 0.59 mmol) and diisopropylethylamine (0.104 ml, 0.60 mmol). Reaction stirred at room temperature overnight. Solvent evaporated under high vacuum. Residue taken up in ethyl acetate and washed with 1N hydrochloric acid, saturated aqueous bicarbonate solution and water, dried over Na_2SO_4 and solvent evaporated under reduced pressure.

Crude purified on flash silica (10g column) eluting with a mixture of ethyl acetate and heptane (2:1) to give Morpholine-4-carboxylic acid ((S)-1-{(S)-1-[(5-tert-butyl-1,2,4-oxadiazol-3-yl)-hydroxy-methyl]-propylcarbamoyl}-3,3-difluoro-hexyl)-amide as a brown oil (60 mg).

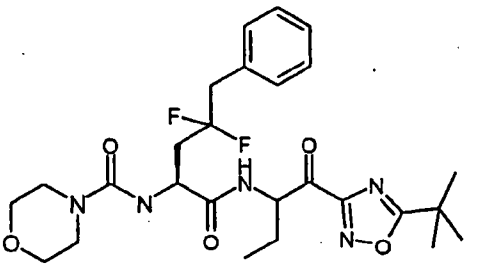
MS : 490 (M+H).

A solution of Morpholine-4-carboxylic acid ((S)-1-{(S)-1-[(5-tert-butyl-1,2,4-oxadiazol-3-yl)-hydroxy-methyl]-propylcarbamoyl}-3,3-difluoro-hexyl)-amide (57 mg, 0.117 mmol) in methylene chloride (3 ml) was treated with Dess-Martin periodinane (59 mg, 0.139 mmol) and stirred at room temperature for 90 minutes. The reaction mixture was washed with a solution of $Na_2S_2O_3$ in water (0.26M), saturated aqueous bicarbonate solution and water, dried over Na_2SO_4 and the solvent evaporated under reduced pressure. The residue was purified by flash chromatography eluting with a mixture of ethyl acetate and heptane (1:1) to give Morpholine-4-carboxylic acid {(S)-1-[(S)-1-(5-tert-butyl-1,2,4-oxadiazole-3-carbonyl)-propylcarbamoyl]-3,3-difluoro-hexyl}-amide as an off white solid (41 mg).

MS : 488 (M+H).

EXAMPLE 24

Morpholine-4-carboxylic acid {(S)-1-[1-(5-tert-butyl-1,2,4-oxadiazole-3-carbonyl)-propylcarbamoyl]-3,3-difluoro-4-phenyl-butyl}-amide



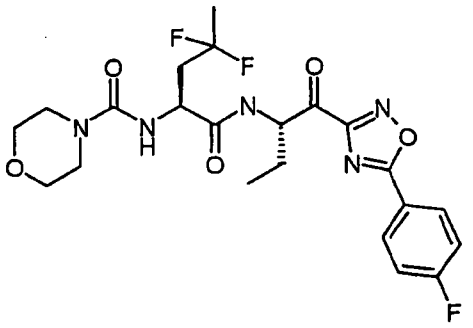
By proceeding in a similar manner to Example 23 above but using (S)-4,4-Difluoro-2-[(morpholine-4-carbonyl)-amino]-5-phenyl-pentanoic acid and (S)-2-Amino-1-(5-tert-butyl-1,2,4-oxadiazol-3-yl)-butan-1-ol there was prepared Morpholine-4-carboxylic acid {(S)-1-[1-(5-tert-butyl-1,2,4-oxadiazole-3-carbonyl)-propylcarbamoyl]-3,3-difluoro-4-phenyl-butyl}-amide as 7:3 mixture of diastereoisomers.

^{1}H NMR ($CDCl_3$) δ: 7.36-7.19 (m, 5H), 7.15 (d, J=7.1Hz, 1H), 5.31 (m, 1H), 5.03 & 4.96 (2xd, J=7Hz, 1H), 4.68 (m, 1H), 3.76-3.59 (m, 4H), 3.45-3.26 (m, 4H), 3.18 (t, J=16.8Hz, 2H), 2.52-2.18 (m, 2H), 2.17-1.94 (m, 1H), 1.88-1.70 (m, 1H), 1.47 (s, 9H), 0.93 (t, J=7.4Hz, 3H).

MS : 536 (M+H).

EXAMPLE 25

Morpholine-4-carboxylic acid ((S)-3,3-difluoro-1-{(S)-1-[5-(4-fluoro-phenyl)-1,2,4-oxadiazole-3-carbonyl]-propylcarbamoyl}-butyl)-amide



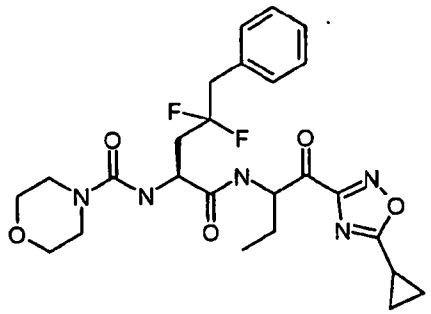
By proceeding in a similar manner to Example 23 above but using (S)-4,4-Difluoro-2-[(morpholine-4-carbonyl)-amino]-pentanoic acid and (S)-2-Amino-1-[5-(4-fluoro-phenyl)-1,2,4-oxadiazol-3-yl]-butan-1-ol there was prepared Morpholine-4-carboxylic acid ((S)-3,3-difluoro-1-{(S)-1-[5-(4-fluoro-phenyl)-1,2,4-oxadiazole-3-carbonyl]-propylcarbamoyl}-butyl)-amide

^{1}H NMR ($CDCl_3$) δ: 8.21 (m, 2H), 7.31 (d, J=6.8Hz, 1H), 7.30-7.20 (m, 2H), 5.38 (m, 1H), 5.07 (d, J=6.8Hz, 1H), 4.63 (m, 1H), 3.75-3.64 (m, 4H), 3.44-3.33 (m, 4H), 2.58-2.28 (m, 2H), 2.22-2.04 (m, 1H), 1.96-1.79 (m, 1H), 1.66 (t, J=18.8Hz, 3H), 0.97 (t, J=7.4Hz, 3H).

MS : 498 (M+H).

EXAMPLE 26

Morpholine-4-carboxylic acid {(S)-1-[1-(5-cyclopropyl-1,2,4-oxadiazole-3-carbonyl)-propylcarbamoyl]-3,3-difluoro-4-phenyl-butyl}-amide



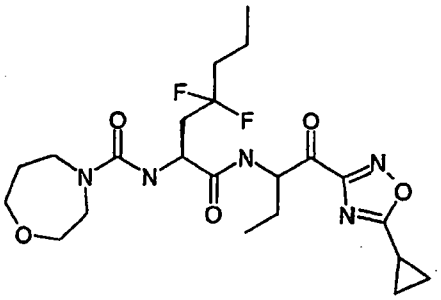
By proceeding in a similar manner to Example 23 above but using (S)-4,4-Difluoro-2-[(morpholine-4-carbonyl)-amino]-5-phenyl-pentanoic acid and (S)-2-Amino-1-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-butan-1-ol there was prepared Morpholine-4-carboxylic acid {(S)-1-[1-(5-cyclopropyl-1,2,4-oxadiazole-3-carbonyl)-propylcarbamoyl]-3,3-difluoro-4-phenyl-butyl}-amide as 3:1 mixture of diastereoisomers.

^{1}H NMR ($CDCl_3$) δ: 7.36-7.20 (m, 5H), 7.14 (d, J=7.1Hz, 1H), 5.26 (m, 1H), 5.02 & 4.96 (2xd, J=7Hz, 1H), 4.70 (m, 1H), 3.73-3.61 (m, 4H), 3.43-3.28 (m, 4H), 3.18 (t, J=16.5Hz, 2H), 2.48-2.21 (m, 3H), 2.14-1.98 (m, 1H), 1.85-1.70 (m, 1H), 1.38-1.21 (m, 4H), 0.91 (t, J=7.5Hz, 3H).

MS : 520 (M+H).

EXAMPLE 27

Perhydro-1,4-oxazepine-4-carboxylic acid {(S)-1-[1-(5-cyclopropyl-1,2,4-oxadiazole-3-carbonyl)-propylcarbamoyl]-3,3-difluoro-hexyl}-amide



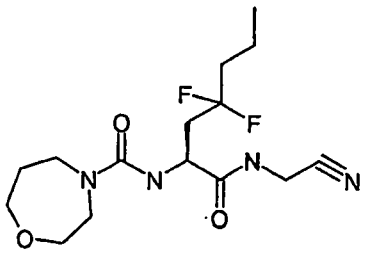
By proceeding in a similar manner to Example 23 above but using (S)-4,4-Difluoro-2-[(perhydro-1,4-oxazepine-4-carbonyl)-amino]-heptanoic acid and (S)-2-Amino-1-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-butan-1-ol there was prepared Perhydro-1,4-oxazepine-4-carboxylic acid {(S)-1-[1-(5-cyclopropyl-1,2,4-oxadiazole-3-carbonyl)-propylcarbamoyl]-3,3-difluoro-hexyl}-amide as 5:1 mixture of diastereoisomers.

^{1}H NMR ($CDCl_3$) : 7.44 & 7.39 (2xd, J=7.3Hz, 1H), 5.30 (m, 1H), 5.05 & 4.98 (2xd, J=6.5Hz, 1H), 4.63 (m, 1H), 3.79-3.73 (m, 4H), 3.59-3.53 (m, 4H), 2.47-2.23 (m, 3H), 2.15-1.76 (m, 6H), 1.57-1.43 (m, 2H), 1.38-1.26 (m, 4H), 0.95 (t, J=7.3Hz, 3H), 0.93 (t, J=7.2Hz, 3H).

MS : 486 (M+H).

EXAMPLE 28

Perhydro-1,4-oxazepine-4-carboxylic acid [(S)-1-(cyanomethyl-carbamoyl)-3,3-difluoro-hexyl]-amide



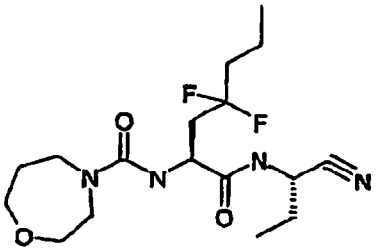
A suspension of Polystyrene bound carbodiimide (570mg, 0.73 mmol) and (S)-4,4-Difluoro-2-[(perhydro-1,4-oxazepine-4-carbonyl)-amino]-heptanoic acid (135 mg) in DCM (10 ml) stirred for 10 min. HOBT (60mg) added, stirred for 10 min. A suspension of amino acetonitrile hydrochloride (34 mg) and triethyl amine (52 uL) in DCM (5ml) added and stirred overnight at room temperature. PS-Trisamine (493 mg) added and stirred at room temperature for 2h 30 min. After filtration, filtrate

diluted with DCM, washed with water, evaporated under reduced pressure and purified by column chromatography eluting with ethyl acetate heptane mixture to give Perhydro-1,4-oxazepine-4-carboxylic acid [(S)-1-(cyanomethyl-carbamoyl)-3,3-difluoro-hexyl]-amide as white solid.

LCMS : 100% 347 (M+H)

EXAMPLE 29

Perhydro-1,4-oxazepine-4-carboxylic acid [(S)-1-((S)-1-cyano-propylcarbamoyl)-3,3-difluoro-hexyl]-amide

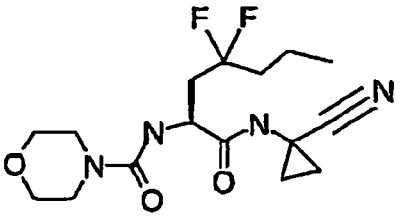


By proceeding in a similar manner to Example 28 above but using 4,4-Difluoro-2-[([1,4]oxazepane-4-carbonyl)-amino]-heptanoic acid and (S)-2-Amino-butyronitrile hydrochloride there was prepared Perhydro-1,4-oxazepine-4-carboxylic acid [(S)-1-((S)-1-cyano-propylcarbamoyl)-3,3-difluoro-hexyl]-amide.

LCMS : 100% 375 (M+H).

EXAMPLE 30

Morpholine-4-carboxylic acid [(S)-1-(1-cyano-cyclopropylcarbamoyl)-3,3-difluoro-hexyl]-amide



Prepared by reacting (S)-4,4-Difluoro-2-[(morpholine-4-carbonyl)-amino]-heptanoic acid and 1-Amino-cyclopropanecarbonitrile hydrochloride, using TOTU as the coupling agent and diisopropyl ethylamine as the base.

LCMS : 359 (M+H)

EXAMPLE 31

Cathepsin S Assay

Solutions of test compounds in varying concentrations were prepared in 10 μL of dimethyl sulfoxide (DMSO) and then diluted into assay buffer (40 μL, comprising: MES, 50 mM (pH 6.5); EDTA, 2.5 mM; and NaCl, 100 mM, 0.5 mM DTT, 0.01% triton X-100).

Human cathepsin S (final concentration in the well is 1.74 nM) was added to the dilutions. The assay solutions were mixed for 5-10 seconds on a shaker plate, covered and incubated for 30 minutes at ambient temperature. Z-Val-Val-Arg-AMC (final concentration in the well is 0.08 mM) was added to the assay solutions and hydrolysis was followed spectrophotometrically at (λ 460 nm) for 5 minutes. Apparent inhibition constants (K_i) were calculated from the enzyme progress curves using standard mathematical models.

EXAMPLE 32

Cathepsin B Assay

Solutions of test compounds in varying concentrations were prepared in 10 μL of dimethyl sulfoxide (DMSO) and then diluted into assay buffer (comprising: MES 50 mM (pH 6); 2.5 mM EDTA , 2% DMSO and dithiothreitol (DTT), 2.5 mM).

Human cathepsin B (final concentration of 0.3 ng/μl) was added to the dilutions. The assay solutions were mixed for 5-10 seconds on a shaker plate, covered and incubated for 30 minutes at ambient temperature. Z-FR-pNa (final concentration of 100 μM) was added to the assay solutions and hydrolysis was followed spectrophotometrically at (λ 405nm) for 60 minutes. Apparent inhibition constants (K_i) were calculated from the enzyme progress curves using standard mathematical models.

EXAMPLE 33

Cathepsin K Assay

Solutions of test compounds in varying concentrations were prepared in 10 μL of dimethyl sulfoxide (DMSO) and then diluted into assay buffer (40 μL, comprising: MES, 50 mM (pH 5.5); EDTA, 2.5 mM; and DTT, 2.5 mM). Human cathepsin K (0.0906 pMoles in 25 μL of assay buffer) was added to the dilutions. The assay solutions were mixed for 5-10 seconds on a shaker plate, covered and incubated for 30 minutes at ambient temperature. Z-Phe-Arg-AMC (4 nMoles in 25 μL of assay buffer) was added to the assay solutions and hydrolysis was followed spectrophotometrically at (λ 460 nm) for 5 minutes. Apparent inhibition constants (K_i) were calculated from the enzyme progress curves using standard mathematical models.

EXAMPLE 34

Cathepsin L Assay

Solutions of test compounds in varying concentrations were prepared in 10 μL of dimethyl sulfoxide (DMSO) and then diluted into assay buffer (40 μL, comprising: MES, 50 mM (pH 6); EDTA, 2.5 mM; and DTT, 2.5 mM). Human cathepsin L (10 μL of 0.2 ng/μL, final concentration of 0.02 ng/μl) was added to the dilutions. The assay solutions were mixed for 5-10 seconds on a shaker plate, covered and incubated for 30 minutes at ambient temperature. Z-Phe-Arg-AMC (10 μL of 0.1 mM, final concentration of 10 μM) was added to the assay solutions and hydrolysis was followed spectrophotometrically at (λ 460 nm) for 30 minutes. Apparent inhibition constants (K_i) were calculated from the enzyme progress curves using standard mathematical models.

Compounds of the invention were tested according to the above-described assays for protease inhibition and observed to exhibit selective cathepsin S inhibitory activity. The apparent inhibition constants (K_i) for compounds of the invention, against Cathepsin S, were in the range from about 10^{-10} M to about 10^{-7}M.

EXAMPLE 35

Representative Pharmaceutical Formulations Containing a Compound of Formula (I):

ORAL FORMULATION

Compound of Formula I,	10-100 mg
Citric Acid Monohydrate	105 mg
Sodium Hydroxide	18 mg
Flavoring	
Water	q.s. to 100 mL

INTRAVENOUS FORMULATION

Compound of Formula I,	0.1-10 mg
Dextrose Monohydrate	q.s. to make isotonic
Citric Acid Monohydrate	1.05 mg
Sodium Hydroxide	0.18 mg
Water for Injection	q.s. to 1.0 mL

TABLET FORMULATION

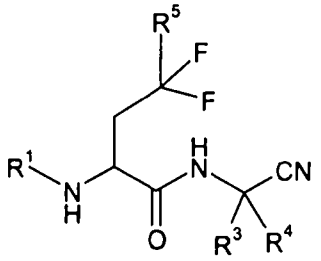
Compound of Formula I,	1%
Microcrystalline Cellulose	73%
Stearic Acid	25%
Colloidal Silica	1%.

While there have been described and pointed out fundamental novel features of the invention as applied to a preferred embodiment thereof, it will be understood that various omissions and substitutions and changes, in the form and details of the composition and methods illustrated, may be made by those skilled in the art without departing from the spirit of the invention. For example, it is expressly intended that chemical radical substitutions and/or method steps, which perform substantially the same function in substantially the same way to achieve the same results are within the scope of the invention.

The invention is not limited by the embodiments described above which are presented as examples only but can be modified in various ways within the scope of protection defined by the appended patent claims.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A compound having a structure of Formula (Ib):



(Ib)

wherein R^1 is $R^{13}C(O)$-, $R^{13}S(O)_2$- , $R^{13}OC(O)$- , $R^8R^7NC(O)$-, $R^8R^7NS(O)_2$-; $R^{13}S(O)_2NC(O)$- or $R^{13}C(O)NS(O)_2$-;

wherein R^{13} is (C_{1-6})alkyl, (C_{3-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl, hetero(C_{3-12})cycloalkyl(C_{0-6})alkyl, hetero(C_{5-13})aryl(C_{0-6})alkyl, and halo substituted (C_{1-6}) alkyl;

wherein R^{13} is optionally substituted by 1 to 5 radicals independently selected from a group consisting of (C_{1-4})alkyl, cyano, halo, halo-substituted (C_{1-4})alkyl, , $-X^6NR^9R^9$, $-X^6OR^9$, $-X^6SR^9$, $-X^6C(O)NR^9R^9$, $-X^6OC(O)NR^9R^9$, $-X^6C(O)OR^9$, , $-X^6NC(O)OR^9$, $-X^6S(O)R^{10}$, $-X^6S(O)_2R^{10}$ and $-X^6C(O)R^{10}$;

X^6 is a bond or (C_{1-2})alkylene;

R^7 is H, (C_{1-6})alkyl, (C_{3-12})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl, hetero(C_{5-13})aryl(C_{0-6})alkyl, and halo substituted (C_{1-6}) alkyl;

wherein R^7 is optionally substituted by 1 to 5 radicals independently selected from a group consisting of (C_{1-4})alkyl, cyano, halo, halo-substituted (C_{1-4})alkyl, $-X^6NR^9R^9$, $-X^6OR^9$, $-X^6SR^9$, $-X^6C(O)NR^9R^9$, $-X^6OC(O)NR^9R^9$, $-X^6C(O)OR^9$, $-X^6NC(O)OR^9$, $-X^6S(O)R^{10}$, $-X^6S(O)_2R^{10}$ and $-X^6C(O)R^{10}$;

R^8 is selected from the group consisting of H, (C_{1-6})alkyl, (C_{3-12})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl, and hetero(C_{5-13})aryl(C_{0-6})alkyl, or

R^7 and R^8 together with the atom attached to form (C_{3-8})cycloalkylene or (C_{3-8})heterocycloalkylene;

R^9 at each occurrence independently is hydrogen, (C_{1-6})alkyl or halo-substituted (C_{1-6})alkyl;

R^{10} is (C_{1-6})alkyl or halo-substituted (C_{1-6})alkyl;

R^3 is selected from the group consisting of H, (C_{1-6})alkyl, (C_{3-12})cycloalkyl(C_{0-6})alkyl, hetero(C_{5-12})cycloalkyl(C_{0-6})alkyl, (C_{6-12})aryl(C_{0-6})alkyl or hetero(C_{5-13})aryl(C_{0-6})alkyl optionally is substituted by 1 to 5 radicals independently selected from a group consisting of (C_{1-4})alkyl, cyano, halo, halo-substituted (C_{1-4})alkyl, $-X^6NR^9R^9$, $-X^6OR^9$, $-X^6SR^9$, $-X^6C(O)NR^9R^9$, $-X^6OC(O)NR^9R^9$, $-X^6C(O)OR^9$, $-X^6NC(O)OR^9$, $-X^6S(O)R^{10}$, $-X^6S(O)_2R^{10}$ and $-X^6C(O)R^{10}$;

R^4 is H or (C_{1-6})alkyl; or

R^3 and R^4 taken together with the carbon atom to which both R^3 and R^4 are attached to form (C_{3-8})cycloalkylene or (C_{3-8})heterocycloalkylene;

R^5 is (C_{6-12})aryl(C_{1-6})alkyl;

wherein aryl is phenyl or naphthyl,

wherein hetero(C_{5-13})aryl is benzimidazolyl, benzoxazolyl, benzothiazolyl, furyl, imidazolyl, indolyl, indolizinyl, isoxazolyl, isoquinolinyl, isothiazolyl, oxadiazolyl, oxazolyl, pyrazinyl, pyridazinyl, pyrazolyl, pyridyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl, 1,3,4-thiadiazolyl, thiazolyl, thienyl and triazolyl,

wherein heterocycloalkyl is imidazolidinyl, morpholinyl, piperazinyl, piperidyl, pyrrolidinyl, pyrrolinyl and quinuclidinyl,

and their corresponding N-oxides, individual diastereomers and mixtures of diastereomers thereof; and the pharmaceutically acceptable salts and solvates (e.g. hydrates) of such compounds of Formula (Ib) and their N-oxides, individual diastereomers and mixtures of diastereomers thereof.

2. A compound having a structure of Formula (Ib) as claimed in claim 1:

wherein R^1 is (i) $R^{13}C(O)$- wherein R^{13} is hetero(C_{5-12})cycloalkyl or (ii) $R^{13}OC(O)$- wherein R^{13} is (C_{6-12})aryl(C_{1-6})alkyl;

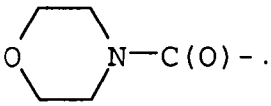
R^3 is H, (C_{6-12})aryl(C_{1-6})alkyl or (C_{1-6})alkyl;

optionally substituted by $-X^6OR^9$ wherein X^6 is a bond and R^9 is (C_{1-6})alkyl;

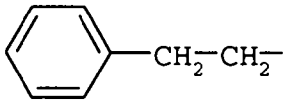
R^4 is H or (C_{1-6})alkyl; and

R^5 is (C_{6-12})aryl(C_{1-6})alkyl.

3. A compound according to claim 1 in which R^1 is $R^{13}C(O)$- wherein R^{13} is hetero(C_{5-12})cycloalkyl.

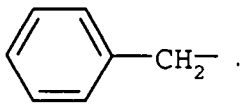
4. A compound according to claim 3 in which R^1 is  .

5. A compound according to any one of claims 1 to 4 in which R^3 is H, (C_{6-12})aryl(C_{1-6})alkyl or (C_{1-6})alkyl.

6. A compound according to claim 5 in which R^3 is H,  or $CH_3CH_2CH_2$-.

7. A compound according to any one of claims 1 to 6 in which R^4 is H or methyl.

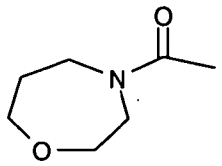
8. A compound according to any one of claims 1 to 7 in which R^5 is (C_{6-12})aryl(C_{1-6})alkyl.

9. A compound according to claim 8 in which R^5 is  .

10. A compound according to claim 1 selected from the group consisting of:
morpholine-4-carboxylic acid [(S)-1-((S)-1-cyano-3-phenyl-propylcarbamoyl)-3,3-difluoro-4-phenyl-butyl]-amide; and
morpholine-4-carboxylic acid [(S)-1-(cyanomethyl-carbamoyl)-3,3-difluoro-4-phenyl-butyl]-amide;
and their corresponding N-oxides, individual diastereomers and mixtures of diastereomers thereof; and the pharmaceutically acceptable salts and solvates (e.g. hydrates) of such compounds of Formula (Ib) and their N-oxides individual diastereomers and mixtures of diastereomers thereof.

11. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable excipient.

12. A compound according to any one of claims 1, 2, 3 or 5 to 9 wherein R^1 is



13. Use of a compound according to claim 1, in the manufacture of a medicament for the treatment of a patient suffering from juvenile onset diabetes, multiple sclerosis, pemphigus vulgaris, Graves' disease, myasthenia gravis, systemic lupus erythemotasus, irritable bowel disease, rheumatoid arthritis, Hashimoto's thyroiditis, asthma, obstructive pulmonary disease, emphysema or bronchiolitis.

AVENTIS PHARMACEUTICALS INC

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