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(54) Title: NOVEL NITRILES USEFUL AS REVERSIBLE INHIBITORS OF CYSTEINE PROTEASES

(57) Abstract: Disclosed are novel nitrile compounds of formula (I) further defined herein, which compounds are useful as re-
versible inhibitors of cysteine proteases such as cathepsin K, S, F, L and B. These compounds are useful for treating diseases and
pathological conditions exacerbated by these proteases such as, but not limited to, osteoporosis, rheumatoid arthritis, multiple scler-
osis, asthma and other autoimmune diseases, Alzheimer's disease, atherosclerosis. Also disclosed are processes for making such
novel compounds.

Novel Nitriles Useful As Reversible Inhibitors of Cysteine Proteases

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FIELD OF THE INVENTION

This invention relates to peptidyl carbamates and related compounds. The compounds are reversible inhibitors of the cysteine proteases cathepsins S, K, F, L and B and certain
10 embodiments described are preferable for inhibition of cathepsin K. The compounds are therefore useful in the treatment of cysteine protease mediated diseases including osteoporosis, autoimmune diseases and other related diseases. The invention also relates to processes for preparing such compounds and pharmaceutical compositions comprising
15 them.

BACKGROUND OF THE INVENTION

20 Cathepsin K and cathepsin S are members of the papain family, within the papain superfamily of cysteine proteases. The papain family is the largest group of cysteine proteases and includes proteases such as cathepsins B, H, K, L, O and S. (A.J. Barrett et al., 1996, Perspectives in Drug Discovery and Design, 6, 1). The cysteine proteases have important roles in human biology and diseases including osteoporosis, chronic
25 inflammation and immune disorders, atherosclerosis, and emphysema (H.A. Chapman et al., 1997, Ann. Rev. Physiol., 59, 63). Cysteine proteases are also involved in the pathogenesis of some infectious diseases, including malaria (A. Semenov et al., Antimicrobial Agents and Chemotherapy, 1998, 42, 2254) and Chagas' disease, (J.C. Engel et al., J. Exp. Med., 1998, 188, 725). Bacterial cysteine proteases contribute to the
30 pathogenesis of gingivitis (J. Potempa et al., Perspectives in Drug Discovery and Design, 1994, 2, 445).

Cathepsin K has been found to be highly expressed in osteoclasts, cells involved in bone resorption (F.H. Drake et al., J. Biol. Chem., 1996, 271, 12511). Collagen and osteonectin, two protein components of bone matrix have been found to be substrates of activated cathepsin K (M.J. Bossard et al., J. Biol. Chem., 1996, 271, 12517). Inhibitors of cathepsin K have been shown to have anti-resorptive activity *in vitro* and *in vivo* (S.K. Thompson et al., Proc. Natl. Acad. Sci. USA, 1997, 94, 14249). The essential role of cathepsin K in bone resorption has also been confirmed in cells and organisms lacking this protease. At the cellular level, cathepsin K deficient osteoclasts, when tested for functional activity on dentine, produced fewer resorption pits as compared to wild-type osteoclasts (P. Saftig et al., Proc Natl Acad Sci U S A 1998, 95,13453). Cathepsin K knockout mice develop osteopetrosis, a disease characterized by an increase in bone mass, due to a deficit in matrix degradation but not demineralization of hydroxyapatite. These knockout mice displayed osteopetrosis of the long bones and vertebrae as well as abnormal joint morphology (M. Gowen et al., J. Bone Miner Res. 1999, 14, 1654). The phenotype of the cathepsin K knockout mice resembles the human genetic disorder pycnodysostosis which is due to a mutation in the cathepsin K gene (W-S Hu et al., Journal of Clinical Investigation, 1999, 103, 731; B. D. Gelb et al, Science, 1996, 273, 1236). Patients with this disease have short, dense bones. These and other findings suggest that cathepsin K may play an important role in diseases involving bone resorption, excessive bone loss or cartilage or bone matrix degradation including osteoporosis (D. S Yamashita et al, Current Pharmaceutical Design, 2000, 6, 1), Gaucher disease (M. T. Moran et al, Blood, 2000, 96, 1969), Paget's disease, gingivitis, and periodontitis (G. A. Rodan et al, Science, 2000, 289, 1508), and rheumatoid arthritis (K. M. Hummel et al, J. Rheumatol., 1998, 25, 1887) (also see for example H. A. Chapman et al, Annu. Rev. Physiol., 1997, 59, 63; M. Gowen, Exp. Opin. Invest. Drugs, 1997, 6, 1199; and W.W. Smith et al., Exp. Opin. Ther. Patents, 1999, 9, 683).

The inhibition of cathepsin K has been described by B. D. Gelb et al (U.S. 5,830,850) as a method to ameliorate symptoms caused by bone resorption disorders, including osteoporosis, arthritides and periodontal disease, and damage caused by macrophage-

mediated inflammatory processes. Studies in breast cancer research have shown that invading breast cancer cells have expressed low levels of Cathepsin K suggesting that these tumor cells may be able to directly resorb bone by the release of Cathepsin K. Inhibition of Cathepsin K may play a role in the metastatic potential and course of the disease (A. J. Littlewood-Evans et al, *Cancer Research*, 1997, 57, 5386). Increases in bone resorption and demineralization of bone are skeletal complications associated with many cancers and with bone metastases of breast and prostate tumors (G. A. Rodan et al, *Science*, 2000, 289, 1508). Cathepsin K has also been observed in giant cell aortitis suggesting that disorders associated with excessive elastin degradation such as lymphangiomyomatosis, vascular inflammation, and cardiovascular disease such as atherosclerosis may be attenuated with Cathepsin K inhibitors (H. A. Chapman et al, *Annu. Rev. Physiol.*, 1997, 59, 63; D. S Yamashita et al, *Current Pharmaceutical Design*, 2000, 6, 1; and G. K. Sukhova et al, *J. Clin. Invest.*, 1998, 102, 576).

Cathepsin S plays a key role in regulating antigen presentation and immunity (H.A. Chapman, 1998, *Current Opinion in Immunology*, 10, 93; R. J. Riese et al., 1998, *J. Clin. Invest.*, 101, 2351; R.J. Riese et al., 1996, *Immunity*, 4, 357). Cathepsin S deficient mice have impaired invariant chain degradation resulting in decreased antigen presentation and germinal center formation, and diminished susceptibility to collagen-induced arthritis indicating the therapeutic potential for a cathepsin S inhibitor (G. Shi et al., 1999, *Immunity*, 10, 197; T.Y. Nakagawa et al, 1999, *Immunity*, 10, 207).

Control of antigen-specific immune responses has long been desirable as a useful therapy for autoimmune diseases. Such diseases include Crohn's disease, rheumatoid arthritis, and Multiple Sclerosis, as well as other T-cell-mediated immune responses (C. Janeway and P. Travers, 1996, *Immunobiology, The Immune System in Health and Disease*, Chapter 12). Furthermore, cathepsin S, which has broad pH specificity, has been implicated in a variety of other diseases involving extracellular proteolysis, such as Alzheimer's disease (U. Muller-Ladner et al., 1996, *Perspectives in Drug Discovery and Design*, 6, 87), atherosclerosis (G.K. Sukhova et al., 1998, *J. Clin. Invest.*, 102, 576) and endometriosis (WO 9963115, 1999). A cathepsin S inhibitor has been found to block the

rise in IgE titers and eosinophil infiltration in the lung in a mouse model of pulmonary hypersensitivity, suggesting that cathepsin S may be involved in asthma (R.J. Riese et al., *J. Clin. Investigation*, 1998, 101, 2351). Cathepsin inhibitors such as Leupeptin and E-64 were shown to have positive effects in a murine model of emphysema (J. A. Elias et al., *J. Clin. Investigation*, 2000, 106, 1081).

Another cysteine protease, cathepsin F has been found in macrophages and is also involved in antigen processing. It has been postulated that cathepsin F in stimulated lung macrophages and possibly other antigen presenting cells could play a role in airway inflammation (G.-P. Shi et al., *J. Exp. Med.*, 2000, 191, 1177).

Cysteine proteases are characterized by having a cysteine residue at the active site which serves as a nucleophile. The active site also contains a histidine residue. The imidazole ring on the histidine serves as a base to generate a thiolate anion on the active site cysteine, increasing its nucleophilicity. When a substrate is recognized by the protease, the amide bond to be cleaved is directed to the active site, where the thiolate attacks the carbonyl carbon forming an acyl-enzyme intermediate and cleaving the amide bond, liberating an amine. Subsequently, water cleaves the acyl-enzyme species regenerating the enzyme and liberating the other cleavage product of the substrate, a carboxylic acid.

Inhibitors of cysteine proteases contain a functionality that can react reversibly or irreversibly with the active site cysteine. Examples of reactive functionalities that have been described (D. Rasnick, 1996, *Perspectives in Drug Discovery and Design*, 6, 47) on cysteine protease inhibitors include peptidyl diazomethanes, epoxides, monofluoroalkanes and acyloxymethanes, which irreversibly alkylate the cysteine thiol. Other irreversible inhibitors include Michael acceptors such as peptidyl vinyl esters and other carboxylic acid derivatives (S. Liu et al., *J. Med Chem.*, 1992, 35, 1067) and vinyl sulfones (J.T. Palmer et al., 1995, *J. Med Chem.*, 38, 3193).

Reactive functionalities that form reversible complexes with the active site cysteine include peptidyl aldehydes (R.P. Hanzlik et al., 1991, *Biochim. Biophys. Acta.*, 1073,

33), which are non-selective, inhibiting both cysteine and serine proteases as well as other nucleophiles. Peptidyl nitriles (R.P. Hanzlik et al., 1990, *Biochim. Biophys. Acta.*, 1035, 62) are less reactive than aldehydes and therefore more selective for the more nucleophilic cysteine proteases. Various reactive ketones have also been reported to be reversible inhibitors of cysteine proteases (D. Rasnick, 1996, *ibid*). In addition to reacting with the nucleophilic cysteine of the active site, reactive ketones may react with water, forming a hemiketal which may act as a transition state inhibitor.

Inhibitors of cathepsin K have been reported in the literature. D.S. Yamashita et al., (*J. Am. Chem. Soc.*, 1997, 119, 11351) described 1,3-diamino-2-propanone inhibitors. S.K. Thompson et al. (*Proc. Natl. Acad. Sci. USA*, 1997, 94, 14249) described bis-aza analogs of these propanones as well as an aza-thiazole derivative. Introduction of a conformational constraint to the 1,3-diamino-2-propanones has led to 3-amido-pyrrolidin-4-one derivatives, 4-amido-piperidin-3-one derivatives, and eventually to azapanone-based inhibitors of Cathepsin K, as reported by R. W. Marquis et al. (*J. Med. Chem.* **1998**, *41*, 3563; *J. Med. Chem.* **2001**, *44*, 725; *J. Med. Chem.* **2001**, *44*, 1380). R.W. Marquis et al. (*Bioorg. and Med. Chem. Letters*, 1999, 7, 581) described peptidic alkoxymethylketones and thiomethylketones as cathepsin K inhibitors. Peptidyl vinyl sulfone cathepsin K inhibitors were described by L. Xia et al. (*Biological Chem.*, 1999, 380, 679). Peptide aldehyde inhibitors of cathepsin K were reported by B. J. Votta et al. (*J. Bone & Mineral Res.*, 1997, 12, 1396). J.-P. Falguyret et al. (*J. Med. Chem.* **2001**, *44*, 94-104) described non-peptidic cyanamides as potent Cathepsin K inhibitors. T. Gamble et al. (49th Annual American Society for Mass Spectrometry Conference, May 27-31, 2001, Chicago, IL) described *in vitro* metabolism studies on cyanamide-containing Cathepsin K inhibitors. D. F. Veber has discussed numerous inhibitors of Cathepsin K including the following: 1,5-diacylcarbohydrazides (*Biochemistry*, **1999**, *38*, 15893; *J. Med. Chem.* **1998**, *41*, 3923), conformationally constrained 1,3-diamino ketones (*J. Med. Chem.* **1998**; *41*, 3563), and 1,3-bis(acylamino)-2-butanones, (*J. Combinatorial Chem.* **1999**, *1*, 207; *J. Am. Chem. Soc.* **1998**, *120*, 9114; *J. Am. Chem. Soc.* **1997**, *119*, 11351).

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Examples of cathepsin S inhibitors have been reported. J.L. Klaus et al. (WO 9640737) described reversible inhibitors of cysteine proteases including cathepsin S, containing an ethylene diamine. In US Patent No. 5,776,718 to Palmer et al. there is disclosed in its broadest generic aspect a protease inhibitor comprising a targeting group linked through a two carbon atom chain to an electron withdrawing group (EWG). The compounds of the present application are structurally distinct and are thus excluded from the disclosure in the 5,776,718 patent. Other examples of cathepsin S inhibitors have been reported by E.T. Altmann et al, (WO 9924460, 1999) which describes dipeptide nitriles asserted to have activity as inhibitors of Cathepsins B, K, L and S. The WO publication does not disclose any compounds possessing a carboxylate linkage, Y-C(O)-O-, and fails to provide any description, methods or examples for particular spiroheterocyclic moieties at the P1 position.

Certain acetamido acetonitrile derivatives have been disclosed by Tucker et al. (WO 00/49007) as inhibitors of cathepsin S and L. This WO publication likewise does not disclose or suggest any compounds possessing the carboxylate linkage, Y-C(O)-O-, as in the novel compounds according to the present invention.

Certain other cathepsin inhibitors have recently been disclosed by Marquis et al., WO 00/38687 and WO 00/39115; Altmann et al, WO 00/48993; Buysse et al., WO 00/55124; Singh et al, WO 00/59881 and Cowen et al. (WO 01/87828). Cathepsin inhibitors containing a cyclic cyanamide functionality were described by P. Prasit et al. (WO 01/77073). The compounds of the present invention are structurally distinct from the compounds disclosed in the aforementioned references.

Additional peptidyl nitriles have been reported as protease inhibitors. For example, both nitriles and ketoheterocycles are described by B.A. Rowe et al. (US 5,714,471) as protease inhibitors useful in the treatment of neurodegenerative diseases. Peptidyl nitriles are reported by B. Malcolm et al. (WO 9222570) as inhibitors of picornavirus protease. B.J. Gour-Salin (Can. J. Chem., 1991, 69, 1288) and T.C. Liang (Arch. Biochim. Biophys., 1987, 252, 626) described peptidyl nitriles as inhibitors of papain.

A reversible inhibitor presents a more attractive therapy than irreversible inhibitors. Even compounds with high specificity for a particular protease can bind non-target enzymes. An irreversible compound could therefore permanently inactivate a non-target enzyme, increasing the likelihood of toxicity. Furthermore, any toxic effects resulting from inactivation of the target enzyme would be mitigated by reversible inhibitors, and could be easily remedied by modified or lower dosing. Finally, covalent modification of an enzyme by an irreversible inhibitor could potentially generate an antibody response by acting as a hapten.

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In light of the above, there is a clear need for compounds which reversibly and selectively inhibit cysteine proteases such as cathepsin K and cathepsin S for indications in which these proteases exacerbate disease.

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BRIEF DESCRIPTION OF THE INVENTION

It is therefore an object of this invention to provide novel compounds according to the formula (I) as described herein which reversibly inhibit the cysteine proteases, such as cathepsins K, S, F, L and B. It is a further object of the invention to provide methods for treating diseases and pathological conditions exacerbated by these cysteine proteases such as, but not limited to, rheumatoid arthritis, multiple sclerosis, and other autoimmune diseases, osteoporosis, asthma, Alzheimer's disease, atherosclerosis and endometriosis. It is yet a further object of the invention to provide novel processes for preparation of the above-mentioned novel compounds.

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DETAILED DESCRIPTION OF THE INVENTION

A proposed mechanism of action of the cysteine protease inhibitors of this invention is that the inhibitors contain a functionality that can react (reversibly or irreversibly) with the active site cysteine. The reactive functionality is attached to a peptide or peptide

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mimic that can be recognized and accommodated by the region of the protease surrounding the active site. The nature of both the reactive functionality and the remaining portion of the inhibitor determine the degree of selectivity and potency toward a particular protease.

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Given the similarity of the active sites in cysteine proteases, it may be anticipated that a given class of inhibitors might have activity against more than one cysteine protease. It may also be expected that due to structural differences between individual cysteine proteases, different compounds of the invention may have different inhibitory potencies against different cysteine proteases. Thus some of the compounds of the invention may also be expected to be most effective in treating diseases mediated by cysteine proteases that they inhibit most potently. The activity of particular compounds disclosed herein against cysteine proteases cathepsin K, S, F, L and B may be determined by the screens described in the section entitled "Assessment of Biological Properties."

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As used herein, each of the following terms, used alone or in conjunction with other terms, are defined as follows (except where noted to the contrary):

The term "alkyl" refers to a saturated aliphatic hydrocarbon radical containing from one to ten carbon atoms or a mono- or polyunsaturated aliphatic hydrocarbon radical containing from two to twelve carbon atoms. The mono- or polyunsaturated aliphatic hydrocarbon radical containing at least one double or triple bond, respectively. "Alkyl" refers to both branched and unbranched alkyl groups, each optionally partially or fully halogenated. Examples of "alkyl" include alkyl groups which are straight chain alkyl groups containing from one to eight carbon atoms and branched alkyl groups containing from three to eight carbon atoms. Other examples include alkyl groups which are straight chain alkyl groups containing from one to six carbon atoms and branched alkyl groups containing from three to six carbon atoms. It should be understood that any combination term using an "alk" or "alkyl" prefix refers to analogs according to the above definition of "alkyl". For example, terms such as "alkoxy", "alkylthio" refer to alkyl groups linked

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to a second group via an oxygen or sulfur atom. "Alkanoyl" refers to an alkyl group linked to a carbonyl group (C=O).

The term "cycloalkyl" refers to the mono- or polycyclic analogs of an alkyl group, as defined above, including fully saturated and mono- or polyunsaturated groups. Examples of cycloalkyl groups are saturated cycloalkyl groups containing from three to eight carbon atoms, for example, three to six carbon atoms. Examples of polycyclic cycloalkyl groups include, for example, tetrahydronaphthalene and indane.

10 The term "aryl" refers to 6-10 membered mono- or polycyclic aromatic carbocycles, for example, phenyl and naphthyl. The term "aryl" includes aryl groups that are optionally partially or fully halogenated.

The term "halo" refers to a halogen radical selected from fluoro, chloro, bromo or iodo. Representative halo groups of the invention are fluoro, chloro and bromo.

The term "heterocycle" or "heterocyclyl" refers to a stable 4-8 membered (but preferably, 5 or 6 membered) monocyclic or 8-11 membered bicyclic heterocycle radical which may be either saturated or unsaturated, and is non-aromatic, and may be optionally partially or fully halogenated. Each heterocycle consists of carbon atoms and from 1 to 4 heteroatoms chosen from nitrogen, oxygen and sulfur. The heterocycle may be attached by any atom of the cycle, which results in the creation of a stable structure. Examples of "heterocycle" include radicals such as pyrrolinyl, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, pyranyl, thiopyranyl, piperazinyl, indolinyl, tetrahydroquinoline, tetrahydroisoquinoline, azetidiny, oxetanyl, dihydrobenzofuranyl, dihydrobenzothienyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrofuranly, hexahydropyrimidinyl, hexahydropyridazinyl, 1,4,5,6-tetrahydropyrimidin-2-ylamine, dihydro-oxazolyl, 1,2-thiazinanyl-1,1-dioxide, 1,2,6-thiadiazinanyl-1,1-dioxide, isothiazolidinyl-1,1-dioxide and imidazolidinyl-2,4-dione.

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The term "heteroaryl" refers to a stable 5-8 membered (but preferably, 5 or 6 membered) monocyclic or 8-11 membered bicyclic aromatic heterocycle radical, each optionally partially or fully halogenated. Each heterocycle consists of carbon atoms and from 1 to 4 heteroatoms chosen from nitrogen, oxygen and sulfur. The heterocycle may be attached
5 by any atom of the cycle, which results in the creation of a stable structure. Examples of "heteroaryl" include radicals such as furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolizinyl, indolyl, isoindolyl, benzofuranyl, benzothienyl, indazolyl, benzimidazolyl, benzothiazolyl,
10 benzoxazolyl, benzisoxazolyl, benzisothiazolyl, purinyl, quinolizinyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, naphthyridinyl, pteridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl and phenoxazinyl,

Each aryl or heteroaryl unless otherwise specified includes its partially or fully
15 hydrogenated derivative. For example, quinolinyl may include decahydroquinolinyl and tetrahydroquinolinyl, naphthyl may include its hydrogenated derivatives such as tetrahydronaphthyl. Other partially or fully hydrogenated derivatives of the aryl and heteroaryl compounds described herein will be apparent to one of ordinary skill in the art.

20 The terms "heterocycle", "heteroaryl" or "aryl", when associated with another moiety, unless otherwise specified shall have the same meaning as given above. For example, "aroyl" refers to aryl linked to a carbonyl group (C=O).

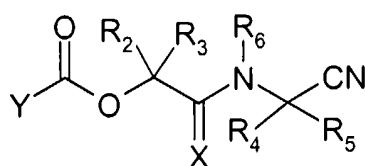
The phrase "C6-C10 bridged bicyclic ring group" means any bicyclic ring group having
25 from 6 to 10 carbon atoms and containing a chemical bridging group, which bicyclic group may also contain one or more double bonds in the rings. Examples of such bicyclic ring groups for this definition of R₄ + R₅ include: aza-bicyclo[3.2.1]octane, aza-bicyclo[2.2.1]heptane, aza-bicyclo[2.2.2]octane, aza-bicyclo[3.2.2]nonane, aza-bicyclo[2.1.1]hexane, aza-bicyclo[3.1.1]heptane, aza-bicyclo[3.3.2]decane and 2-oxa and
30 2-thia-5-aza-bicyclo[2.2.1]heptane.

As used herein above and throughout this application, "nitrogen" and "sulfur" include any oxidized form of nitrogen and sulfur and the quaternized form of any basic nitrogen, including protonated species and quaternary ammonium salt forms.

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In the broadest generic aspect, the invention provides novel compounds of the formula (I):

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(I)

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wherein:

Y is R₁, R₁O-, R₁S-, (R₁)₂N-, (R₁)₃C-;

- 20 Each R₁ is independently hydrogen, C1-10 alkyl, C3-8 cycloalkyl, aryl, benzyl, tetrahydronaphthyl, indenyl, indanyl, C1-10alkylsulfonylC1-10alkyl, C3-8cycloalkylsulfonylC1-10alkyl, arylsulfonylC1-10alkyl, a heterocyclyl or heteroaryl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolynyl, pyranyl, tetrahydropyranyl, tetrahydrothiopyranyl, thiopyranyl, furanyl, 25 tetrahydrofuranlyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, tetrazolyl, pyrazolyl, indolyl, benzofuranlyl, benzothienyl, dihydrobenzofuranlyl, dihydrobenzothienyl, benzimidazolyl, benzothiazolyl, benzisoxazolyl, benzisothiazolyl, quinolinyl, tetrahydroquinolinyl,

isoquinolinyl, tetrahydroisoquinolinyl, quinazolinyl, tetrahydroquinazolinyl,
benzoxazolyl, 2*H*-benzo[e][1,3]oxazine and quinoxalinyl,
wherein each R₁ is optionally substituted by one or more R_a; or R₁ is R_a or R_b;

5 Each R_a is independently hydrogen, C1-10 alkyl, C3-8 cycloalkyl, aryl,
tetrahydronaphthyl, indenyl, indanyl, a heterocycle or heteroaryl selected from the
group consisting of pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl,
piperazinyl, indolinyl, furanyl, thienyl, pyrrolyl, oxazolyl, dihydro-oxazolyl,
thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl,
10 indolyl, benzofuranyl, benzothienyl, dihydrobenzofuranyl, dihydrobenzothienyl,
benzimidazolyl, benzothiazolyl, benzoxazolyl, benzisoxazolyl, quinolinyl,
isoquinolinyl, quinazolinyl, and quinoxalinyl, C1-10 alkoxy, C1-10alkanoyl, C1-
10alkanoyloxy, aryloxy, benzyloxy, aroyl, C1-10 alkoxycarbonyl,
aryloxycarbonyl, aroyloxy, heterocyclyloxy, heterocyclyl-C1-6alkoxy,
15 heteroaryloxy or heteroaryl-C1-6alkoxy, wherein the heterocyclyl or
heteroaryloxy moiety is selected from those described in this paragraph,
carbamoyl wherein the nitrogen atom may be independently mono or di-
substituted by C1-10 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl,
thiomorpholinyl, piperazinyl, indolinyl, furanyl, thienyl, pyrrolyl, oxazolyl,
20 thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl,
indolyl, benzofuranyl, benzothienyl, dihydrobenzofuranyl, dihydrobenzothienyl,
benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or
quinoxalinyl,
or R_a is C1-10 mono- or dialkyl amino, C1-10 alkanoylamino, aroylamino, C1-10
25 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone,
arylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido
wherein either nitrogen atom may be independently substituted by one or more
C1-10 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl,
piperazinyl, indolinyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl,
30 triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl,

benzothienyl, dihydrobenzofuranyl, dihydrobenzothienyl, benzimidazolyl,
benzothiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or quinoxalinyl,
or R_a is C1-10 alkoxy-carbonylamino, aryloxy-carbonylamino,
heterocyclyl-carbonylamino, heteroaryl-carbonylamino, C1-10 alkyl-carbamoyloxy,
5 aryl-carbamoyloxy, C1-10 alkyl-sulfonylamino, aryl-sulfonylamino, C1-10
alkyl-aminosulfonyl, aryl-aminosulfonyl, amino wherein the nitrogen atom may be
independently mono or di-substituted by C1-10 alkyl, aryl, pyrrolidinyl,
piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, thienyl,
pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl,
10 pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, dihydrobenzofuranyl,
dihydrobenzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl,
quinazolinyl or quinoxalinyl,
or R_a is halogen, hydroxy, oxo, carboxy, cyano, nitro, carboxamide, amidino or
guanidino,
15 wherein R_a may be further optionally substituted by one or more R_b;

R_b is a C1-6 saturated or unsaturated alkyl group wherein one or more
carbon atoms are optionally replaced by O, N, S(O), S(O)₂ or S and
wherein said alkyl group is optionally independently substituted with one
20 or two oxo groups, and/or one or more: -NH₂, C1-4 alkyl, aryl,
pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl,
indolinyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl,
triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl,
benzofuranyl, benzothienyl, dihydrobenzofuranyl, dihydrobenzothienyl,
25 benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or
quinoxalinyl;

or R_b is C3-6 cycloalkyl, C1-6 alkoxy, aryl, aryloxy, benzyloxy, halogen,
hydroxy, oxo, carboxy, cyano, nitro, mono-C1-5alkylamino, di-C1-
30 5alkylamino, carboxamide, amidino or guanidino;

R₂ and R₃ are each independently a hydrogen, C3-8 cycloalkyl, arylC1-5alkyl, aryl, or a C1-10 saturated or unsaturated alkyl group wherein one or more C atoms are optionally replaced by O, NH, S(O), S(O)₂ or S and wherein said alkyl group is optionally independently substituted with one or two oxo groups, and/or one or more: -NH₂, C₁₋₄ 5 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, pyranyl, thiopyranyl, furanyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, dihydrobenzofuranyl, dihydrobenzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, quinazolinyl, benzoxazolyl or quinoxalinyl; wherein each R₂ and R₃ is 10 independently optionally substituted by one or more R_c; or R₂ and R₃ are each independently R_c;

R_c is C1-10 alkyl, C3-8 cycloalkyl, aryl, indanyl, indenyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, bicyclo[4.1.0]heptanyl, bicyclo[3.1.0]hexanyl, 15 bicyclo[1.1.1]pentanyl, spiro[2.5]octanyl, cubanyl, tetrahydronaphthyl, decahydronaphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, tetrahydrofuranyl, pyranyl, tetrahydropyranyl, tetrahydrothiopyranyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, 20 dihydrobenzofuranyl, octahydrobenzofuranyl, benzofuranyl, benzothienyl, dihydrobenzofuranyl, dihydrobenzothienyl, benzimidazolyl, benzothiazolyl, tetrahydroquinolinyl, quinolinyl, tetrahydroisoquinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, C1-10 alkoxy, aryloxy, C1-10 alkanoyl, aroyl, C1-10 alkoxy carbonyl, aryloxy carbonyl, C1-10 alkanoyloxy, aroyloxy, carbamoyl 25 wherein the nitrogen atom may be independently mono or di-substituted by C1-10 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, dihydrobenzofuranyl, dihydrobenzothienyl, benzimidazolyl, benzothiazolyl, 30 quinolinyl, isoquinolinyl, quinazolinyl or quinoxalinyl,

or R_c is C1-10 alkanoylamino, aroylamino, C1-10 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, arylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-10 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, dihydrobenzofuranyl, dihydrobenzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, quinazolinyll or quinoxalinyll,

or R_c is C1-10 alkoxy-carbonylamino, aryloxy-carbonylamino, C1-10 alkyl-carbamoyloxy, aryl-carbamoyloxy, C1-10 alkyl-sulfonylamino, aryl-sulfonylamino, C1-10 alkyl-aminosulfonyl, aryl-aminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-10 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, dihydrobenzofuranyl, dihydrobenzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, quinazolinyll or quinoxalinyll,

or R_c is halogen, hydroxy, oxo, carboxy, cyano, nitro, amidino or guanidino;

Each R_c may be further optionally substituted by one or more R_d;

R_d is C1-5 alkyl, C3-6 cycloalkyl, aryl, arylC1-5alkyl, C1-5 alkoxy, aryloxy, arylC1-5alkoxy, aroyl, amino, halogen, hydroxy, oxo, carboxy, cyano, nitro, amidino or guanidino; or

R₂ and R₃ together with the carbon they are attached optionally form a nonaromatic 3-10 membered mono- or bicyclic optionally partially unsaturated cycloalkyl or a 3-10 membered mono- or bicyclic heterocycle each in turn optionally substituted by one or more R_c as described hereinabove;

R₄ and R₅ are each independently a hydrogen, or a C1-10 saturated or unsaturated alkyl group wherein one or more C atoms are optionally replaced by O, NH, S(O), S(O)₂ or S

and wherein said alkyl group is optionally independently substituted with one or two oxo groups, and/or one or more: -NH₂, C₁₋₄ alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, pyranyl, thiopyranyl, furanyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, 5 benzofuranyl, benzothienyl, dihydrobenzofuranyl, dihydrobenzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, quinazoliny, benzoxazolyl or quinoxaliny; or R₄ and R₅ are each independently C1-10alkoxyC1-10alkyl, C1-10alkylaminoC1-10alkyl, C1-10alkylthioC1-10alkyl wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, C3-8 cycloalkyl, aryl, tetrahydronaphthyl, indenyl, indanyl, C3-10 7cycloalkylsulfonylC1-5alkyl, arylsulfonylC1-5alkyl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, pyranyl, tetrahydropyranyl, thiopyranyl, tetrahydrothiopyranyl, furanyl, tetrahydrofuranyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridiziny, tetrazolyl, triazolyl, pyrazolyl, indolyl, benzofuranyl, benzothienyl, 15 dihydrobenzofuranyl, dihydrobenzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl, tetrahydroquinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, quinazoliny, tetrahydroquinazoliny, benzoxazolyl and quinoxaliny, C1-10alkanoyl, aroyl, C1-10alkoxycarbonyl, arylC1-5alkoxycarbonyl, aryloxycarbonyl, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-10 alkyl, aryl, 20 pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, dihydrobenzofuranyl, dihydrobenzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, quinazoliny or quinoxaliny, 25 or R₄ and R₅ are each independently C1-10 alkanoylamino, aroylamino, C1-10 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, arylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-10 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, thienyl, pyrrolyl, oxazolyl, 30 thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl,

benzofuranyl, benzothienyl, dihydrobenzofuranyl, dihydrobenzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or quinoxaliny, or R₄ and R₅ are each independently C1-10 alkoxy-carbonylamino, aryloxy-carbonylamino, C1-10 alkyl-carbamoyloxy, aryl-carbamoyloxy, C1-10 alkyl-sulfonylamino, aryl-sulfonylamino, C1-10 alkyl-aminosulfonyl, aryl-aminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-10 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, dihydrobenzofuranyl, dihydrobenzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or quinoxaliny, or R₄ and R₅ are each independently halogen, hydroxy, carboxy, cyano, nitro, carboxamide, amidino or guanidino; wherein each R₄ and R₅ may be further optionally independently substituted by one or more R_e;

or R₄ and R₅ together with the carbon they are attached to optionally form a heterocyclic ring said heterocyclic ring being selected from:

azepanyl, piperidinyl, pyrrolidinyl, azetidiny, oxepanyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrofuranyl, oxetanyl, azocanyl, oxocanyl, 1,3-diazocanyl, 1,4-diazocanyl, 1,5-diazocanyl, 1,3-dioxocanyl, 1,4-dioxocanyl, 1,5-dioxocanyl, 1,3-oxazocanyl, 1,4-oxazocanyl, 1,5-oxazocanyl, 1,3-diazepanyl, 1,4-diazepanyl, 1,3-dioxepanyl, 1,4-dioxepanyl, 1,3-oxazepanyl, 1,4-oxazepanyl, 1,2-thiazocanyl-1,1-dioxide, 1,2,8-thiadiazocanyl-1,1-dioxide, 1,2-thiazepanyl-1,1-dioxide, 1,2,7-thiadiazepanyl-1,1-dioxide, tetrahydrothiophenyl, hexahydropyrimidinyl, hexahydropyridazinyl, piperazinyl, 1,4,5,6-tetrahydropyrimidinyl, pyrazolidinyl, dihydro-oxazolyl, dihydrothiazolyl, dihydroimidazolyl, isoxazoliny, oxazolidinyl, 1,2-thiazinanyl-1,1-dioxide, 1,2,6-thiadiazinanyl-1,1-dioxide, isothiazolidinyl-1,1-dioxide, imidazolidinyl-2,4-dione, imidazolidinyl, morpholinyl, dioxanyl, tetrahydropyridinyl, thiomorpholinyl, thiazolidinyl, dihydropyranyl, dithianyl, decahydro-quinolinyl, decahydro-isoquinolinyl, 1,2,3,4-tetrahydro-quinolinyl, indolinyl, octahydro-quinoliziny, 30

dihydro-indoliziny, octahydro-indoliziny, octahydro-indoly, decahydroquinazoliny, decahydroquinoxaliny, 1,2,3,4-tetrahydroquinazoliny or 1,2,3,4-tetrahydroquinoxaliny;

or R₄ and R₅ together with the carbon they are attached to optionally form a C₆-C₁₀
5 bridged bicyclic ring group wherein one or more carbon atoms are optionally replaced by a heteroatom chosen from N, O, S, S(O) or S(O)₂;

or R₄ and R₅ together with the carbon they are attached to optionally form a carbocyclic ring group, said carbocyclic ring group being selected from:

10 cyclopropanyl, cyclobutanyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, cyclooctanyl, cyclononanyl, cyclodecanyl, cubanyl, bicyclo[1.1.0]propanyl, bicyclo[2.1.0]butanyl, bicyclo[3.1.0]hexanyl, bicyclo[4.1.0]heptanyl, bicyclo[5.1.0]octanyl, bicyclo[2.2.0]hexanyl, bicyclo[3.2.0]heptanyl, bicyclo[4.2.0]octanyl, bicyclo[5.2.0]nonanyl, bicyclo[3.3.0]octanyl, bicyclo[4.3.0]nonanyl,
15 bicyclo[5.3.0]decanyl, bicyclo[4.4.0]decanyl, bicyclo[5.4.0]undecanyl, bicyclo[1.1.1]pentanyl, bicyclo[2.1.1]hexanyl, bicyclo[3.1.1]heptanyl, bicyclo[4.1.1]octanyl, bicyclo[5.1.1]nonanyl, bicyclo[2.2.1]heptanyl, bicyclo[3.2.1]octanyl, bicyclo[4.2.1]nonanyl, bicyclo[5.2.1]decanyl, bicyclo[2.2.2]octanyl, bicyclo[3.2.2]nonanyl, bicyclo[4.2.2]decanyl,
20 bicyclo[5.2.2]undecanyl, bicyclo[3.3.2]decanyl, bicyclo[4.3.2]undecanyl, bicyclo[5.3.2]dodecanyl, bicyclo[3.3.3]undecanyl, bicyclo[4.3.3]dodecanyl, bicyclo[5.3.3]tridecanyl;

25 each of the above ring groups formed by the combination of R₄ and R₅ being optionally substituted with one or more R_e; or R₄ and R₅ are each independently R_e;

R_e is a C₁-10 saturated or unsaturated alkyl group wherein one or more C atoms
30 are optionally replaced by O, NH, S(O), S(O)₂ or S and wherein said alkyl group is optionally independently substituted with one or two oxo groups, and/or one or

more: -NH₂, C₁₋₄ alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl,
thiomorpholinyl, piperazinyl, indolinyl, pyranyl, thiopyranyl, furanyl, thienyl,
pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl,
pyrazinyl, indolyl, benzofuranyl, benzothienyl, dihydrobenzofuranyl,
5 dihydrobenzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl,
quinazoliny, benzoxazolyl or quinoxaliny;
or R_e is a C1-10alkoxy, C1-10alkoxyC1-10alkyl, C1-10alkylaminoC1-10alkyl,
C1-10alkylthioC1-10alkyl wherein the sulfur atom may be oxidized to a sulfoxide
or sulfone, C3-8 cycloalkyl, C3-8 cycloalkyloxy, aryl, tetrahydronaphthyl,
10 indenyl, indanyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl,
piperazinyl, indolinyl, thiopyranyl, tetrahydrothiopyranyl, pyranyl,
tetrahydropyranyl, tetrahydrofuran, furanyl, thienyl, pyrrolyl, oxazolyl,
thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl,
indolyl, benzofuranyl, benzothienyl, dihydrobenzofuranyl, dihydrobenzothienyl,
15 benzimidazolyl, benzothiazolyl, benzoxazolyl, benzisoxazolyl, quinolinyl,
isoquinolinyl, quinazoliny, quinoxaliny, C1-10alkanoyl, aroyl, C1-
10alkanoyloxy, aryloxy, benzyloxy, C1-10 alkoxy carbonyl, arylC1-
3alkoxy carbonyl, aryloxy carbonyl, aroyloxy, carbamoyl wherein the nitrogen
atom may be independently mono or di-substituted by C1-10 alkyl, aryl,
20 pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl,
furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl,
pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl,
dihydrobenzofuranyl, dihydrobenzothienyl, benzimidazolyl, benzothiazolyl,
quinolinyl, isoquinolinyl, quinazoliny or quinoxaliny,
25 or R_e is ureido wherein either nitrogen atom may be independently substituted by
C1-10 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl,
piperazinyl, indolinyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl,
triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl,
benzothienyl, dihydrobenzofuranyl, dihydrobenzothienyl, benzimidazolyl,
30 benzothiazolyl, quinolinyl, isoquinolinyl, quinazoliny or quinoxaliny,

or R_e is amino wherein the nitrogen atom may be independently mono or di-substituted by C1-10 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, dihydrobenzofuranyl, dihydrobenzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or quinoxalinyl,
5 or R_e is halogen, hydroxy, oxo, carboxy, cyano, nitro, carboxamide, amidino or guanidino,
10 wherein R_e may be further optionally substituted by one or more R_f;

R_f is C1-5 alkyl, C3-6 cycloalkyl, tolylsulfonyl, C1-5 alkoxy, aryl, aryloxy, benzyloxy, halogen, hydroxy, oxo, carboxy, cyano, nitro, carboxamide, amidino or guanidino;
15 or R_f is aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, dihydrobenzofuranyl, dihydrobenzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or quinoxalinyl,
20 or R_f is amino wherein the nitrogen atom may be independently mono or di-substituted by C1-10 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, dihydrobenzofuranyl, dihydrobenzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or quinoxalinyl;
25 or R_f is a C1-10 saturated or unsaturated alkyl group wherein one or more C atoms are optionally replaced by O, NH, S(O), S(O)₂ or S and wherein said alkyl group is optionally independently substituted with one or two
30 oxo groups, and/or one or more: -NH₂, C₁₋₄ alkyl, aryl, pyrrolidinyl,

5 piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, pyranyl, thiopyranyl, furanyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, dihydrobenzofuranyl, dihydrobenzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, quinazolinyl, benzoxazolyl or quinoxalinyl;

R₆ is hydrogen, hydroxy, C1-3 alkyl, or C3-6 cycloalkyl;

10 X is O or S; or

the pharmaceutically acceptable derivatives thereof;

with the provisos that:

- (1) when R₂ is hydrogen; and R₃ is hydrogen, propyl or phenyl; and R₄ is hydrogen, methyl, ethyl or benzyl; and R₅ is alkoxy carbonyl; and R₆ is hydrogen; then Y is not methyl or chloromethyl;
- 15 (2) when R₂ is hydrogen; and R₃ is phenyl; and R₄ is phenyl; and R₅ is trifluoromethyl; and R₆ is hydrogen; then Y is not methyl;
- (3) when R₂ is hydrogen or alkyl; and R₃ is hydrogen, alkyl or benzyl; and R₄ is hydrogen, alkyl or cycloalkyl; and R₅ is hydrogen, alkyl or cycloalkyl; or R₄ and R₅ together with the carbon atom they are attached to form cyclopentanyl, cyclohexanyl or cycloheptanyl; and R₆ is hydrogen; then Y is not methyl or phenyl substituted by optionally substituted pyrimidinyl.
- 20

25

In another embodiment of the invention, there are provided novel compounds of the formula (I) as described immediately above, and wherein:

Y is R₁, R₁O-, (R₁)₂N- or (R₁)₃C-;

30

Each R₁ is independently hydrogen, C1-7 alkyl, C3-7 cycloalkyl, phenyl, naphthyl, benzyl, tetrahydronaphthyl, C1-7alkylsulfonylC1-7alkyl, C3-7cycloalkylsulfonylC1-7alkyl, arylsulfonylC1-7alkyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, pyranyl, thiopyranyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, isoxazolyl, pyrimidinyl, pyrazinyl, pyridazinyl, indolyl, quinolinyl, isoquinolyl, tetrahydroisoquinolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzothiazolyl, benzoisoxazolyl, benzoisothiazolyl, benzoxazolyl, or 2*H*-benzo[e][1,3]oxazine; wherein each R₁ is optionally substituted by one or more R_a; or R₁ is R_a or R_b;

10

Each R_a is independently hydrogen, C1-7 alkyl, C3-6 cycloalkyl, phenyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl, dihydro-oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, C1-7 alkoxy, C1-7alkanoyl, C1-7alkanoyloxy, aryloxy, benzyloxy, aroyl, C1-7 alkoxy carbonyl, aryloxy carbonyl, aroyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-7 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or quinoxalinyl, or R_a is C1-7 alkanoylamino, aroylamino, C1-7 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, arylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-7 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or quinoxalinyl,

25

30

or R_a is C1-7 alkoxycarbonylamino, aryloxy carbonylamino, heterocyclyl carbonylamino, heteroaryl carbonylamino, C1-7 alkyl carbamoyloxy, aryl carbamoyloxy, C1-7 alkyl sulfonylamino, aryl sulfonylamino, C1-7 alkyl aminosulfonyl, aryl aminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-7 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or quinoxalinyl,
5 or R_a is halogen, hydroxy, oxo, carboxy, cyano, nitro, carboxamide, amidino or guanidino,
10 wherein R_a may be further optionally substituted by one or more R_b;

R_b is a C1-6 saturated alkyl group wherein one or two carbon atoms are optionally replaced by O or S and wherein said alkyl group is optionally independently substituted with one or two oxo groups and/or one or more: C1-4 alkyl, aryl, piperidinyl, morpholinyl, thiomorpholinyl or piperazine;

or R_b is C3-6 cycloalkyl, aryl, C1-6 alkoxy, aryloxy, benzyloxy, halogen, hydroxy, oxo, carboxy, cyano, nitro, carboxamide, amidino or guanidino;

R₂ is hydrogen or methyl or ethyl;

R₃ is a hydrogen, C2-5 alkylene, C3-7 cycloalkyl, aryl C1-3 alkyl, aryl or a C1-6 saturated alkyl group wherein one or two of the C atoms are optionally replaced by O, NH or S; wherein R₃ is optionally substituted by one or more R_c; or R₃ is R_c;

R_c is C1-5 alkyl, C3-7 cycloalkyl, aryl, indanyl, indenyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, bicyclo[4.1.0]heptanyl, bicyclo[3.1.0]hexanyl, bicyclo[1.1.1]pentanyl, spiro[2.5]octanyl, cubanyl, 1,2,3,4-tetrahydronaphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl,

5 furanyl, tetrahydrofuranyl, pyranal, tetrahydropyranal, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, quinazoliny, quinoxaliny, C1-5 alkoxy, aryloxy, C1-5
10 alkanoyl, aroyl, C1-5 alkoxy-carbonyl, aryloxy-carbonyl, C1-5 alkanoyloxy, aroyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-5 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, quinazoliny or quinoxaliny,
15 or R_c is C1-5 alkanoylamino, aroylamino, C1-5 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, arylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-5 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, quinazoliny or quinoxaliny,
20 or R_c is C1-5 alkoxy-carbonylamino, aryloxy-carbonylamino, C1-5 alkylcarbamoyloxy, arylcarbamoyloxy, C1-5 alkylsulfonylamino, arylsulfonylamino, C1-5 alkylaminosulfonyl, arylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-5 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, quinazoliny or quinoxaliny,
25 or R_c is halogen, hydroxy, oxo, carboxy, cyano, nitro, amidino or guanidino;
30 Each R_c may be further optionally substituted by one or more R_d;

R_d is C1-5 alkyl, C3-6 cycloalkyl, aryl, arylC1-4-alkyl, C1-5 alkoxy, aryloxy, arylC1-5alkoxy, aroyl, halogen, hydroxy, oxo or cyano;

or R₂ and R₃ together with the carbon they are attached optionally form a nonaromatic 5-7 membered cycloalkyl or a 5-7 membered heterocycle, each optionally substituted by R_c as described hereinabove;

R₄ and R₅ are each independently hydrogen, or a C1-8 saturated alkyl group wherein one or two C atoms are optionally replaced by O, S(O), S(O)₂ or S and wherein said alkyl group is optionally substituted with one or two oxo groups and/or one or more: aryl, indolyl or indolinyl;

or R₄ and R₅ are each independently C1-8alkoxyC1-8alkyl, C1-8alkylaminoC1-8alkyl, C1-8alkylthioC1-8alkyl wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, C3-7 cycloalkyl, aryl, tetrahydronaphthyl, indanyl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, pyranyl, tetrahydropyranyl, thiopyranyl, tetrahydrothiopyranyl, furanyl, tetrahydrofuranlyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, tetrazolyl, triazolyl, pyrazolyl, indolyl, benzofuranlyl, benzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, quinazoliny, benzoxazolyl and quinoxaliny, C1-7alkanoyl, aroyl, C1-7 alkoxy carbonyl, arylC1-4alkoxy carbonyl, aryloxy carbonyl, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-7 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranlyl, benzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, quinazoliny or quinoxaliny,

or R₄ and R₅ are each independently C1-7 alkanoylamino, aroylamino, C1-7 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, arylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-7 alkyl, aryl, pyrrolidinyl, piperidinyl,

morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or quinoxalinyl,

5 or R₄ and R₅ are each independently C1-7 alkoxy-carbonylamino, aryloxy-carbonylamino, C1-7 alkyl-carbamoyloxy, aryl-carbamoyloxy, C1-7 alkyl-sulfonylamino, aryl-sulfonylamino, C1-7 alkyl-aminosulfonyl, aryl-aminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-7 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl,
10 pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or quinoxalinyl,
or R₄ and R₅ are each independently halogen, hydroxy, carboxy, cyano, nitro or carboxamide,

15 wherein each R₄ and R₅ may be further optionally independently substituted by one or more R_e;

or R₄ and R₅ together with the carbon they are attached optionally form a heterocyclic ring said heterocyclic ring being selected from:

20 piperidinyl, pyrrolidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, azetidiny, azepanyl, oxepanyl, tetrahydrofuranyl, oxetanyl, hexahydropyrimidinyl, hexahydropryridazinyl, piperazinyl, 1,4,5,6-tetrahydropyrimidinyl, octahydro-indoliziny, octahydro-quinoliziny, decahydro-quinoliny, 1,2,3,4-tetrahydro-quinoliny, dihydro-oxazolyl, 1,2-thiazinanyl-1,1-dioxide, 1,2,6-thiadiazinanyl-1,1-dioxide, isothiazolidinyl-1,1-dioxide,
25 imidazolidinyl, pyrazolidinyl or

R₄ and R₅ together with the carbon atom they are attached to form a cyclopropanyl, cyclobutanyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, or a bridged bicyclo group chosen from aza-bicyclo[3.2.1]octane, aza-bicyclo[2.2.1]heptane, aza-
30 bicyclo[2.2.2]octane, aza-bicyclo[3.2.2]nonane, aza-bicyclo[2.1.1]hexane, aza-

bicyclo[3.1.1]heptane, aza-bicyclo[3.3.2]decane and 2-oxa or 2-thia-5-aza-bicyclo[2.2.1]heptane;
each ring being substituted with one or more R_e;

5

R_e is C1-8 saturated alkyl group wherein one or two of the C atoms are optionally replaced by O, S(O), S(O)₂ or S, and wherein said alkyl group is optionally independently substituted with one or two oxo groups and/or one or more: C₁₋₄alkyl or aryl;

10

or R_e is C1-7alkoxy, C1-7alkoxyC1-7alkyl, C1-7alkylaminoC1-7alkyl, C1-7alkylthioC1-7alkyl wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, C3-7 cycloalkyl, aryl, tetrahydronaphthyl, indanyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, thiopyranyl, tetrahydrothiopyranyl, tetrahydropyranyl, tetrahydrofuranyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, quinolinyl, isoquinolinyl, quinazoliny, quinoxaliny, C1-5 alkanoyl, aroyl, C1-5alkanoyloxy, aryloxy, benzyloxy, C1-5 alkoxy carbonyl, aryloxy carbonyl, aroyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-5 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, quinazoliny or quinoxaliny,

15

20

25

or R_e is ureido wherein either nitrogen atom may be independently substituted by C1-5 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, quinazoliny or quinoxaliny,

30

or R_e is amino wherein the nitrogen atom may be independently mono or di-substituted by C1-5 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl,

thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or quinoxalinyl,

5 or R_e is halogen, hydroxy, oxo, carboxy, cyano, nitro, carboxamide, amidino or guanidino,

wherein R_e may be further optionally substituted by one or more R_f;

10 R_f is methyl, ethyl, t-butyl, tolylsulfonyl, C1-3 alkoxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, naphthyl, phenoxy, benzyloxy, fluoro, chloro, bromo, hydroxy, oxo, carboxy, cyano, nitro amino or carboxamide;

15 R_g is hydrogen or methyl;

and

X is O.

In yet another embodiment of the invention, there are provided novel compounds of the
20 formula (I) as described immediately above, and wherein:

wherein:

25 Each R₁ is independently hydrogen, C1-5 alkyl, C3-6 cycloalkyl, phenyl, benzyl, naphthyl, C1-3alkylsulfonylC1-3alkyl, C3-6cycloalkylsulfonylC1-3alkyl, arylsulfonylC1-3alkyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, isoxazolyl, pyrimidinyl, pyrazinyl, pyridazinyl, indolyl, quinolinyl, tetrahydroisoquinolyl,
30 benzofuranyl, benzthienyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, 2H-

benzo[e][1,3]oxazine; wherein each R₁ is optionally substituted by one or more R_a; or R₁ is R_a or R_b;

Each R_a is independently hydrogen, C1-3 alkyl, cyclopropyl, cyclopentyl,
5 cyclohexyl, phenyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl,
thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl, dihydro-oxazolyl,
thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, benzimidazolyl, benzothiazolyl,
benzoxazolyl, C1-3 alkoxy, C1-3alkanoyl, C1-3alkanoyloxy, aryloxy, benzyloxy,
aroyl, C1-3 alkoxy carbonyl, aryloxy carbonyl, aroyloxy, carbamoyl wherein the
10 nitrogen atom may be independently mono or di-substituted by C1-3 alkyl, aryl,
pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, thienyl,
oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, benzimidazolyl or
benzothiazolyl,
or R_a is C1-3 alkanoylamino, aroylamino, C1-3 alkylthio wherein the sulfur atom
15 may be oxidized to a sulfoxide or sulfone, arylthio wherein the sulfur atom may
be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be
independently substituted by C1-3 alkyl, aryl, pyrrolidinyl, piperidinyl,
morpholinyl, thiomorpholinyl or piperazinyl,
or R_a is C1-5 alkoxy carbonylamino, aryloxy carbonylamino,
20 heterocyclyl carbonylamino, heteroaryl carbonylamino, C1-5 alkyl carbamoyloxy,
aryl carbamoyloxy, C1-5 alkyl sulfonylamino, aryl sulfonylamino, C1-5
alkyl aminosulfonyl, aryl aminosulfonyl, amino wherein the nitrogen atom may be
independently mono or di-substituted by C1-6 alkyl, aryl, pyrrolidinyl,
piperidinyl, morpholinyl, thiomorpholinyl or piperazinyl,
25 or R_a is halogen, hydroxy, oxo, carboxy, cyano, nitro, carboxamide, amidino or
guanidino,
wherein R_a may be further optionally substituted by one or more R_b;

R_b is a C1-6 saturated alkyl group wherein one or two carbon atoms are optionally
30 replaced by O or S and wherein said alkyl group is optionally independently

substituted with an oxo group and/or one or more: C1-4 alkyl, aryl, piperidinyl, morpholinyl, thiomorpholinyl or piperazine;

5 or R_b is C3-6 cycloalkyl, aryl, C1-3 alkoxy, aryloxy, benzyloxy, halogen, hydroxy, oxo, carboxy, cyano, nitro, carboxamide, amidino or guanidino;

R₂ is hydrogen or methyl;

10 R₃ is hydrogen, C2-5alkylene, C3-6 cycloalkyl or arylC1-2alkyl, phenyl, naphthyl, or a C1-6 saturated alkyl group wherein one or two of the C atoms are optionally replaced by O, NH or S; wherein R₃ is optionally substituted by one or more R_c; or R₃ is R_c;

R_c is C1-4 alkyl, C5-6 cycloalkyl, phenyl, naphthyl, indanyl,
15 bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, bicyclo[4.1.0]heptanyl,
bicyclo[3.1.0]hexanyl, bicyclo[1.1.1]pentanyl, spiro[2.5]octanyl, cubanyl, 1,2,3,4-
tetrahydronaphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl,
indolinyl, furanyl, tetrahydrofuranyl, pyranyl, tetrahydropyranyl, thienyl, pyrrolyl,
oxazolyl, thiazolyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl,
20 indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl,
isoquinolinyl, quinazoliny, quinoxaliny, C1-4 alkoxy, phenoxy, naphthyloxy,
C1-3 alkanoyl, benzoyl, C1-3 alkoxy-carbonyl, phenoxy-carbonyl, C1-3
alkanoyloxy, benzoyloxy, carbamoyl wherein the nitrogen atom may be
independently mono or di-substituted by C1-5 alkyl or aryl,
25 or R_c is C1-3 alkanoylamino, benzoylamino, C1-3 alkylthio wherein the sulfur
atom may be oxidized to a sulfoxide or sulfone, phenylthio wherein the sulfur
atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen
atom may be independently substituted by C1-5 alkyl or aryl,
or R_c is C1-3 alkoxy-carbonylamino, aryloxy-carbonylamino, C1-3
30 alkylcarbamoyloxy, arylcarbamoyloxy, C1-3 alkylsulfonylamino,
arylsulfonylamino, C1-3 alkylaminosulfonyl, arylaminosulfonyl, amino wherein

the nitrogen atom may be independently mono or di-substituted by C1-5 alkyl or aryl,

or R_c is halogen, hydroxy, oxo, carboxy, cyano, nitro, amidino or guanidino, wherein each R_c may be further optionally substituted by one or more R_d;

5

R_d is C1-3 alkyl, C3-6 cycloalkyl, phenyl, benzyl, C1-3 alkoxy, phenoxy, phenylC1-3alkoxy, benzoyl, halogen, hydroxy, oxo or cyano;

10 R₂ and R₃ together with the carbon they are attached optionally form a nonaromatic 5-6 membered cycloalkyl or a 5-6 membered heterocycle, each optionally substituted by R_c as described hereinabove;

R₄ and R₅ are each independently hydrogen, or a C1-5 saturated alkyl group wherein one or two C atoms are optionally replaced by O, S(O), S(O)₂ or S and wherein said alkyl group is optionally substituted with one oxo group and/or one or more: phenyl, naphthyl or indolyl;

or R₄ and R₅ are each independently C1-6alkoxyC1-6alkyl, C1-6alkylaminoC1-6alkyl, C1-6alkylthioC1-6alkyl wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, C3-6 cycloalkyl, phenyl, naphthyl, indanyl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, tetrahydropyranyl, tetrahydrothiopyranyl, furanyl, tetrahydrofuranyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl and benzoxazolyl, C1-3alkanoyl, benzoyl, naphthoyl, C1-4 alkoxy carbonyl, arylC1-2alkoxy carbonyl, phenoxy carbonyl, benzoyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-3 alkyl, phenyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl or pyrimidinyl,

or R₄ and R₅ are each independently C1-4 alkanoylamino, aroylamino, C1-4 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, arylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen

atom may be independently substituted by C1-3 alkyl, phenyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl or benzothiazolyl,

5 or R₄ and R₅ are each independently C1-4 alkoxy-carbonylamino, phenoxy-carbonylamino, C1-4 alkyl-carbamoyloxy, phenyl-carbamoyloxy, C1-4 alkyl-sulfonylamino, phenyl-sulfonylamino, C1-3 alkyl-aminosulfonyl, phenyl-aminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-4 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl,
10 oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, benzimidazolyl or benzothiazolyl, or R₄ and R₅ are each independently halogen, hydroxy, carboxy, cyano, nitro or carboxamide,

wherein each R₄ and R₅ may be further optionally independently substituted by one or
15 more R_e;

or R₄ and R₅ together with the carbon they are attached optionally form cyclopropyl, cyclopentanyl, cyclohexanyl, or a heterocyclic ring said heterocyclic ring being selected from: piperidinyl, pyrrolidinyl, azetidyl, tetrahydropyranyl, tetrahydrothiopyranyl,
20 tetrahydrofuranyl, each ring being optionally substituted with one or more R_e;

R_e is C1-5 saturated alkyl group wherein one or two of the C atoms are optionally replaced by O, S(O), S(O)₂ or S, and wherein said alkyl group is optionally independently substituted with one oxo group and/or one or more: C₁₋₄alkyl,
25 phenyl or naphthyl;

or R_e is C1-4 alkoxy, C3-7 cycloalkyl, phenyl, naphthyl, indanyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, tetrahydrothiopyranyl, tetrahydropyranyl, tetrahydrofuranyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzimidazolyl, benzothiazolyl,
30 benzoxazolyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, C1-4 alkanoyl, aroyl, C1-4alkanoyloxy, phenoxy, naphthyloxy, benzyloxy, C1-4

alkoxycarbonyl, phenoxycarbonyl, benzoyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-3 alkyl, phenyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, 5 benzimidazolyl, or benzothiazolyl, or R_e is ureido wherein either nitrogen atom may be independently substituted by C1-3 alkyl, phenyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, benzimidazolyl or benzothiazolyl, 10 or R_e is amino wherein the nitrogen atom may be independently mono or di-substituted by C1-3 alkyl, phenyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, benzimidazolyl or benzothiazolyl, or R_e is halogen, hydroxy, oxo, carboxy, cyano, nitro or carboxamide, 15 wherein R_e may be further optionally substituted by one or more R_f;

R_f is methyl, ethyl, t-butyl, tolylsulfonyl, methoxy, cyclopropyl, cyclopentyl, cyclohexyl, phenyl, phenoxy, benzyloxy, fluoro, chloro, bromo, hydroxy, oxo, carboxy or carboxamide;

20 and
R_g is hydrogen.

In yet still another embodiment of the invention, there are provided novel compounds of the formula (I) as described immediately above, and wherein:

25

Each R₁ is independently hydrogen, C1-5 alkyl, C3-6 cycloalkyl, phenyl, benzyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, 30 indolyl, quinolinyl, tetrahydroisoquinolyl; benzofuranyl, benzthienyl, benzimidazolyl,

benzothiazolyl, benzoxazolyl, 2-*H*-benzo[e][1,3]oxazine ; wherein each R₁ is optionally substituted by one or more R_a; or R₁ is R_a or R_b;

Each R_a is independently C1-3 alkyl, cyclopropyl, cyclohexyl, phenyl,
5 pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, thienyl,
oxazolyl, dihydro-oxazolyl, imidazolyl, pyridinyl, C1-3 alkoxy, C1-3alkanoyl,
C1-3alkanoyloxy, aryloxy, benzyloxy, benzoyl, C1-3 alkoxy-carbonyl,
aryloxy-carbonyl, aryloxy, carbamoyl wherein the nitrogen atom may be
independently mono or di-substituted by C1-3 alkyl, aryl, pyrrolidinyl,
10 piperidinyl, morpholinyl, thiomorpholinyl or piperazinyl,
or R_a is C1-3 alkanoylamino, aroylamino, C1-3 alkylthio wherein the sulfur atom
may be oxidized to a sulfoxide or sulfone, arylthio wherein the sulfur atom may
be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be
independently substituted by C1-3 alkyl, aryl, pyrrolidinyl, piperidinyl,
15 morpholinyl, thiomorpholinyl or piperazinyl,
or R_a is C1-3 alkoxy-carbonylamino, aryloxy-carbonylamino,
heterocyclyl-carbonylamino, C1-3 alkyl-carbamoyloxy, aryl-carbamoyloxy, C1-3
alkyl-sulfonylamino, aryl-sulfonylamino, C1-3 alkyl-aminosulfonyl,
aryl-aminosulfonyl, amino wherein the nitrogen atom may be independently mono
20 or di-substituted by C1-3 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl,
thiomorpholinyl or piperazinyl,
or R_a is halogen, hydroxy, oxo, carboxy, cyano, nitro, carboxamide, amidino or
guanidino,
wherein R_a may be further optionally substituted by one or more R_b;

25

R_b is C1-4 saturated alkyl wherein one carbon atom is optionally replaced
by O and wherein said alkyl group is optionally independently substituted
with an oxo group and/or one or two: C1-4 alkyl, phenyl, morpholinyl or
thiomorpholinyl;

30

or R_b is cyclopropyl, cyclopentyl, cyclohexyl, phenyl, methoxy, ethoxy, n-propoxy, i-propoxy, phenoxy, benzyloxy, fluoro, chloro, bromo, iodo, hydroxy, oxo, carboxy, cyano, nitro or carboxamide;

5 R₂ is hydrogen;

R₃ is a hydrogen, C2-4alkylene, C5-6 cycloalkyl, benzyl or naphthylmethyl, phenyl, or a C1-4 saturated alkyl group wherein one of the C atoms is optionally replaced by O, NH or S; wherein R₃ is optionally substituted by one or more R_c; or R₃ is R_c;

10

R_c is C1-3 alkyl, C3-6 cycloalkyl, phenyl, naphthyl, indanyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, bicyclo[4.1.0]heptanyl, bicyclo[3.1.0]hexanyl, bicyclo[1.1.1]pentanyl, spiro[2.5]octanyl, cubanyl, 1,2,3,4-tetrahydronaphthyl, furanyl, tetrahydropyranyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, indolyl, benzofuranyl, benzothienyl, benzothiazolyl, C1-3 alkoxy, phenoxy, naphthyloxy, C1-2 alkanoyl, benzoyl, C1-2 alkoxy carbonyl, phenoxy carbonyl, C1-2 alkanoyloxy, benzoyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-3 alkyl or aryl,

15

or R_c is C1-2 alkanoylamino, benzoylamino, C1-2 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, phenylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-3 alkyl or aryl,

20

or R_c is C1-2 alkoxy carbonylamino, phenoxy carbonylamino, C1-2 alkyl carbamoyloxy, aryl carbamoyloxy, C1-2 alkyl sulfonylamino,

25

phenyl sulfonylamino, C1-2 alkyl aminosulfonyl, phenyl aminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-3 alkyl or phenyl,

or R_c is halogen, hydroxy, oxo, carboxy or cyano,

30

wherein each R_c may be further optionally substituted by one or more R_d;

R₄ is methyl, cyclopropyl, cyclohexyl, phenyl, benzyl, methoxy, phenoxy, benzyloxy, benzoyl, fluoro, chloro, oxo or cyano;

R₂ and R₃ together with the carbon they are attached optionally form cyclohexyl
5 optionally substituted by R_c as described hereinabove;

R₄ and R₅ are each independently hydrogen, or a C1-5 saturated alkyl group wherein one C atom is optionally replaced by O, S or S(O)₂ and wherein said alkyl group is optionally substituted with phenyl or indolyl;

10

or R₄ and R₅ are each independently C1-5alkoxyC1-5alkyl, C1-5alkylaminoC1-5alkyl, C1-5alkylthioC1-5alkyl wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, C3-6 cycloalkyl, phenyl, naphthyl, indanyl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, tetrahydropyranyl,
15 oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, benzimidazolyl and benzothiazolyl, C1-3alkanoyl, benzoyl, naphthoyl, C1-3 alkoxy-carbonyl, benzyloxycarbonyl, phenoxy-carbonyl, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-3 alkyl, phenyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl or pyrimidinyl,

20

or R₄ and R₅ are each independently C1-3 alkanoylamino, aroylamino, C1-3 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, phenylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-3 alkyl, phenyl, pyrrolidinyl, piperidinyl,
25 morpholinyl, piperazinyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, benzofuranyl, benzothienyl, benzimidazolyl or benzothiazolyl,

or R₄ and R₅ are each independently is C1-3 alkoxy-carbonylamino, phenoxy-carbonylamino, C1-3 alkyl-carbamoyloxy, phenyl-carbamoyloxy, C1-3 alkylsulfonylamino, phenylsulfonylamino, C1-3 alkylaminosulfonyl,
30 phenylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-3 alkyl, phenyl, pyrrolidinyl, piperidinyl, morpholinyl,

thiomorpholinyl, piperazinyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, benzimidazolyl or benzothiazolyl,

or R₄ and R₅ are each independently halogen, hydroxy, oxo, carboxy, cyano or carboxamide, each R₄ and R₅ may be further optionally independently substituted by one
5 or more R_e;

or R₄ and R₅ together with the carbon they are attached optionally form a cyclopropanyl or a heterocyclic ring said heterocyclic ring being selected from:

piperidinyl, pyrrolidinyl and tetrahydropyranyl, each ring being optionally substituted
10 with one or more R_e;

R_e is C1-5 saturated alkyl group wherein one of the C atoms is optionally replaced by O, S(O), S(O)₂ or S, and wherein said alkyl group is optionally independently substituted with one oxo group and/or a C₁₋₄alkyl or phenyl;

15 or R_e is C1-3 alkoxy, C3-7 cycloalkyl, phenyl, naphthyl, indanyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, tetrahydropyranyl, indolyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, C1-3 alkanoyl, aroyl, C1-3alkanoyloxy, phenoxy, benzyloxy, C1-3 alkoxy-carbonyl, phenoxy-carbonyl, benzoyloxy, carbamoyl
20 wherein the nitrogen atom may be independently mono or di-substituted by C1-3 alkyl, phenyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, benzimidazolyl or benzothiazolyl,
or R_e is ureido wherein either nitrogen atom may be independently substituted by C1-3 alkyl, phenyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, oxazolyl,
25 thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, benzimidazolyl or benzothiazolyl,
or R_e is amino wherein the nitrogen atom may be independently mono or di-substituted by C1-3 alkyl, phenyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, benzimidazolyl or benzothiazolyl,
30 or R_e is halogen, hydroxy, oxo, carboxy, cyano or carboxamide,
wherein R_e may be further optionally substituted by one or more R_f;

and

R_f is methyl, cyclopentyl, cyclohexyl, phenyl, tolylsulfonyl, methoxy, phenoxy, benzyloxy, fluoro, chloro, bromo, hydroxy, oxo, carboxy or carboxamide.

5

In yet still another embodiment of the invention, there are provided novel compounds of the formula (I) as described immediately above, and wherein:

Each R₁ is independently a hydrogen, methyl, ethyl, i-propyl, cyclopropyl, cyclopentyl, 10 cyclohexyl, phenyl, benzyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, thiazolyl, quinolyl, tetrahydroisoquinolyl, imidazolyl, pyridinyl, pyrazinyl, or 2*H*-benzo[e][1,3]oxazine; wherein each R₁ is optionally substituted by one or more R_a; or R₁ is R_a or R_b;

15 Each R_a is independently methyl, ethyl, cyclopropyl, phenyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, thienyl, dihyrdo-oxazolyl, imidazolyl, pyridinyl, methoxy, acetyl, acetoxyl, phenoxy, benzyloxy, benzoyl, methoxycarbonyl, phenoxycarbonyl, benzoyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by methyl, ethyl or phenyl, 20 or R_a is acetylamino, benzoylamino, methylthio, phenylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by methyl, ethyl or phenyl, or R_a is C1-3alkoxycarbonylamino, phenoxycarbonylamino, piperazinylcarbonylamino, methylcarbamoxyloxy, phenylcarbamoxyloxy, 25 methylsulfonylamino, phenylsulfonylamino, methylaminosulfonyl, phenylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by methyl, phenyl, or piperidinyl, or R_a is fluoro, chloro, bromo, iodo, hydroxy, oxo, carboxy, cyano, nitro or carboxamide, 30 wherein R_a may be further optionally substituted by one or more R_b;

R_b is C1-4 saturated alkyl group, wherein one carbon atom is optionally replaced by O and wherein said alkyl group is optionally independently substituted with an oxo group and/or a C1-4 alkyl, phenyl or morpholinyl;

5 or R_b is cyclopropyl, phenyl, methoxy, phenoxy, benzyloxy, fluoro, chloro, hydroxy, oxo, carboxy or carboxamide;

R₃ is a hydrogen, C2-4alkylene, C5-6 cycloalkyl, phenyl, benzyl or naphthylmethyl or a C1-4 saturated alkyl group wherein one of the C atoms is optionally replaced by O or S;
10 wherein R₃ is optionally substituted by one or more R_c; or R₃ is R_c;

R_c is methyl, ethyl, n-propyl, i-propyl, C3-6 cycloalkyl, phenyl, indanyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, bicyclo[4.1.0]heptanyl, bicyclo[3.1.0]hexanyl, bicyclo[1.1.1]pentanyl, spiro[2.5]octanyl, cubanyl, 1,2,3,4-
15 tetrahydronaphthyl, thienyl, oxazolyl, thiazolyl, pyridinyl, indolyl, benzofuranyl, benzothienyl, benzothiazolyl, methoxy, ethoxy, phenoxy, acetyl, benzoyl, methoxycarbonyl, phenoxycarbonyl, acetoxy, benzoyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by methyl, ethyl or aryl,
20 or R_c is acetylamino, benzoylamino, methylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, phenylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by methyl, ethyl or aryl,
or R_c is methoxycarbonylamino, phenoxycarbonylamino, methylcarbamoyloxy, 25 phenylcarbamoyloxy, methylsulfonylamino, phenylsulfonylamino, methylaminosulfonyl, phenylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by methyl, ethyl or phenyl,
or R_c is fluoro, chloro or oxo,
wherein each R_c may be further optionally substituted by one or more R_d;

30

R_d is methyl, cyclopropyl, phenyl, methoxy, fluoro, chloro or oxo;

R₄ and R₅ are each independently hydrogen, C1-4 saturated alkyl, C1-4alkoxyC1-4alkyl, C1-4alkylaminoC1-4alkyl, C1-4alkylthioC1-4alkyl wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, cyclopropyl, cyclopentyl, cyclohexyl, phenyl, naphthyl, benzyl, indanyl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, tetrahydropyranyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, benzimidazolyl and benzothiazolyl, C1-2alkanoyl, benzoyl, naphthoyl, C1-2 alkoxy carbonyl, benzyloxy carbonyl, phenoxy carbonyl, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-2 alkyl, phenyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl or pyrimidinyl, or R₄ and R₅ are each independently C1-2 alkanoylamino, benzoylamino, C1-2 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, phenylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-2 alkyl, phenyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, benzimidazolyl or benzothiazolyl, or R₄ and R₅ are each independently C1-2 alkoxy carbonylamino, phenoxy carbonylamino, C1-2 alkyl carbamoyloxy, phenyl carbamoyloxy, C1-2 alkyl sulfonylamino, phenyl sulfonylamino, C1-2 alkyl aminosulfonyl, phenyl aminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-2 alkyl, phenyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl or pyrimidinyl, or R₄ and R₅ are each independently fluoro, chloro, bromo, hydroxy, oxo, carboxy or carboxamide,

wherein each R₄ and R₅ may be further optionally indenpendtly substituted by one or more R_e;

30

R_e is C1-3 saturated alkyl, C1-3 alkoxy, C3-6 cycloalkyl, phenyl, naphthyl, indanyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, tetrahydropyranyl, indolyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, C1-2 alkanoyl, aroyl, C1-2alkanoyloxy, phenoxy, benzyloxy, C1-2 alkoxy carbonyl, phenoxycarbonyl, benzoyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-2 alkyl, phenyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl or pyrimidinyl, or R_e is ureido wherein either nitrogen atom may be independently substituted by C1-2 alkyl, phenyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl or pyrimidinyl, or R_e is amino wherein the nitrogen atom may be independently mono or di-substituted by C1-2 alkyl, phenyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl or pyrimidinyl, or R_e is fluoro, chloro, bromo, hydroxy, oxo, carboxy or carboxamide, wherein R_e may be further optionally substituted by one or more R_f; and

R_f is methyl, cyclopentyl, cyclohexyl, phenyl, tolylsulfonyl, methoxy, phenoxy, benzyloxy, fluoro, chloro, hydroxy, oxo, carboxy or carboxamide.

In yet a further embodiment of the invention, there are provided novel compounds of the formula (I) as described immediately above, and wherein:

Each R₁ is independently hydrogen, methyl, ethyl, i-propyl, cyclopropyl, cyclohexyl, phenyl, benzyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, thiazolyl, imidazolyl, pyridinyl, pyrazinyl, quinolyl,

tetrahydroisoquinolyl, or 2H-benzo[e][1,3]oxazine; wherein each R₁ is optionally substituted by one or more R_a; or R₁ is R_a or R_b;

Each R_a is independently methyl, phenyl, thienyl, dihydro-oxazolyl, pyridinyl,
5 methoxy, acetyl, acetoxy, phenoxy, benzyloxy, benzoyl, methoxycarbonyl,
benzoyloxy, carbamoyl wherein the nitrogen atom may be independently mono or
di-substituted by methyl or phenyl,
or R_a is acetylamino, methylthio, phenylthio wherein the sulfur atom may be
oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be
10 independently substituted by methyl or phenyl,
or R_a is methoxycarbonylamino, piperazinylcarbonylamino, methylcarbamoyloxy,
phenylcarbamoyloxy, methylsulfonylamino, phenylsulfonylamino, amino wherein
the nitrogen atom may be independently mono or di-substituted by methyl or
phenyl,
15 or R_a is fluoro, chloro, hydroxy, oxo, carboxy, cyano or carboxamide;

wherein R_a may be further optionally substituted by one or more R_b;

R_b is an alkyl group selected from methyl, ethyl, n-propyl or i-propyl,
20 wherein one carbon atom is optionally replaced by O and wherein said
alkyl group is optionally independently substituted with an oxo group
and/or phenyl or morpholinyl;

or R_b is phenyl, methoxy, phenoxy, fluoro, chloro or oxo;

25 R₃ is a hydrogen, methyl, ethyl, n-propyl, n-butyl, i-butyl, methoxymethyl,
methylthiomethyl, propenyl, butenyl, i-butenyl, cyclohexyl, phenyl, benzyl or
naphthylmethyl wherein R₃ is optionally substituted by one or more R_c;

30 R_c is methyl, ethyl, n-propyl, i-propyl, cyclopropyl, cyclopentyl, cyclohexyl,
phenyl, indanyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl,

bicyclo[4.1.0]heptanyl, bicyclo[3.1.0]hexanyl, bicyclo[1.1.1]pentanyl, cubanyl,
1,2,3,4-tetrahydronaphthyl, pyridinyl, methoxy, phenoxy, acetyl, benzoyl,
methoxycarbonyl, phenoxycarbonyl, acetoxyl, benzoyloxy, methylthio wherein the
sulfur atom may be oxidized to a sulfoxide or sulfone, phenylthio wherein the
5 sulfur atom may be oxidized to a sulfoxide or sulfone, dimethylamino,
diethylamino, fluoro, chloro or oxo;

R₄ and R₅ are each independently hydrogen, C1-4 saturated alkyl, C1-2alkoxyC1-2alkyl,
10 C1-2alkylaminoC1-2alkyl, C1-2alkylthioC1-2alkyl wherein the sulfur atom may be
oxidized to a sulfoxide or sulfone, cyclopropyl, cyclopentyl, cyclohexyl, phenyl, benzyl,
heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, tetrahydropyranyl,
pyridinyl, and pyrimidinyl, acetyl, benzoyl, methoxycarbonyl, ethoxycarbonyl,
benzyloxycarbonyl, carbamoyl wherein the nitrogen atom may be independently mono or
15 di-substituted by methyl, ethyl or phenyl,
or R₄ and R₅ are each independently acetylamino, benzoylamino, methylthio wherein the
sulfur atom may be oxidized to a sulfoxide or sulfone, phenylthio wherein the sulfur atom
may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be
independently substituted by methyl, ethyl or phenyl,
20 or R₄ and R₅ are each independently methoxycarbonylamino, ethoxycarbonylamino,
phenoxycarbonylamino, methylcarbamoyloxy, phenylcarbamoyloxy,
methylsulfonylamino, phenylsulfonylamino, methylaminosulfonyl, phenylaminosulfonyl,
amino wherein the nitrogen atom may be independently mono or di-substituted by
methyl, ethyl or phenyl,
25 or R₄ and R₅ are each independently fluoro, chloro, hydroxy, oxo, carboxy or
carboxamide,
wherein each R₄ and R₅ may be further optionally independently substituted by one or
more R_e;

30

R_e is methyl, methoxy, ethoxy, cyclopropyl, cyclopentyl, cyclohexyl, phenyl, naphthyl, indanyl, piperidinyl, morpholinyl, indolyl, thienyl, pyridinyl, acetyl, benzoyl, acetyloxy, phenoxy, benzyloxy, methoxycarbonyl, ethoxycarbonyl, carbamoyl wherein the nitrogen atom may be independently mono or di-
5 substituted by methyl, ethyl or phenyl,
or R_e is ureido wherein either nitrogen atom may be independently substituted by methyl, ethyl or phenyl,
or R_e is amino wherein the nitrogen atom may be independently mono or di-
substituted by methyl, ethyl or phenyl,
10 or R_e is fluoro, chloro, hydroxy, oxo, carboxy or carboxamide,
wherein R_e may be further optionally substituted by one or more R_g;
and
R_f is methyl, cyclopentyl, cyclohexyl, phenyl, tolylsulfonyl, methoxy,
phenoxy, benzyloxy, carboxy, fluoro, chloro or oxo.

15

In yet still a further embodiment of the invention, there are provided novel compounds of
20 the formula (I) as described immediately above, and wherein:

Each R₁ is independently hydrogen, i-propyl, benzyloxy, cyclohexyl, benzyl, phenyl, carboxyphenyl, naphthyl, 4-(acetylamino)-phenyl, 4-(methanesulfonylamino)-phenyl, 4-methoxyphenyl, 3-phenoxyphenyl, 4-chlorophenyl, 3,4-dichlorophenyl, 4-fluorophenyl,
25 2-fluorophenyl, 2-fluoro-4-chlorophenyl, naphthyl, thienylmethyl, piperidinyl, morpholinyl, pyrrolidinyl, piperazinyl, furanyl, thienyl, thiazolyl, quinolyl, tetrahydroisoquinolyl, 5-chlorothieryl, pyridin-4-yl, pyrazinyl, 2*H*-benzo[e][1,3]oxazine, methylamino, ethylamino, dimethylamino or diethylamino;

R₃ is methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, methoxymethyl, methylthiomethyl, vinyl, propenyl, butenyl, i-butenyl, cyclohexyl, phenyl, benzyl or naphthylmethyl wherein R₃ is optionally substituted by one or more R_c;

5 R_c is methyl, cyclopropyl, cyclohexyl, cyclopentyl, phenyl, indanyl, 1,2,3,4-tetrahydronaphthyl, methoxy, methylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, dimethylamino, fluoro or chloro;

R₄ and R₅ are each independently hydrogen, methyl, ethyl, n-propyl, n-butyl, t-butyl, i-propyl, i-butyl, methoxymethyl, methylthiomethyl or methylthioethyl wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, cyclopropyl, cyclopentyl, cyclohexyl, phenyl, benzyl, piperidinyl, tetrahydropyranyl, pyrimidinyl, acetyl, benzoyl, ethoxycarbonyl, benzyloxycarbonyl, methylsulfonylamino, phenylsulfonylamino, methylamino, dimethylamino, fluoro, oxo or carboxy,
10 wherein each R₄ and R₅ may each be further optionally independently substituted by one or more R_e;

R_e is methyl, cyclopropyl, cyclopentyl, cyclohexyl, phenyl, carboxyphenyl, naphthyl, indanyl, thienyl, methylthienyl, methoxy, phenoxy, benzyloxy, piperidinyl, pyridinyl, indolyl, 1-(tolyl-sulfonyl)-indolyl, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by methyl, phenyl or benzyl,
20 or R_e is hydroxy, fluoro, chloro, oxo, dimethylamino or trifluoromethyl.

25

In yet another embodiment of the invention, there are provided novel compounds of the formula (I) as described immediately above, and wherein:

30

Y is R₁, R₁O- or R₁NH-;

Each R₁ is independently hydrogen, phenyl, benzyl, naphthyl, 4-(acetylamino)-phenyl, 4-(methanesulfonylamino)-phenyl, 3-phenoxyphenyl, 4-chlorophenyl, 3,4-dichlorophenyl, 4-fluorophenyl, thienylmethyl, morpholinyl, pyrrolidinyl, piperidinyl, piperazinyl,
5 furanyl, thienyl, thiazolyl, quinolyl, tetrahydroisoquinolyl, 5-chlorothieryl, pyridin-4-yl, 2*H*-benzo[e][1,3]oxazine or pyrazinyl;

R₃ is ethyl, n-propyl, n-butyl, i-butyl, 2,2-dimethylpropyl, 3-methylbutyl, 3,3-dimethylbutyl, 2,2,3-trimethylbutyl, 2,2,3,3-tetramethylbutyl, cyclopropylmethyl,
10 cyclohexylmethyl, methoxymethyl, methylthiomethyl, methylsulfonylmethyl, dimethylaminomethyl, propenyl, i-butenyl, cyclohexyl, phenyl, benzyl, 4-methoxybenzyl, 4-chlorobenzyl, 3,4-dichlorobenzyl, 3-chlorobenzyl, 2,4-dichlorobenzyl, 4-methylbenzyl, 3-methylbenzyl or naphth-2-ylmethyl;

and

15 R₄ and R₅ are each independently hydrogen, methyl, ethyl, n-propyl, n-butyl, n-pentyl, 2-pentyl, 3-pentyl, phenylethyl, phenylpropyl, 2,2-dimethylpropyl, t-butyl, i-propyl, i-butyl, cyclopropyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, phenyl, benzyl, naphthylmethyl, indanylmethyl, pyridinylmethyl, indolylmethyl, thienylmethyl, 5-methylthienylmethyl, piperidinyl, piperidinylcarbonyl,
20 pyridinylcarbonyl, tetrahydropyranyl, pyrimidinyl, acetyl, benzoyl, ethoxycarbonyl, benzyloxycarbonyl, t-butoxycarbonyl, methylcarbamoyl, phenylcarbamoyl, benzylcarbamoyl, methylsulfonylamino, phenylsulfonylamino, methylamino, dimethylamino, methylcyclohexyl, methylbenzyl, trifluoromethylbenzyl, methoxybenzyl, 3-carboxyphenylmethoxymethyl, phenoxybenzyl, benzyloxybenzyl, benzyloxymethyl, N-
25 [(4-methylphenyl)-sulfonyl]-indolylmethyl, fluorobenzyl, difluorobenzyl, chlorobenzyl, N,N-dimethylaminoacetyl, trifluoromethylbenzyl, fluoro, oxo or carboxy.

In yet even still another embodiment of the invention, there are provided novel
30 compounds of the formula (I) as described immediately above, and wherein:

Each R₁ is independently hydrogen, phenyl, benzyl, naphthyl, tetrahydroisoquinolin-2-yl or morpholin-4-yl,

R₃ is ethyl, n-propyl, n-butyl, i-butyl, 2,2-dimethylpropyl, cyclopropylmethyl,
5 cyclohexylmethyl, dimethylaminomethyl, phenyl or benzyl;
and

R₄ is hydrogen;
and

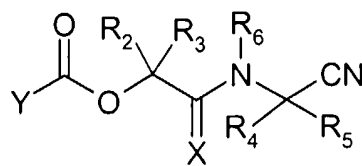
10

R₅ is methyl, ethyl, n-propyl, n-butyl, n-pentyl, 2-pentyl, 3-pentyl, phenylethyl,
phenylpropyl, 2,2-dimethylpropyl, t-butyl, i-propyl, i-butyl, cyclopropyl, cyclopentyl,
cyclohexyl, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, phenyl, benzyl,
naphthylmethyl, indanylmethyl, pyridinylmethyl, indolylmethyl, thienylmethyl,
15 methylthienylmethyl, methylbenzyl, methoxybenzyl, methoxybenzyl-m-carboxylic acid,
phenoxybenzyl, benzyloxybenzyl, benzyloxymethyl, N-[(4-methylphenyl)-sulfonyl]-
indolylmethyl, fluorobenzyl, difluorobenzyl, chlorobenzyl, N,N-dimethylaminoacetyl or
trifluoromethylbenzyl.

20 In still another embodiment of the invention, there are provided novel compounds of the
formula (I) as described immediately above, and wherein:

R₅ phenylethyl, phenylpropyl, 2,2-dimethylpropyl, cyclopropylmethyl,
cyclopentylmethyl, cyclohexylmethyl, benzyl, naphthylmethyl, indanylmethyl,
25 pyridinylmethyl, indolylmethyl, thienylmethyl, methylthienylmethyl, methylbenzyl,
methoxybenzyl, phenoxybenzyl, benzyloxybenzyl, benzyloxymethyl.

An additional subgeneric aspect of the invention is directed to a compound of formula (I):
30



(I)

wherein:

- 5 Y is C1-6alkoxy, C1-6alkylamino, naphthyl, morpholinyl, tetrahydroisoquinolinyl, phenylamino, benzylamino, naphthylamino, benzyloxy, benzofuranyl, benzothienyl, phenylpiperazinyl, pyridinylthienyl, C1-3alkoxyphenylpiperidinyl- amino, C1-3alkoxycarbonylpiperidinylamino-thiazolyl, benzylpiperazinyl- carbonylamino-phenyl, morpholin-4-yl-C1-3alkoxybenzofuranyl, C1- 10 3alkoxycarbonylamino-phenyl, quinolinylamino, wherein each is optionally substituted by one or more C1-3alkyl or halogen;

R₂ is hydrogen or methyl;

- 15 R₃ is hydrogen;
 C1-10 saturated alkyl group optionally substituted by one or more:
 halogen;
 C3-6cycloalkyl optionally substituted by one or more C1-3alkyl;
 phenyl or naphthyl optionally substituted by one or more halogen, C1- 20 3alkyl or C1-3alkoxy;
 decahydronaphthyl;
 spiro[2.5]octyl optionally substituted by one or more C1-3alkyl;
 indanyl;
 C1-3alkylthio wherein the sulfur atom may oxidized to a sulfoxide or a 25 sulfone;
 or biphenyl;
 C2-6alkenyl;

C3-6cycloalkyl optionally substituted by one or more C1-3alkyl;
dialkylaminomethyl;
phenyl
or pyridyl;

5

or R₂ and R₃ together with the carbon atom they are attached to form cyclopentyl,
cyclohexyl, tetrahydropyranyl, pyrrolidinyl optionally substituted with C1-3alkyl,
C3-6cycloalkyl, C3-6cycloalkyl-C1-3-alkyl or phenyl-C1-3alkyl, or piperidinyl
optionally substituted with C1-3alkyl, C3-6cycloalkyl, C3-6cycloalkyl-C1-3-alkyl
or phenyl-C1-3alkyl;

10

R₄ is hydrogen or C1-6 saturated alkyl group;

R₅ is hydrogen, C1-6 saturated alkyl group, C1-3alkyl-sulfonyl-C1-3alkyl, phenyl-C1-
3alkyl, trifluoromethylbenzyl, phenylethylindolyl-C1-3-alkyl or benzyloxy-C1-3-alkyl,
wherein each is optionally substituted by halo, carboxy, or C1-3alkoxy;

15

or R₄ and R₅ together with the carbon atom they are attached to form a cyclopropanyl,
cyclobutanyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, tetrahydropyranyl; or
pyrrolidinyl, piperidinyl or azepanyl, each being optionally substituted with one or more:
oxo, C1-3alkyl, hydroxyC1-3alkyl, benzyloxyC1-3alkyl, C3-6cycloalkyl, C3-
6cycloalkyl-C1-3-alkyl, phenyl-C1-3alkyl, tosyl-indolylC1-3alkyl, C1-3alkanoyl,
phenylC1-3alkanoyl, pyridinylC1-3alkanoyl, morpholinylC1-3alkanoyl, C1-
3alkylcarbamoyl, C1-3alkoxy-C1-3alkylcarbamoyl, C1-3alkoxycarbamoyl, C1-3alkoxy-
C1-3alkoxycarbamoyl, phenylcarbamoyl, phenylC1-3alkylcarbamoyl,
benzyloxycarbamoyl, cyclohexanylethylcarbonyl, cyclohexylC1-3alkoxycarbonyl,
phenylcarbonyl, phenylC1-3alkoxycarbonyl, piperidinylethylcarbonyl, piperazinylethylcarbonyl, or
tetrahydropyranylethylcarbonyl, wherein each of the foregoing substituents on the
pyrrolidinyl, piperidinyl or azepanyl can be further optionally substituted by one or more
C1-3alkyl or halogen;

25

30

and

R₆ is hydrogen or methyl.

5

In another embodiment of the invention, there are provided compounds within the subgeneric aspect described immediately above wherein:

10

Y is naphthyl, morpholinyl, tetrahydroisoquinolinyl, benzylamino, naphthylamino, benzyloxy, 4-phenylpiperazin-1-yl, 5-(pyridin-4-yl)-2-thienyl, 1-(4-alkoxyphenyl)-piperidin-4-yl amino, 2-[1-(alkoxycarbonyl)-piperidin-4-yl amino] thiazol-4-yl, 4-[4-(benzyl)-piperazin-1-yl carbonylamino]phenyl or 4-(alkoxycarbonylamino)phenyl, quinolin-2-yl amino, wherein each is optionally substituted by one or more halogen;

15

R₂ is hydrogen or methyl;

20

R₃ is ethyl, n-propyl, n-butyl, i-butyl, 2,2-dimethylpropyl, cyclopropyl, cyclopropylmethyl, cyclobutanylmethyl, cyclopentanylmethyl, cyclohexylmethyl, cyclohexylethyl, dialkylaminomethyl, phenyl, benzyl, phenylethyl or pyridyl;

25

or R₂ and R₃ together with the carbon atom they are attached to form cyclopentyl or cyclohexyl;

R₄ is hydrogen, methyl or ethyl;

R₅ is hydrogen, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, methylsulfonyl, benzyl, trifluoromethylbenzyl, phenylethyl, indolylmethyl, benzyloxymethyl, methoxybenzyloxymethyl or halo-benzyloxymethyl;

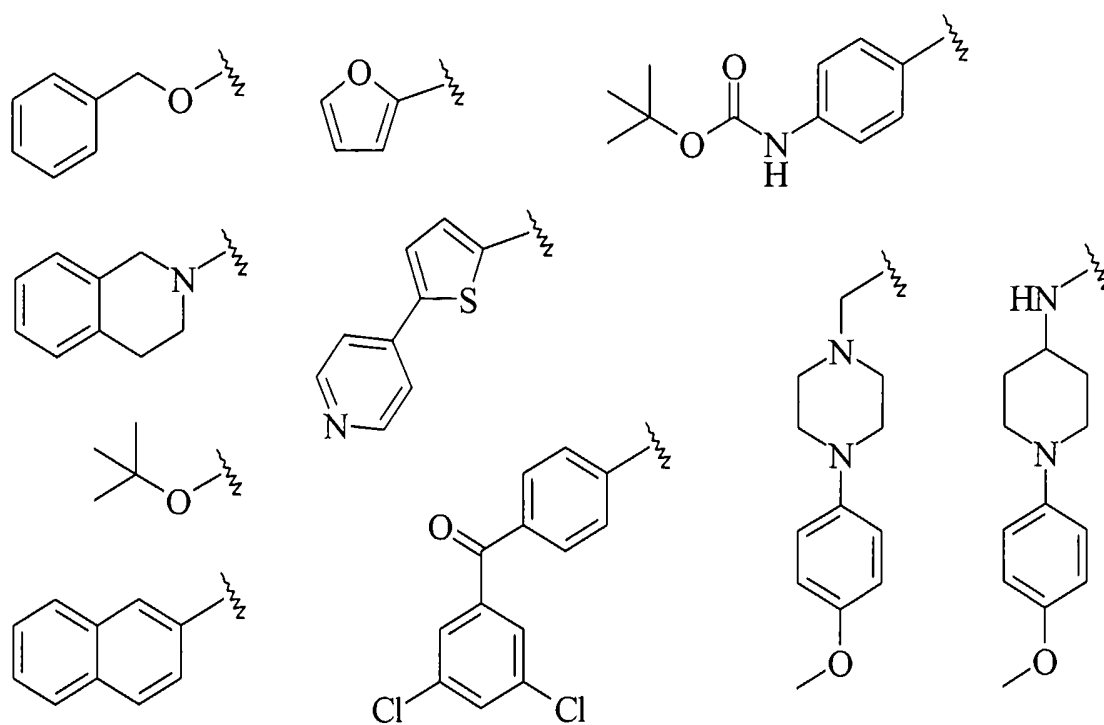
5 or R₄ and R₅ together with the carbon atom they are attached to form a cyclohexanyl;

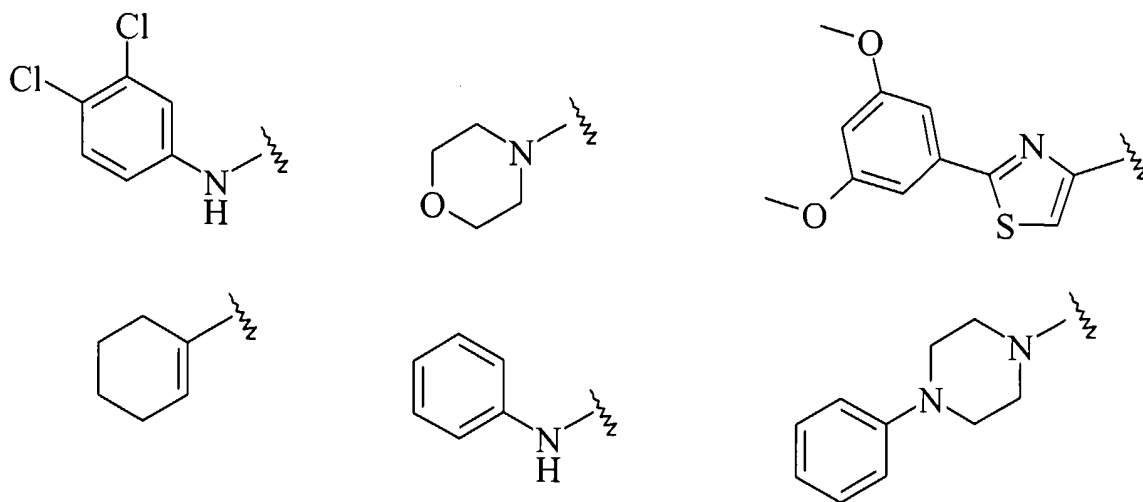
and

R₆ is hydrogen.

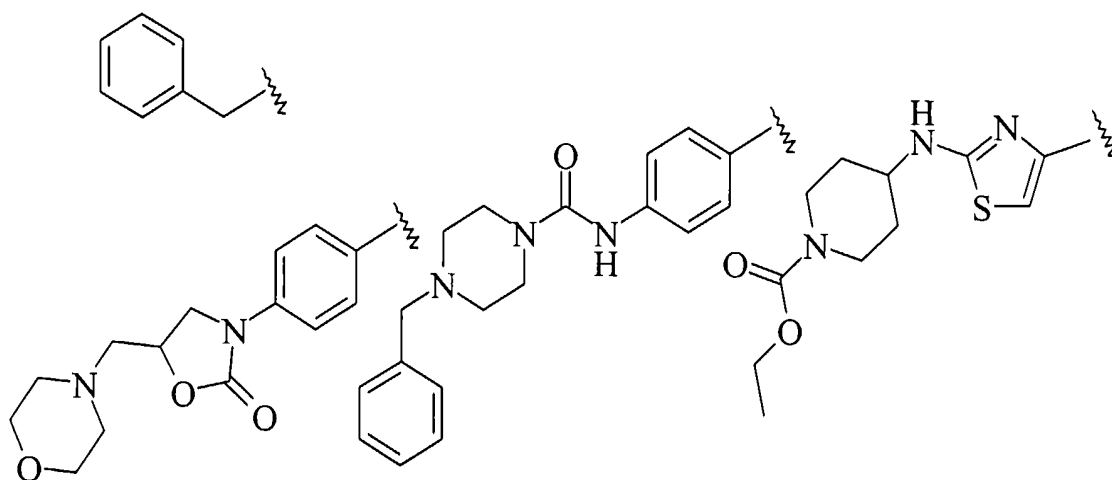
10

Some preferred examples of possible R₁ groups are shown below:

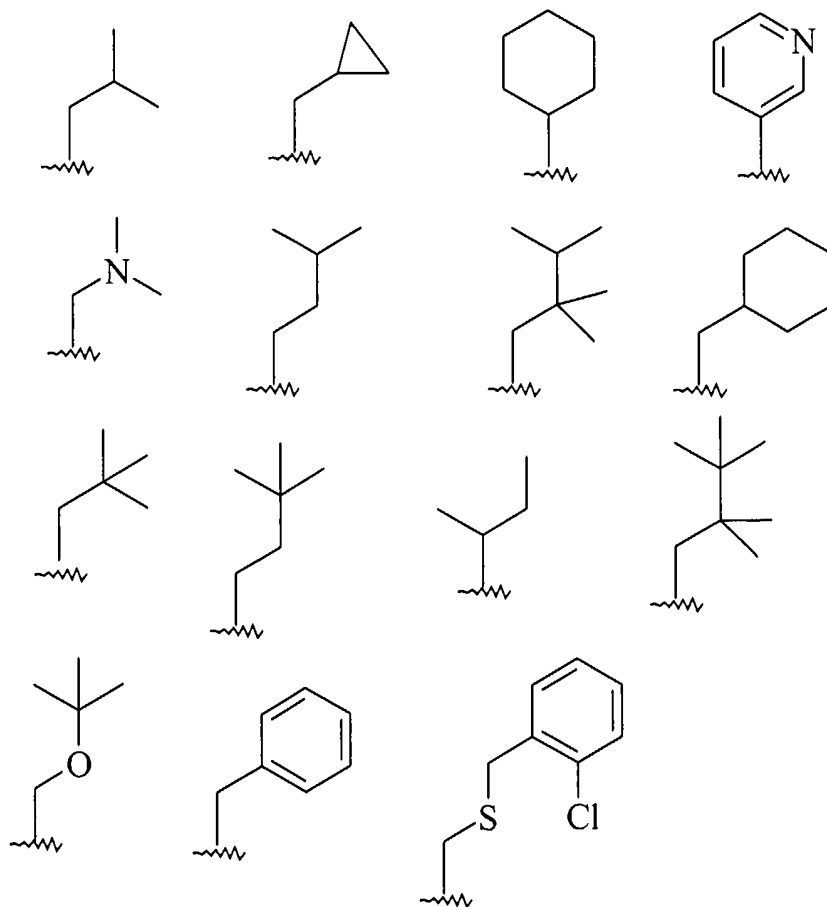




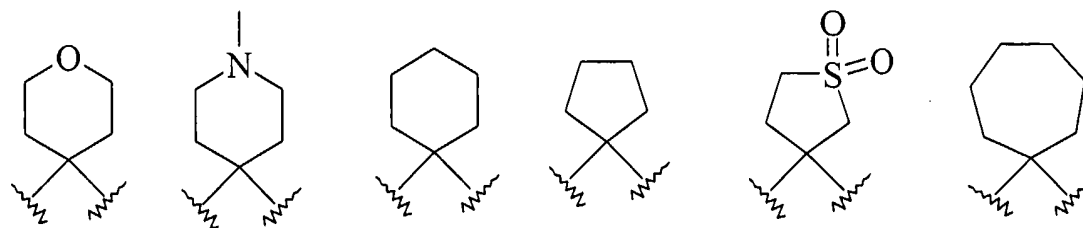
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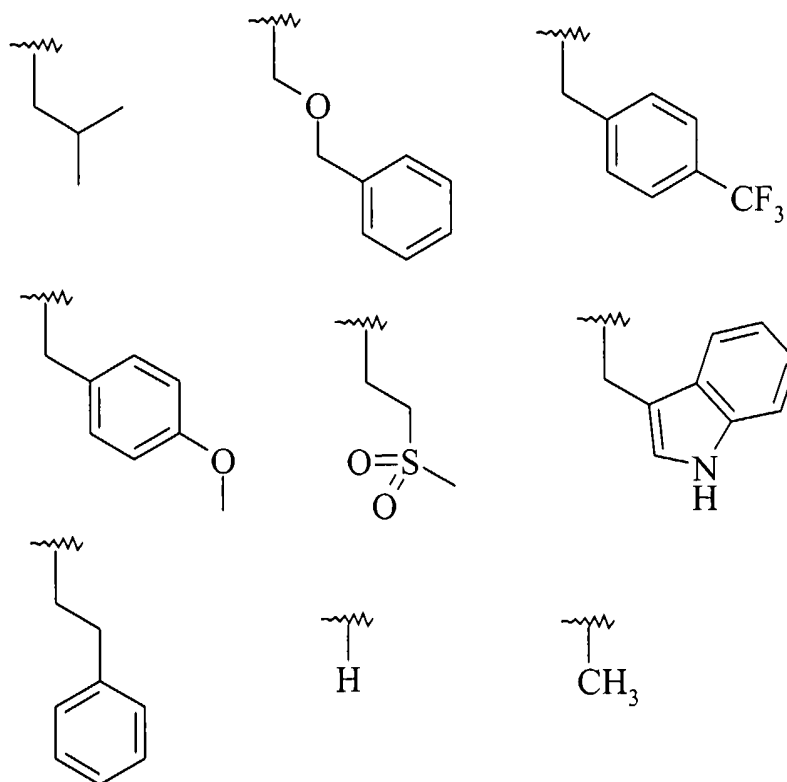
Some preferred examples of possible R₃ group are as shown below:



- 5 Some preferred examples of possible spirocyclic groups when R₂ and R₃ combine to form a ring are shown below:

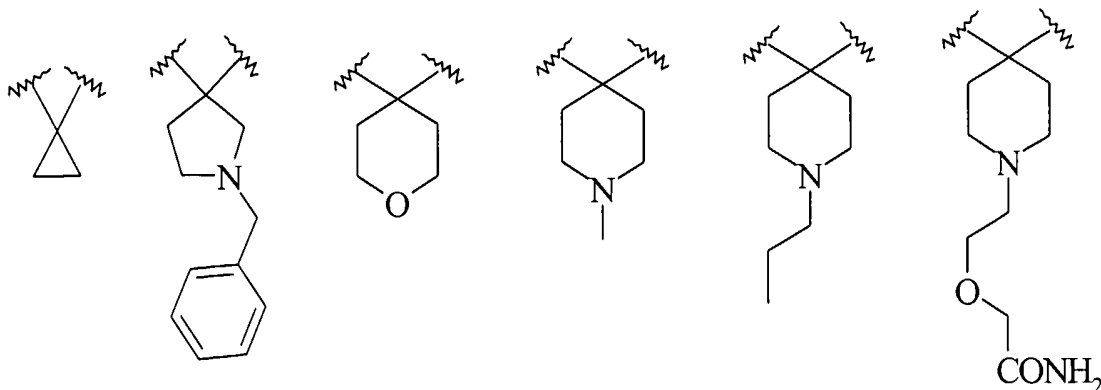


Some preferred examples of possible R₅ groups are shown below:

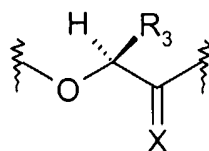


5

Some preferred examples of possible spirocyclic groups when R_4 and R_5 combine to form
10 a ring are shown below:

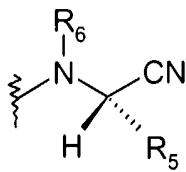


Any compounds of this invention containing one or more asymmetric carbon atoms may occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. All such isomeric forms of these compounds are expressly included in the present invention. Each stereogenic carbon may be in the R or S configuration unless otherwise specified, or a combination of configurations. In one preferred embodiment, in the compounds of the invention where R_2 is hydrogen and R_3 is other than hydrogen, the stereoconfiguration about the carbon atom to which R_2 and R_3 are attached is as shown below:



15

In further preferred embodiment, when R_4 is hydrogen and R_5 is other than hydrogen, the stereoconfiguration about the carbon atom to which R_4 and R_5 are attached is as shown below:



Of course, both these preferred stereoconfigurations may occur in the same compound.

5

Some of the compounds of formula (I) can exist in more than one tautomeric form. The invention includes all such tautomers.

It shall be understood by one of ordinary skill in the art that all compounds of the
10 invention are those which are chemically stable.

The invention includes pharmaceutically acceptable derivatives of compounds of formula (I). A "pharmaceutically acceptable derivative" refers to any pharmaceutically acceptable acid, salt or ester of a compound of this invention, or any other compound
15 such as a prodrug which, upon administration to a patient, is capable of providing (directly or indirectly) a compound of this invention, a pharmacologically active metabolite thereof or pharmacologically active residue thereof.

In addition, the compounds of this invention include prodrugs of compounds of the
20 formula (I). Prodrugs include those compounds that, upon simple transformation, are modified to produce the compounds of the invention. Simple chemical transformations include hydrolysis, oxidation and reduction which occur enzymatically, metabolically or otherwise. Specifically, when a prodrug of this invention is administered to a patient, the prodrug may be transformed into a compound of formula (I), thereby imparting the
25 desired pharmacological effect.

In order that the invention herein described may be more fully understood, the following detailed description is set forth. As used herein, the following abbreviations are used:

BOC or t-BOC is tertiary-butoxycarbonyl;

t-Bu is tertiary-butyl;

DMF is dimethylformamide;

5 EtOAc is ethyl acetate;

THF is tetrahydrofuran;

Ar is argon;

EDC is 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and

HOBT is 1-hydroxybenzotriazole.

10

GENERAL SYNTHETIC METHODS

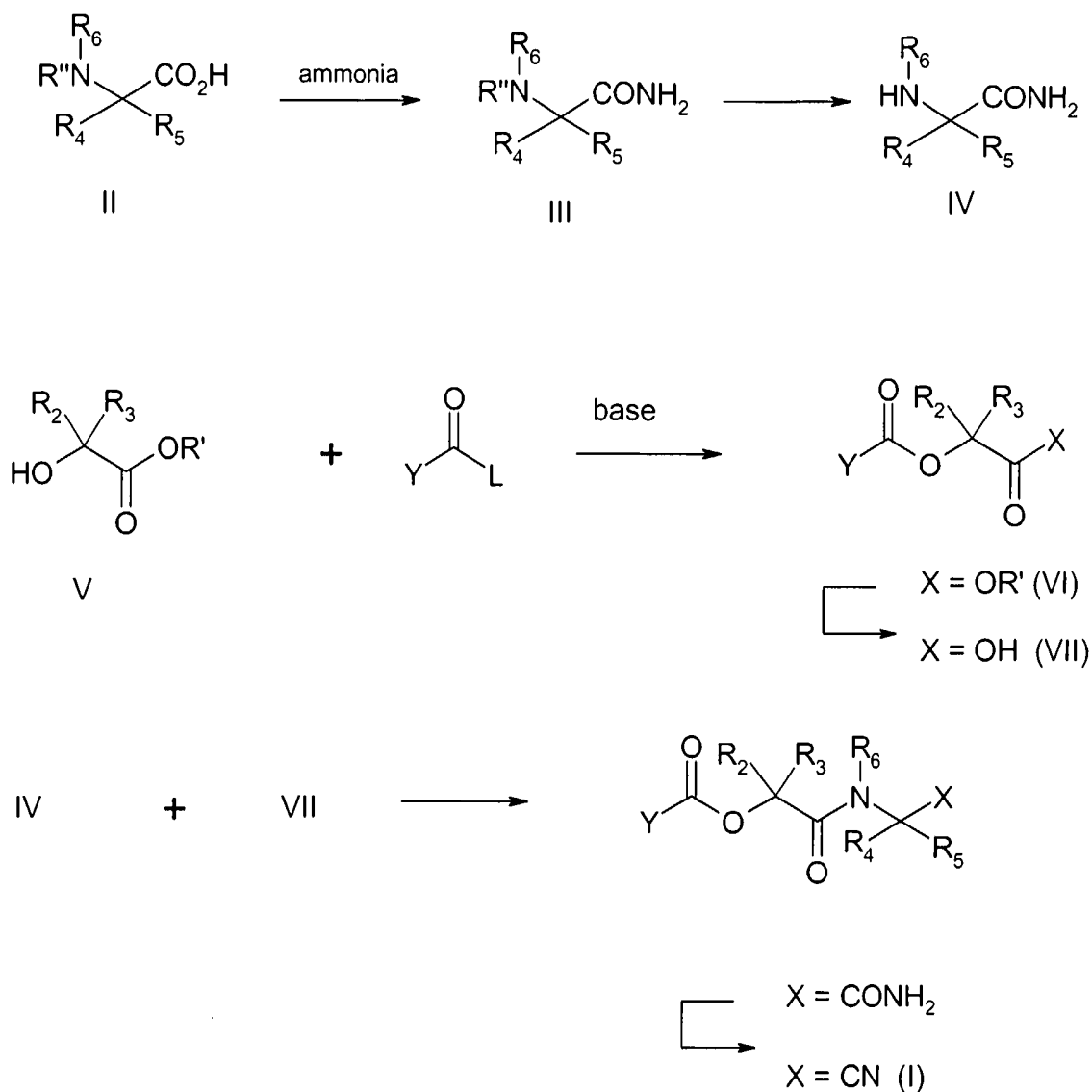
The invention also provides processes of making the present novel compounds.

15 Compounds of the invention may be prepared by methods described below. Standard peptide coupling, protection and deprotection reactions (see for example M. Bodanszky, 1984, The Practice of Peptide Synthesis, Springer-Verlag) are employed in these syntheses and are incorporated herein by reference in their entirety. Methods of preparing the carbamate functionality are also well known in the chemical literature (see
20 for example R. Warras et al., Tetrahedron Letters, 1998, 39, 2715 and G. Papageorgiou and J.E.T. Corrie, Tetrahedron, 1997, 53, 3917). Intermediates used in the preparation of the compounds of the invention are either commercially available or readily prepared by methods known to those skilled in the art. The synthesis of a number of intermediates useful in the preparation of compounds of the invention are described and exemplified in
25 U.S. Patent Application 09/655,351, filed September 8, 2000 (Emmanuel et al.) which is incorporated by reference.

Compounds of the invention having formula (I) may be prepared by Method A as illustrated in Scheme I:

30

Scheme I (Method A)



5

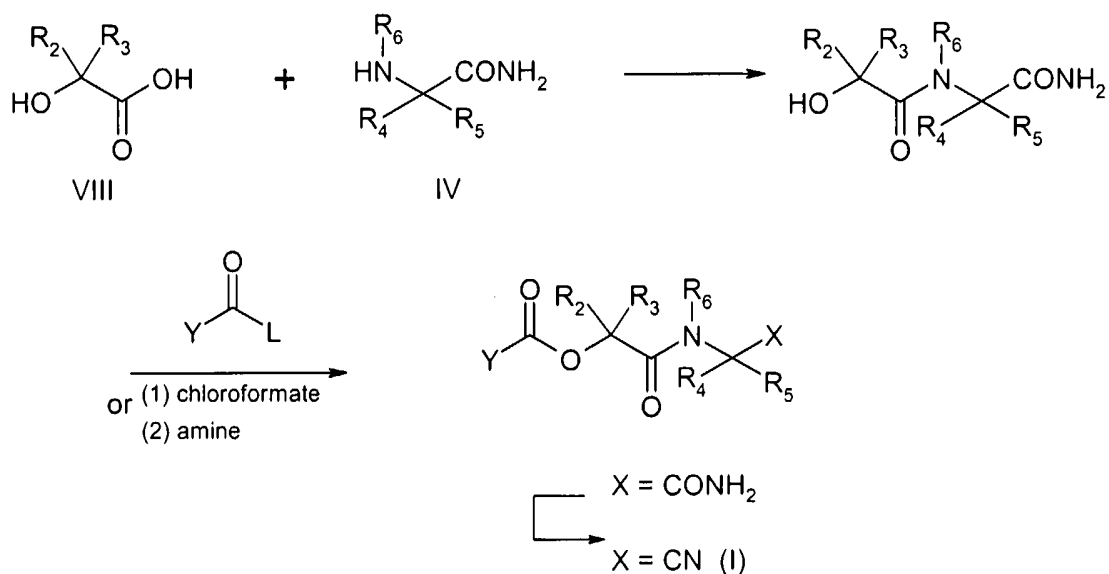
According to Method A a suitably protected amino acid bearing R₄ and R₅ (II) is allowed to react with ammonia under standard coupling conditions to provide amide (III). An example of a suitable protecting group R'' is the *t*-butoxycarbonyl (BOC) group. An example of standard coupling conditions would be combining the starting materials in the presence of a coupling reagent such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) with 1-hydroxybenzotriazole (HOBT), in a suitable solvent such as DMF or

10

methylene chloride. A base such as N-methylmorpholine may be added. This is followed by deprotection to give amino acid amide IV. A protected hydroxy ester (V) bearing R_2 and R_3 , where R' is a suitable protecting group, is then reacted with an appropriate activated acid $[YC(O)L]$ such as an acid chloride ($Y = (R_1)_3C-$, $L = Cl$), or a chloroformate derivative ($Y = R_1O$, $L = Cl$) in the presence of a suitable base such as N,N-diisopropylethylamine to provide VI. Alternately, if one desires a compound of formula (I) where $Y = (R_1)_2N$, one may prepare a mixed anhydride from the hydroxy group of formula (V) by reacting formula (V) with a suitable chloroformate such as *p*-nitrophenyl chloroformate, followed by reaction with the desired amine to provide the necessary intermediate (VI) where $Y = (R_1)_2N$ (see Synthetic Example 2, part c). Conversion to the carboxylic acid provides VII. Standard peptide coupling of IV and VII, followed by dehydration of the amide provides the desired nitrile I. An example of suitable dehydration conditions is cyanuric chloride in DMF.

In a variation (Method B) illustrated in Scheme II, an amino acid amide bearing R_4 and R_5 (IV) is coupled with a hydroxy acid (VIII) bearing R_2 and R_3 . Coupling conditions would be as described above. This is then followed by reaction with $YC(O)L$ or coupling via the mixed anhydride (as described in Method A). Conversion of the resulting amide to the nitrile by dehydration as above provides I.

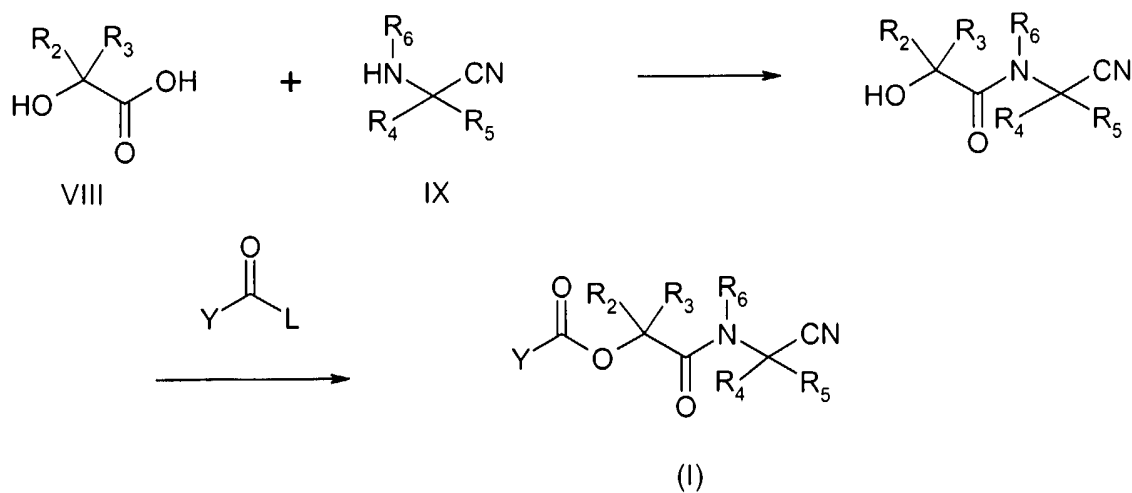
Scheme II (Method B)



Compounds of the invention having formula (I) may also be prepared by Method C as illustrated in Scheme III.

Scheme III (Method C)

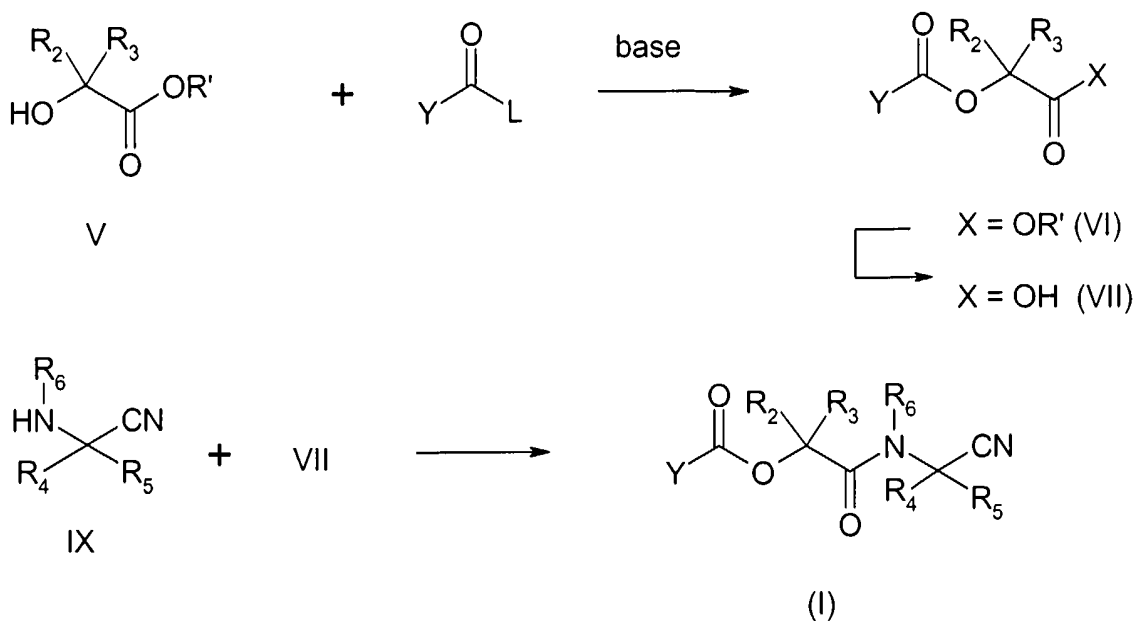
5



In this variation (Method C) an amino nitrile bearing R₄ and R₅ (IX) is coupled with a hydroxy acid bearing R₂ and R₃ (VIII) under the coupling conditions described above. This is followed by reaction with YC(O)L or coupling via the mixed anhydride as
 10 described above to furnish the nitrile (I).

Compounds of the invention having formula (I) may also be prepared by as outlined below in Scheme IV (Method D).

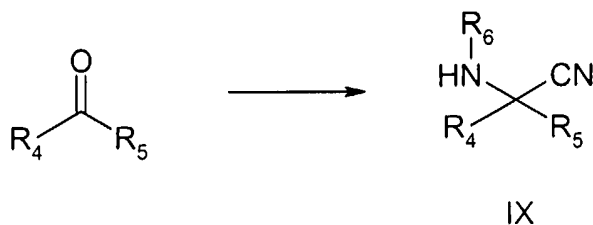
Scheme IV (Method D)



In this variation, a hydroxy ester (V) bearing R_2 and R_3 is reacted with $YC(O)L$, or
 5 coupling via the mixed anhydride, to provide the compound of formula (VI) as described
 in Method A. Conversion to the carboxylic acid provides VII is as described in Method
 A. Standard peptide coupling of an amino nitrile bearing R_4 and R_5 (IX) with (VII) yields
 the desired nitrile (I).

10 In cases where R_4 and R_5 form a heterocycle in the intermediate aminonitrile (IX) used in
 Methods C and D above, the required intermediate may be prepared from the
 corresponding ketone, as outlined in Scheme V

Scheme V



15

In this method, the corresponding ketone is reacted with a primary amine or an ammonium salt, such as ammonium chloride, and a cyanide salt, such as potassium cyanide or sodium cyanide, in a suitable solvent, such as water or a solution of ammonia in methanol, at about room temperature to reflux temperature.

5

The amide functionality at P2 of the compounds of formula (I) (i.e., -C(O)-N(R₆)-) may be converted to the thioamide to provide compounds of formula (I) with X = S by methods known in the art, for example by the use of Lawesson's reagent (K. Klausen et al., *Tetrahedron*, 1981, 37, 3635).

10

In each of the methods described above, required starting materials are either commercially available or easily prepared by those skilled in the art, for example see: Leung, M.-k.; Lai, J.-L.; Lau, K.-H.-; Yu, H.-h.; Hsiao, J.-J. *J. Org. Chem.* **1996**, *61*, 4175-4179;

15

Mee, J. D. *J. Org. Chem.* **1975**, *40*, 2135-2136;
Micovic, I. V.; Roglic, G. M.; Ivanovic, M. D.; Dosen-Micovic, L.; Kiricojevic, V. D.; Popovic, J. B. *J. Chem. Soc, Perkin Trans. 1*, **1996**, 2041-2050;
Tornus, I.; Schaumann, E. *Tetrahedron* **1996**, *52*, 725-732;
Jadhav, P. K.; Woerner, F. J. *Tetrahedron Letters* **1995**, *36*, 6383-6386;
20 Kochhar, K. S.; et al. *Tetrahedron Letters* **1984**, *25*, 1871-1874; and
Fordon, K. J.; Crane, C. G.; Burrows, C. J. *Tetrahedron Letters* **1994**, *35*, 6215-6216.
These references are incorporated herein by reference in their entirety,

25

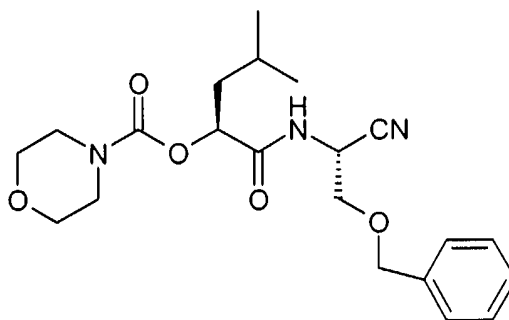
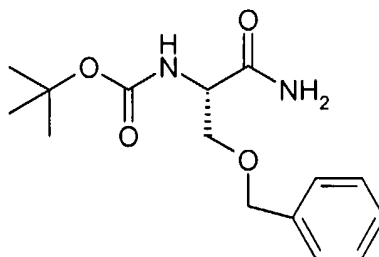
In order that this invention be more fully understood, the following examples are set forth. These examples are for the purpose of illustrating embodiments of this invention, and are not to be construed as limiting the scope of the invention in any way.

30

The examples which follow are illustrative and, as recognized by one skilled in the art, particular reagents or conditions could be modified as needed for individual compounds. Starting materials used in the scheme below are either commercially available or easily prepared from commercially available materials by those skilled in the art.

SYNTHETIC EXAMPLES**EXAMPLE 1**

- 5 Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3-methyl-butyl ester

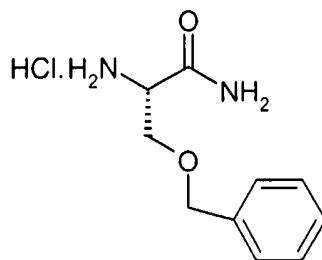
**(a) *N*-(*t*-butoxycarbonyl)-L-(O-benzyl)serinamide**

10

NH₄OH (10 mL) was added to a premixed (15 min) solution of *N*-(*t*-butoxycarbonyl)-L-(O-benzyl)serine (10.0 g, 33.9 mmol), EDC (7.80 g, 40.7 mmol), and 1-hydroxybenzotriazole (HOBT) (5.50 g, 40.7 mmol) in DMF (120 mL) at room temperature. After 16 h the reaction mixture was diluted with CH₂Cl₂ and filtered, washed sequentially with 10% aq. HCl, satd. NaHCO₃, H₂O (×3), brine, then dried over Na₂SO₄, and concentrated giving *N*-(*t*-butoxycarbonyl)-L-(O-benzyl)serinamide (11.5 g) as a white solid.

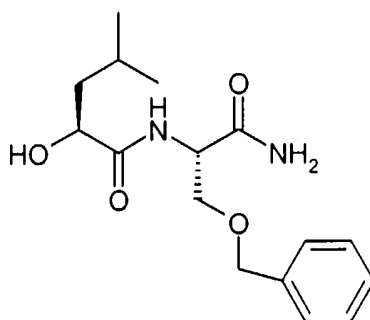
(b) 2-Amino-3-benzyloxy-propionamide hydrochloride

20



N-(*t*-butoxycarbonyl)-*L*-(*O*-benzyl)serinamide (1.00 g) was dissolved in anhydrous THF (5 mL) and cooled in an ice/water bath. A 4 M solution of HCl in dioxane (5 mL) was added and the reaction stirred for two h and then concentrated under reduced pressure to provide a glass which was triturated with diethyl ether to obtain 2-amino-3-benzyloxy-propionamide hydrochloride as a white solid (0.9 g). This material was used without further purification.

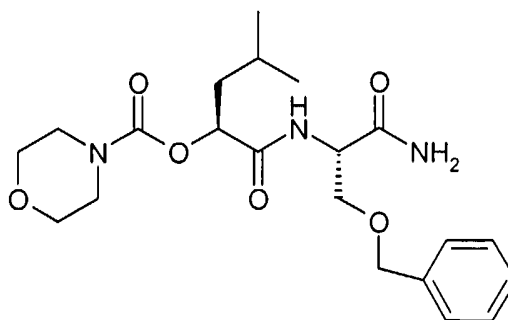
10 (c) **2-Hydroxy-4-methyl-pentanoic acid (2-benzyloxy-1-carbamoyl-ethyl)-amide**



2-Hydroxyisocaproic acid (0.143 g, 1.0 mmol) was dissolved in 4 mL of DMF and cooled to 0 °C with an ice-water bath. EDC (0.278 g, 1.4 mmol) and HOBT (0.190 g, 1.4 mmol) were added and stirring, under argon, continued for 25 min. To the cold solution was added 2-amino-3-benzyloxy-propionamide hydrochloride (0.250 g, 1.0 mmol), followed by addition of *N*-methylmorpholine (0.35 mL, 3.2 mmol) and stirring was continued overnight (16 h). The solution was diluted with 100 mL of EtOAc and washed sequentially with a 1.0 M solution of HCl (3 x 10 mL), a saturated solution of NaHCO₃ (3 x 10 mL), water (100 mL) and brine (100 mL). The organic

layer was dried over MgSO_4 , filtered and concentrated by rotary evaporation to give (0.17 g, 55%) of the crude product which was chromatographed (SiO_2 , 3% MeOH in EtOAc) to give the desired product (0.11 g, 35%).

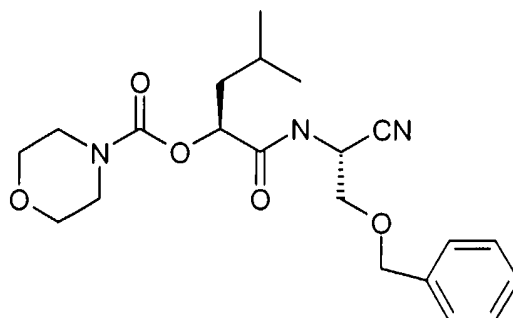
5 (d) **Morpholine-4-carboxylic acid 1-(2-benzyloxy-1-carbamoyl-ethylcarbamoyl)-3-methyl-butyl ester**



10 To a solution of 2-hydroxy-4-methyl-pentanoic acid (2-benzyloxy-1-carbamoyl-ethyl)-amide (0.169 g, 0.55 mmol) in CH_2Cl_2 (5 mL) was added 4-morpholinecarbonyl chloride (0.082 g, 0.55 mmol), Et_3N (0.15 mL, 1.1 mmol) and DMAP (0.034 g, 0.27 mmol). The resulting mixture was allowed to stir overnight (20 h) under argon at room temperature. When the reaction was complete the mixture was
 15 diluted with CH_2Cl_2 (10 mL), then washed with HCl (1.0 N, 10 mL), water and brine, dried over Na_2SO_4 , and concentrated to give the desired product as an off-white oil in 0.20 g 86% yield of the crude product which was chromatographed (SiO_2 , 5% hexanes in EtOAc) to give desired product in (0.12 g, 52%).

20

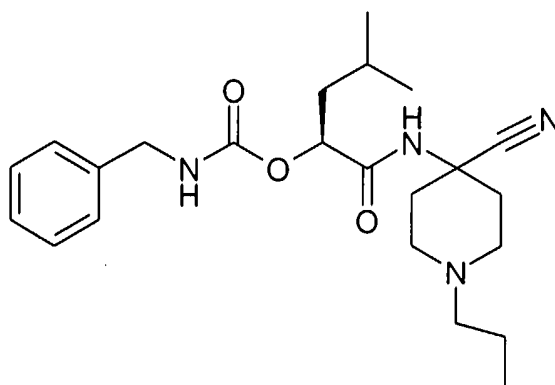
(e) **Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3-methyl-butyl ester**



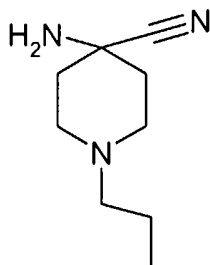
Morpholine-4-carboxylic acid 1-(2-benzyloxy-1-carbamoyl-ethylcarbamoyl)-3-methyl-butyl ester (0.100 g, 0.23 mmol) was dissolved in 3 mL of DMF and cooled to 0 °C with an ice-water bath. To this solution was added cyanuric chloride (0.044 g, 0.23 mmol) and the reaction mixture was stirred for 1 h. The reaction was quenched with cold water (2 mL), extracted with EtOAc (3 x 100 mL), and the organic layers were combined and washed with 100 mL brine. The organic layer was dried over MgSO₄, filtered and concentrated to give the crude residue. The residue was purified by chromatography (SiO₂, 50% hexane in EtOAc) to give the title compound as a clear oil (0.055 g, 60%); ¹H NMR (CDCl₃) 7.35 (5H, m), 6.76 (1H, d), 5.1 (2H, m), 4.65 (2H, m), 3.82-3.35 (10H, m), 1.7 (3H, m), 0.95 (6H, m). MS: m/z = 404 M+1.

EXAMPLE 2

15 Benzyl-carbamic acid 1-(4-cyano-1-propyl-piperidin-4-ylcarbamoyl)-3-methyl-butyl ester



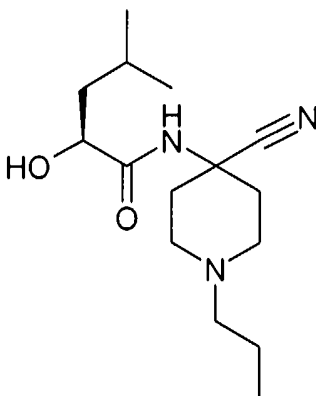
(a) 4-Amino-1-propyl-piperidine-4-carbonitrile



5

To a suspension of ammonium chloride (5.02 g, 93.8 mmol), sodium cyanide (8.51 g, 173.6 mmol) and MgSO₄ (7.0 g) in 200 mL of NH₃/MeOH (2.0 M) was added 1-propyl-4-piperidone (23.4 g, 165 mmol). Stirring was continued for 3.5 h at 60 °C. The solution
10 was cooled to room temperature and filtered. The filtrate was concentrated and the residue was taken up in Et₂O (200 mL) treated with MgSO₄ and stirred under argon for 3 h. The mixture was then filtered and concentrated to provide the product as a light brown oil (20 g crude).

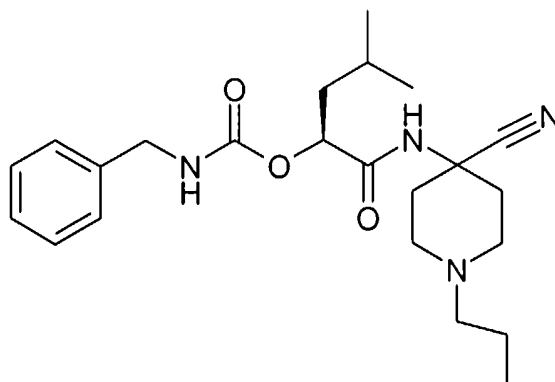
15 (b) 2-Hydroxy-4-methyl-pentanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide



2-Hydroxy-4-methyl-pentanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide was prepared by a method analogous to that of Example 1, part (c). The product was used in the next step without purification.

5

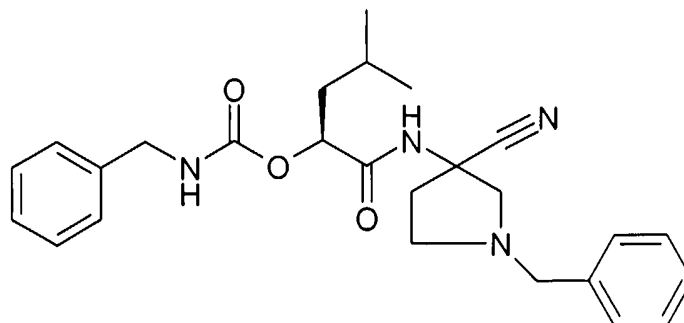
(c) **Benzyl-carbamic acid 1-(4-cyano-1-propyl-piperidin-4-ylcarbamoyl)-3-methyl-butyl ester**



10 To a solution of 2-hydroxy-4-methyl-pentanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide (0.316 g, 1.1 mmol) in CH₂Cl₂ (30 mL) was added DMAP (0.192 g, 1.6 mmol), p-nitrophenyl chloroformate (0.249 g, 1.2 mmol), and *N*-methylmorpholine (0.136 mL, 1.2 mmol). The resulting mixture was allowed to stir overnight (20 h) under argon at room temperature, then treated with benzylamine (1.68 g, 16 mmol) and allowed to stir overnight (20 h). When the reaction was complete the mixture was
15 diluted with CH₂Cl₂ (50 mL), then washed with saturated aq. NaHCO₃ (50 mL), water and brine, dried over Na₂SO₄, filtered and evaporated in vacuo to give 0.200 g (50% yield) of the desired product after purification by prep-HPLC;
20 ¹H NMR (CDCl₃) 7.3 (5H, m), 6.3 (1H, s), 5.2 (1H, m), 5.0 (1H, m), 4.42 (2H, m), 2.75 (1H, m), 2.35 (5H, m), 1.98-1.35 (9H, m), 1.0-0.8 (9H, m). MS: m/z = 415 M+1.

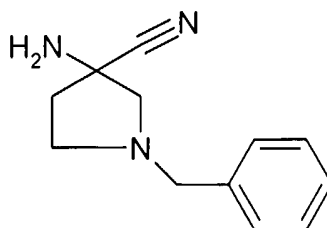
EXAMPLE 3

Benzyl-carbamic acid 1-(1-benzyl-3-cyano-pyrrolidin-3-ylcarbamoyl)-3-methyl-butyl ester



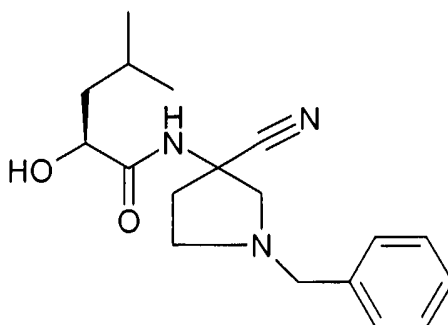
5

(a) 3-Amino-1-benzyl-pyrrolidine-3-carbonitrile



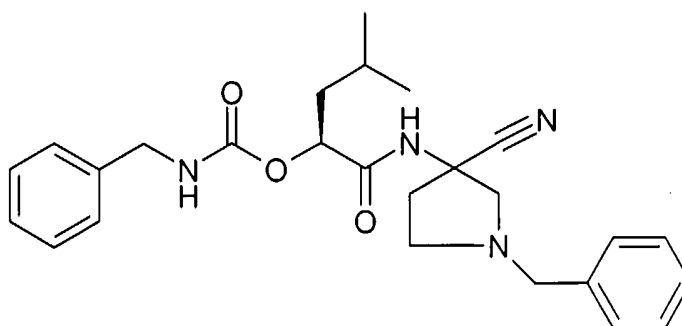
10 3-Amino-3-cyano-1-benzylpyrrolidine was prepared by a method analogous to that of Example 2-part (a) with the exception that no sodium carbonate was added to the reaction mixture. The product was extracted from the crude reaction with EtOAc (3 X 100 mL) and was used without further purification.

15 **(b) 2-Hydroxy-4-methyl-pentanoic acid (1-benzyl-3-cyano-pyrrolidin-3-yl)-amide**



2-Hydroxy-4-methyl-pentanoic acid (1-benzyl-3-cyano-pyrrolidin-3-yl)-amide was prepared by a method analogous to that of Example 1, part (c). The product was used in the next step without purification.

(c) Benzyl-carbamic acid 1-(1-benzyl-3-cyano-pyrrolidin-3-ylcarbonyl)-3-methyl-butyl ester



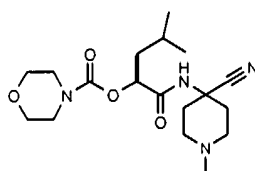
10

To a solution of 2-hydroxy-4-methyl-pentanoic acid (1-benzyl-3-cyano-pyrrolidin-3-yl)-amide (0.315 g, 1.0 mmol) in dry THF (27 mL) was added DMAP (0.171 g, 1.4 mmol), *p*-nitrophenyl chloroformate (0.221 g, 1.1 mmol), and *N*-methylmorpholine (0.121 mL, 1.1 mmol). The resulting mixture was allowed to stir overnight (20 h) under argon at room temperature, then treated with benzylamine (0.150 g, 1.4 mmol) and allowed to stir overnight (24 h). When the reaction was complete, the mixture was diluted with EtOAc (50 mL), then washed sequentially with saturated aq. NaHCO₃ (50 mL), water and brine, dried over Na₂SO₄, filtered and concentrated to give 0.180 g (40% yield) of the desired

product after purification by prep-HPLC; ^1H NMR (CDCl_3) 7.25 (10H, m), 6.25 (1H, s), 5.4-5.1 (2H, m), 4.45 (2H, m), 3.65 (2H, m), 3.1-3.0 (1H, m), 2.98-2.57 (5H, m), 2.16 (1H, m), 1.73 (2H, m), 0.9 (6H, m). MS, m/z 449 = M+1.

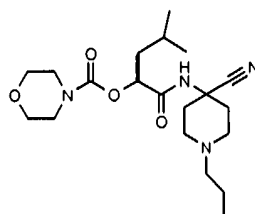
- 5 Using the procedures described in the General Synthetic Methods section and in the synthetic examples above, the following compounds may be prepared:

Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-3-methyl-butyl ester



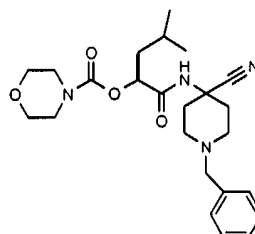
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Morpholine-4-carboxylic acid 1-(4-cyano-1-propyl-piperidin-4-ylcarbamoyl)-3-methyl-butyl ester

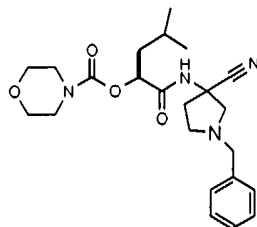


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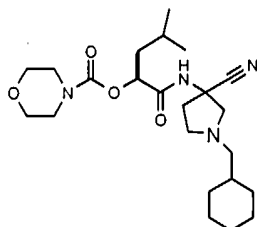
Morpholine-4-carboxylic acid 1-(1-benzyl-4-cyano-piperidin-4-ylcarbamoyl)-3-methyl-butyl ester



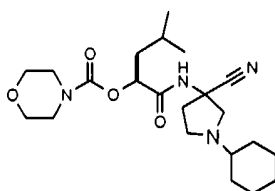
Morpholine-4-carboxylic acid 1-(1-benzyl-3-cyano-pyrrolidin-3-ylcarbamoyl)-3-methyl-butyl ester



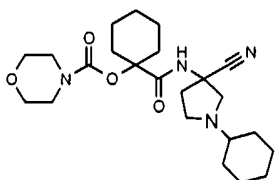
5 Morpholine-4-carboxylic acid 1-(3-cyano-1-cyclohexylmethyl-pyrrolidin-3-ylcarbamoyl)-3-methyl-butyl ester



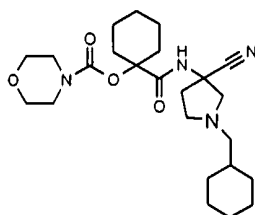
10 Morpholine-4-carboxylic acid 1-(3-cyano-1-cyclohexyl-pyrrolidin-3-ylcarbamoyl)-3-methyl-butyl ester



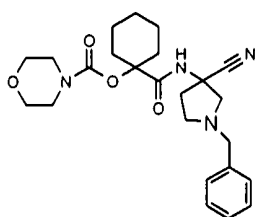
Morpholine-4-carboxylic acid 1-(3-cyano-1-cyclohexyl-pyrrolidin-3-ylcarbamoyl)-cyclohexyl ester



15 Morpholine-4-carboxylic acid 1-(3-cyano-1-cyclohexylmethyl-pyrrolidin-3-ylcarbamoyl)-cyclohexyl ester

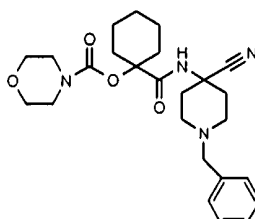


Morpholine-4-carboxylic acid 1-(1-benzyl-3-cyano-pyrrolidin-3-ylcarbamoyl)-cyclohexyl ester



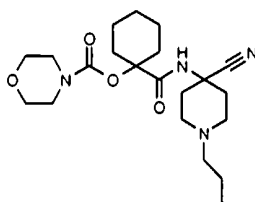
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Morpholine-4-carboxylic acid 1-(1-benzyl-4-cyano-piperidin-4-ylcarbamoyl)-cyclohexyl ester

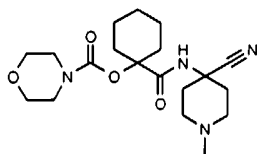


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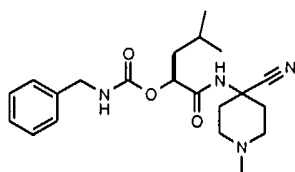
Morpholine-4-carboxylic acid 1-(4-cyano-1-propyl-piperidin-4-ylcarbamoyl)-cyclohexyl ester



15 Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-cyclohexyl ester

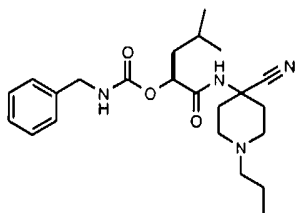


Benzyl-carbamic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbonyl)-3-methyl-butyl ester



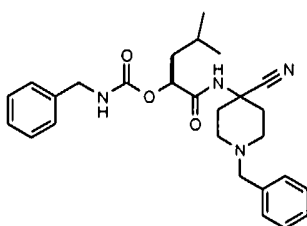
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Benzyl-carbamic acid 1-(4-cyano-1-propyl-piperidin-4-ylcarbonyl)-3-methyl-butyl ester

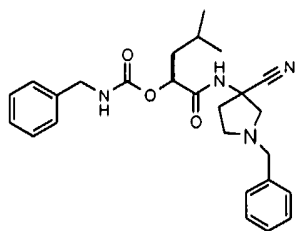


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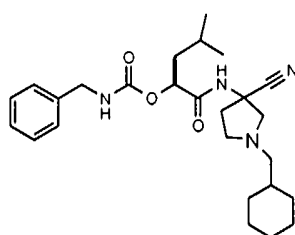
Benzyl-carbamic acid 1-(1-benzyl-4-cyano-piperidin-4-ylcarbonyl)-3-methyl-butyl ester



15 Benzyl-carbamic acid 1-(1-benzyl-3-cyano-pyrrolidin-3-ylcarbonyl)-3-methyl-butyl ester

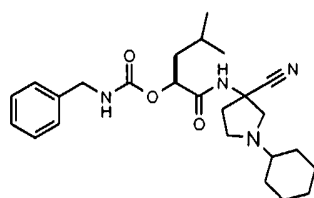


Benzyl-carbamic acid 1-(3-cyano-1-cyclohexylmethyl-pyrrolidin-3-ylcarbamoyl)-3-methyl-butyl ester



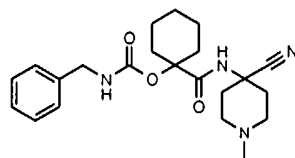
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Benzyl-carbamic acid 1-(3-cyano-1-cyclohexyl-pyrrolidin-3-ylcarbamoyl)-3-methyl-butyl ester

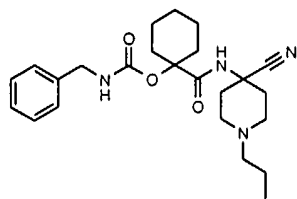


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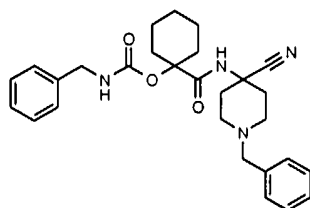
Benzyl-carbamic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-cyclohexyl ester



Benzyl-carbamic acid 1-(4-cyano-1-propyl-piperidin-4-ylcarbamoyl)-cyclohexyl ester

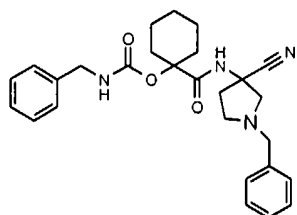
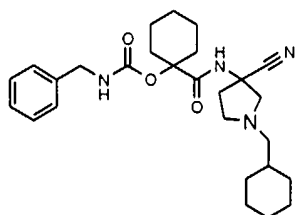


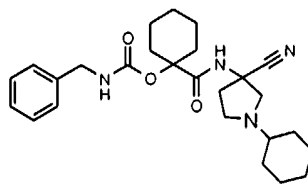
Benzyl-carbamic acid 1-(1-benzyl-4-cyano-piperidin-4-ylcarbamoyl)-cyclohexyl ester



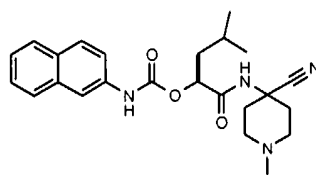
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Benzyl-carbamic acid 1-(1-benzyl-3-cyano-pyrrolidin-3-ylcarbamoyl)-cyclohexyl ester

10 Benzyl-carbamic acid 1-(3-cyano-1-cyclohexylmethyl-pyrrolidin-3-ylcarbamoyl)-
cyclohexyl esterBenzyl-carbamic acid 1-(3-cyano-1-cyclohexyl-pyrrolidin-3-ylcarbamoyl)-cyclohexyl
ester

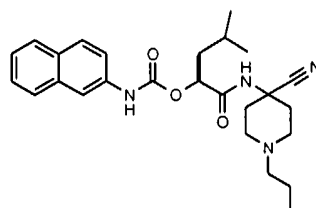


Naphthalen-2-yl-carbamic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-3-methyl-butyl ester



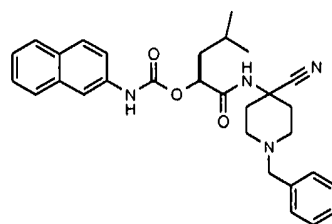
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Naphthalen-2-yl-carbamic acid 1-(4-cyano-1-propyl-piperidin-4-ylcarbamoyl)-3-methyl-butyl ester

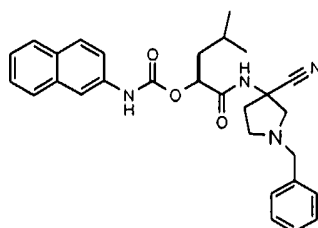


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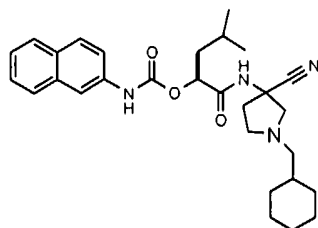
Naphthalen-2-yl-carbamic acid 1-(1-benzyl-4-cyano-piperidin-4-ylcarbamoyl)-3-methyl-butyl ester



15 Naphthalen-2-yl-carbamic acid 1-(1-benzyl-3-cyano-pyrrolidin-3-ylcarbamoyl)-3-methyl-butyl ester

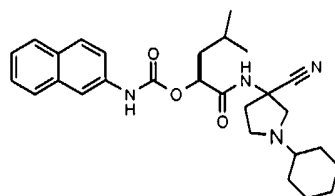


Naphthalen-2-yl-carbamic acid 1-(3-cyano-1-cyclohexylmethyl-pyrrolidin-3-ylcarbamoyl)-3-methyl-butyl ester

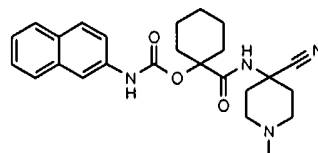


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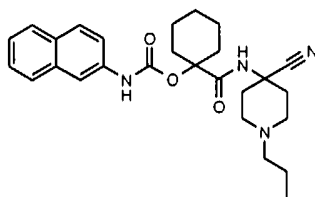
Naphthalen-2-yl-carbamic acid 1-(3-cyano-1-cyclohexyl-pyrrolidin-3-ylcarbamoyl)-3-methyl-butyl ester



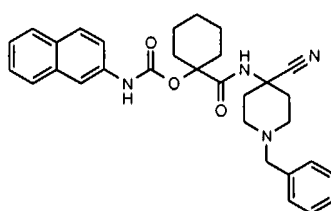
10 Naphthalen-2-yl-carbamic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-cyclohexyl ester



15 Naphthalen-2-yl-carbamic acid 1-(4-cyano-1-propyl-piperidin-4-ylcarbamoyl)-cyclohexyl ester

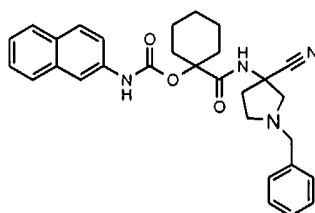


Naphthalen-2-yl-carbamic acid 1-(1-benzyl-4-cyano-piperidin-4-ylcarbamoyl)-
cyclohexyl ester



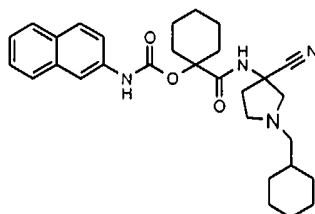
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Naphthalen-2-yl-carbamic acid 1-(1-benzyl-3-cyano-pyrrolidin-3-ylcarbamoyl)-
cyclohexyl ester

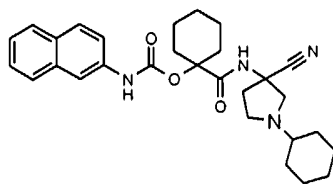


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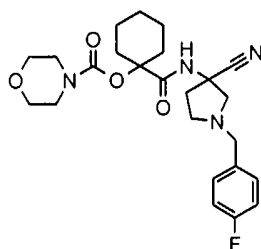
Naphthalen-2-yl-carbamic acid 1-(3-cyano-1-cyclohexylmethyl-pyrrolidin-3-
ylcarbamoyl)-cyclohexyl ester



15 Naphthalen-2-yl-carbamic acid 1-(3-cyano-1-cyclohexyl-pyrrolidin-3-ylcarbamoyl)-
cyclohexyl ester

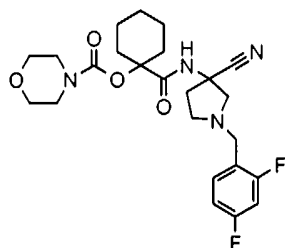


Morpholine-4-carboxylic acid 1-[3-cyano-1-(4-fluoro benzyl)-pyrrolidin-3-ylcarbamoyl]-cyclohexyl ester



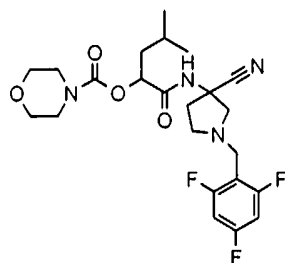
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Morpholine-4-carboxylic acid 1-[3-cyano-1-(2,4-difluoro benzyl)-pyrrolidin-3-ylcarbamoyl]-cyclohexyl ester

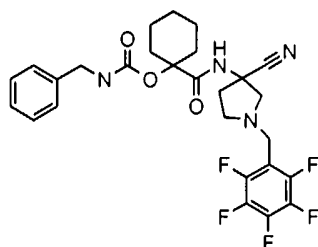


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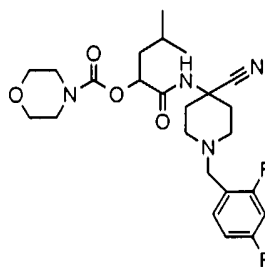
Morpholine-4-carboxylic acid 1-[3-cyano-1-(2,4,6-trifluoro-benzyl)-pyrrolidin-3-ylcarbamoyl]-3-methyl-butyl ester



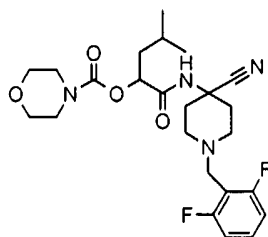
Benzyl-carbamic acid 1-[3-cyano-1-(2,3,4,5,6-pentafluoro-benzyl)-pyrrolidin-3-ylcarbamoyl]-cyclohexyl ester



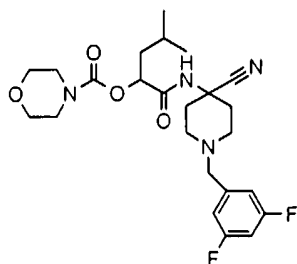
5 Morpholine-4-carboxylic acid 1-[4-cyano-1-(2,4-difluoro benzyl)-piperidin-4-ylcarbamoyl]-3-methyl-butyl ester



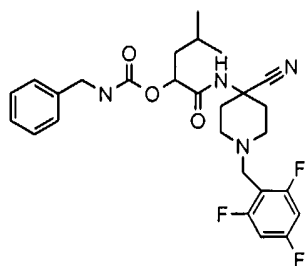
10 Morpholine-4-carboxylic acid 1-[4-cyano-1-(2,6-difluoro benzyl)-piperidin-4-ylcarbamoyl]-3-methyl-butyl ester



Morpholine-4-carboxylic acid 1-[4-cyano-1-(3,5-difluoro benzyl)-piperidin-4-ylcarbamoyl]-3-methyl-butyl ester

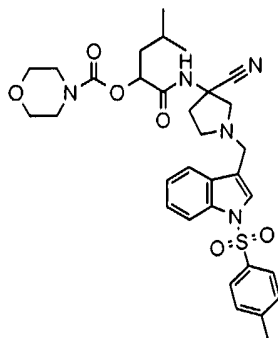


Benzyl-carbamic acid 1-[4-cyano-1-(2,4,6-trifluoro benzyl)-piperidin-4-ylcarbamoyl]-3-methyl-butyl ester



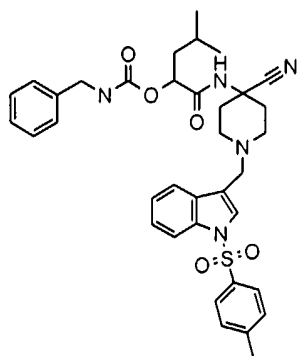
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Morpholine-4-carboxylic acid 1-{3-cyano-1-[1-(toluene-4-sulfonyl)-1*H*-indol-3-ylmethyl]-pyrrolidin-3-ylcarbamoyl}-3-methyl-butyl ester



10

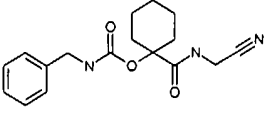
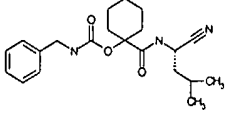
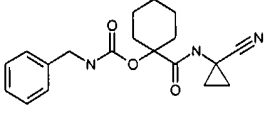
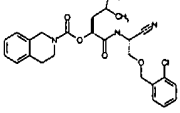
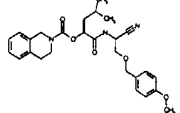
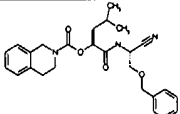
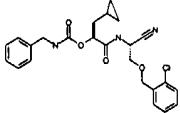
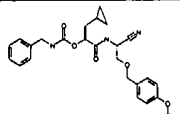
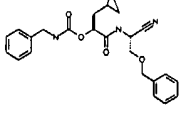
Benzyl-carbamic acid 1-{4-cyano-1-[1-(toluene-4-sulfonyl)-1*H*-indol-3-ylmethyl]-piperidin-4-ylcarbamoyl}-3-methyl-butyl ester



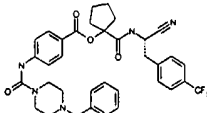
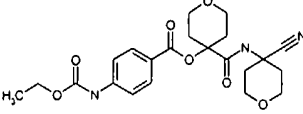
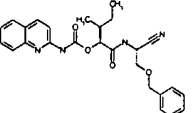
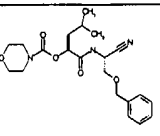
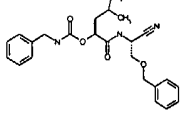
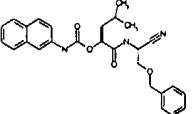
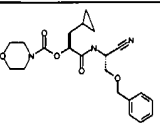
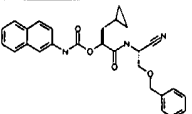
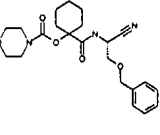
Additional compounds that may be prepared using the procedures described above are shown in the Tables below:

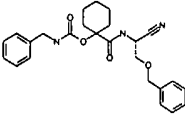
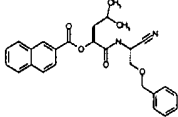
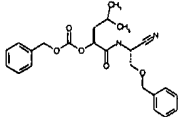
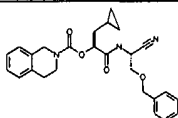
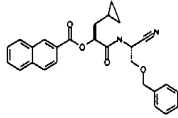
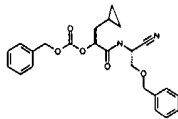
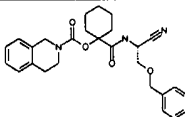
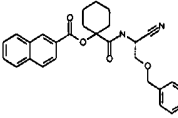
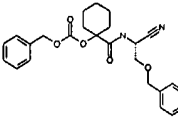
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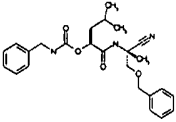
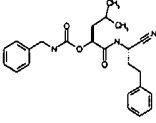
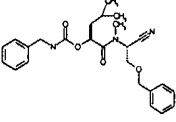
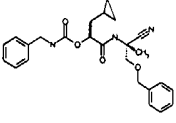
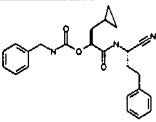
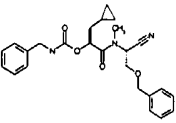
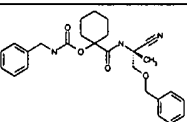
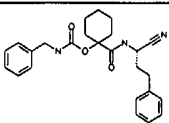
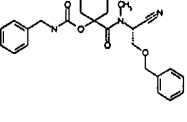
Structure	Chemical Name*
	Benzyl-carbamic acid 1-(1-cyanomethyl-3-methyl-butyl ester)
	Benzyl-carbamic acid 1-(1-cyano-3-methyl-butylcarbamoyl)-3-methyl-butyl ester
	Benzyl-carbamic acid 1-(1-cyano-cyclopropylcarbamoyl)-3-methyl-butyl ester
	Benzyl-carbamic acid 1-(1-cyanomethyl-2-cyclopropyl-ethyl ester)
	Benzyl-carbamic acid 1-(1-cyano-3-methyl-butylcarbamoyl)-2-cyclopropyl-ethyl ester
	Benzyl-carbamic acid 1-(1-cyano-cyclopropylcarbamoyl)-2-cyclopropyl-ethyl ester

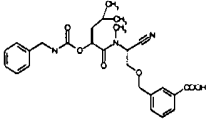
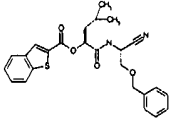
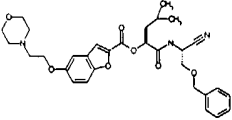
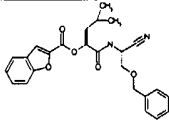
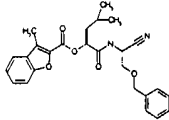
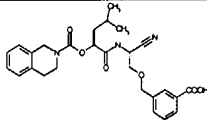
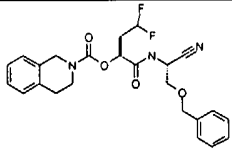
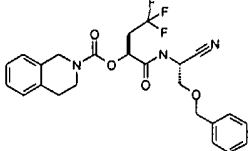
Structure	Chemical Name*
	Benzyl-carbamic acid 1-(cyanomethyl-carbamoyl)-cyclohexyl ester
	Benzyl-carbamic acid 1-(1-cyano-3-methyl-butylcarbamoyl)-cyclohexyl ester
	Benzyl-carbamic acid 1-(1-cyano-cyclopropylcarbamoyl)-cyclohexyl ester
	3,4-Dihydro-1H-isoquinoline-2-carboxylic acid 1-{{(2-chloro-benzyloxymethyl)-cyano-methyl}-carbamoyl}-3-methyl-butyl ester
	3,4-Dihydro-1H-isoquinoline-2-carboxylic acid 1-{{cyano-(4-methoxy-benzyloxymethyl)-methyl}-carbamoyl}-3-methyl-butyl ester
	3,4-Dihydro-1H-isoquinoline-2-carboxylic acid 1-[(benzyloxymethyl)-cyano-methyl]-carbamoyl}-3-methyl-butyl ester
	Benzyl-carbamic acid 1-{{(2-chloro-benzyloxymethyl)-cyano-methyl}-carbamoyl}-2-cyclopropyl-ethyl ester
	Benzyl-carbamic acid 1-{{cyano-(4-methoxy-benzyloxymethyl)-methyl}-carbamoyl}-2-cyclopropyl-ethyl ester
	Benzyl-carbamic acid 1-[(benzyloxymethyl)-cyano-methyl]-carbamoyl}-2-cyclopropyl-ethyl ester

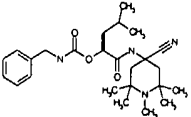
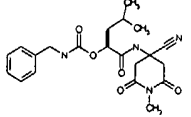
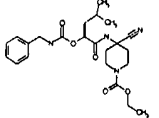
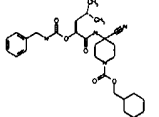
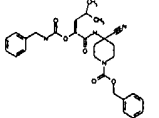
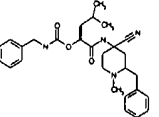
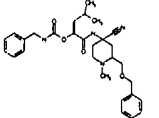
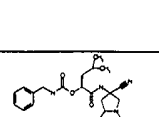
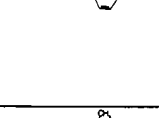
Structure	Chemical Name*
	Naphthalen-2-yl-carbamic acid 1-[[2-chloro-benzyloxymethyl)-cyano-methyl]-carbamoylester
	Naphthalen-2-yl-carbamic acid 1-[[cyano-(4-methoxy-benzyloxymethyl)-methyl]-carbamoylester
	Naphthalen-2-yl-carbamic acid 1-[[benzyloxymethyl)-cyano-methyl]-carbamoylester
	Phenyl-carbamic acid 1-(cyanomethyl)-2-dimethylamino-ethyl ester
	(3,4-Dichloro-phenyl)-carbamic acid 1-[[cyano-methyl-methyl)-carbamoylester]-3,3-dimethyl-butyl ester
	4-Phenyl-piperazine-1-carboxylic acid [(cyano-dimethyl-methyl)-carbamoylester]-phenyl-methyl ester
	5-Pyridin-4-yl-thiophene-2-carboxylic acid (1-cyano-3-methanesulfonyl-propylcarbamoylester)-pyridin-3-yl-methyl ester
	5-Pyridin-4-yl-thiophene-2-carboxylic acid (1-cyano-3-methanesulfonyl-propylcarbamoylester)-pyridin-3-yl-methyl ester
	4-(4-{1-[(Benzyl)-cyano-methyl)-carbamoylester}-propoxycarbonyl)-thiazol-2-ylamino)-piperidine-1-carboxylic acid ethyl ester

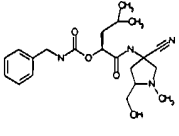
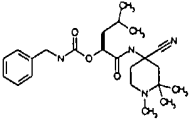
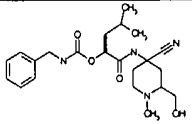
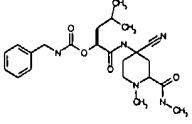
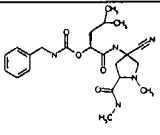
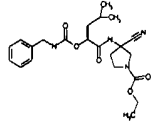
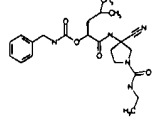
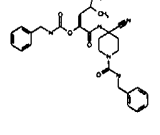
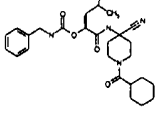
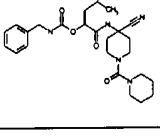
Structure	Chemical Name*
	4-[(4-Benzyl-piperazine-1-carbonyl)-amino]-benzoic acid 1- {[cyano-(4-methyl-benzyl)-methyl]-carbamoyl}-cyclopentyl ester
	4-Ethoxycarbonylamino-benzoic acid 4-(4-cyano-tetrahydro-pyran-4-ylcarbamoyl)-tetrahydro-pyran-4-yl ester
	Quinolin-2-yl-carbamic acid 1- [(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-methyl-butyl ester
	Morpholine-4-carboxylic acid 1- [(benzyloxymethyl-cyano-methyl)-carbamoyl]-3-methyl-butyl ester
	Benzyl-carbamic acid 1- [(benzyloxymethyl-cyano-methyl)-carbamoyl]-3-methyl-butyl ester
	Naphthalen-2-yl-carbamic acid 1- [(benzyloxymethyl-cyano-methyl)-carbamoyl]-3-methyl-butyl ester
	Morpholine-4-carboxylic acid 1- [(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-cyclopropyl-ethyl ester
	Naphthalen-2-yl-carbamic acid 1- [(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-cyclopropyl-ethyl ester
	Morpholine-4-carboxylic acid 1- [(benzyloxymethyl-cyano-methyl)-carbamoyl]-cyclohexyl ester

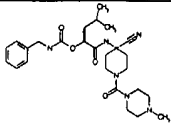
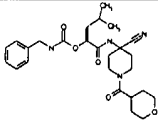
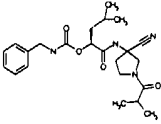
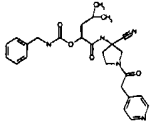
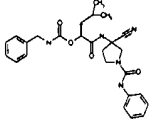
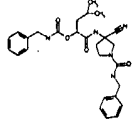
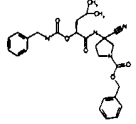
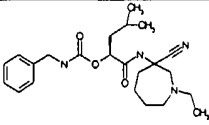
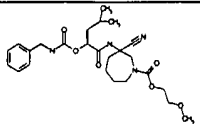
Structure	Chemical Name*
	Benzyl-carbamic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-cyclohexyl ester
	Naphthalene-2-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3-methyl-butyl ester
	Carbonic acid benzyl ester 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3-methyl-butyl ester
	3,4-Dihydro-1H-isoquinoline-2-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-cyclopropyl-ethyl ester
	Naphthalene-2-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-cyclopropyl-ethyl ester
	Carbonic acid benzyl ester 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-cyclopropyl-ethyl ester
	3,4-Dihydro-1H-isoquinoline-2-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-cyclohexyl ester
	Naphthalene-2-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-cyclohexyl ester
	Carbonic acid benzyl ester 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-cyclohexyl ester

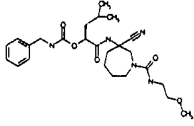
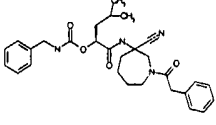
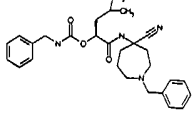
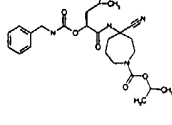
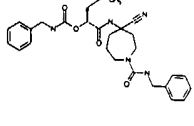
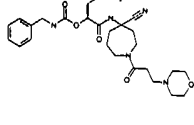
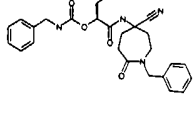
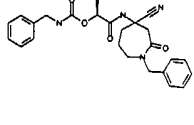
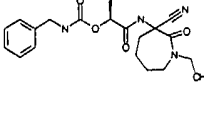
Structure	Chemical Name*
	Benzyl-carbamic acid 1-[(benzyloxymethyl-cyano-methyl-methyl)-carbamoyl]-3-methyl-butyl ester
	Benzyl-carbamic acid 1-(1-cyano-3-phenyl-propylcarbamoyl)-3-methyl-butyl ester
	Benzyl-carbamic acid 1-[(benzyloxymethyl-cyano-methyl)-methyl-carbamoyl]-3-methyl-butyl ester
	Benzyl-carbamic acid 1-[(benzyloxymethyl-cyano-methyl-methyl)-carbamoyl]-2-cyclopropyl-ethyl ester
	Benzyl-carbamic acid 1-(1-cyano-3-phenyl-propylcarbamoyl)-2-cyclopropyl-ethyl ester
	Benzyl-carbamic acid 1-[(benzyloxymethyl-cyano-methyl)-methyl-carbamoyl]-2-cyclopropyl-ethyl ester
	Benzyl-carbamic acid 1-[(benzyloxymethyl-cyano-methyl-methyl)-carbamoyl]-cyclohexyl ester
	Benzyl-carbamic acid 1-(1-cyano-3-phenyl-propylcarbamoyl)-cyclohexyl ester
	Benzyl-carbamic acid 1-[(benzyloxymethyl-cyano-methyl)-methyl-carbamoyl]-cyclohexyl ester

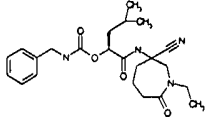
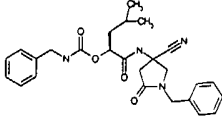
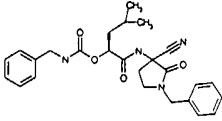
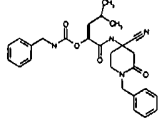
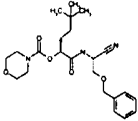
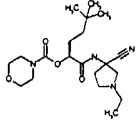
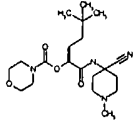
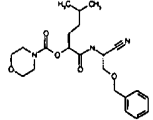
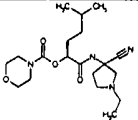
Structure	Chemical Name*
	3-{2-[(2-Benzylcarbamoyloxy-4-methyl-pentanoyl)-methyl-amino]-2-cyano-ethoxymethyl}-benzoic acid
	Benzo[b]thiophene-2-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3-methyl-butyl ester
	5-(2-Morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3-methyl-butyl ester
	Benzofuran-2-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3-methyl-butyl ester
	3-Methyl-benzofuran-2-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3-methyl-butyl ester
	3,4-Dihydro-1H-isoquinoline-2-carboxylic acid 1-[(3-carboxy-benzyloxymethyl)-cyano-methyl]-carbamoyl]-3-methyl-butyl ester
	3,4-Dihydro-1H-isoquinoline-2-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3,3-difluoro-propyl ester
	3,4-Dihydro-1H-isoquinoline-2-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3,3,3-trifluoro-propyl ester

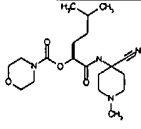
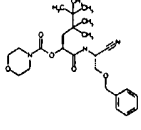
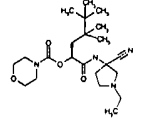
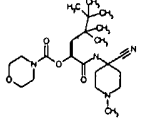
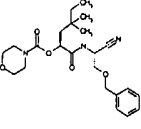
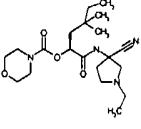
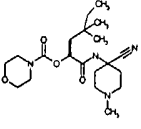
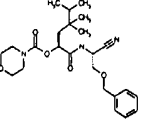
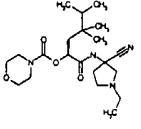
Structure	Chemical Name*
	Benzyl-carbamic acid 1-(4-cyano-1,2,2,6,6-pentamethyl-piperidin-4-ylcarbamoyl)-3-methyl-butyl ester
	Benzyl-carbamic acid 1-(4-cyano-1-methyl-2,6-dioxo-piperidin-4-ylcarbamoyl)-3-methyl-butyl ester
	4-(2-Benzylcarbamoxyloxy-4-methyl-pentanoylamino)-4-cyano-piperidine-1-carboxylic acid ethyl ester
	4-(2-Benzylcarbamoxyloxy-4-methyl-pentanoylamino)-4-cyano-piperidine-1-carboxylic acid cyclohexylmethyl ester
	4-(2-Benzylcarbamoxyloxy-4-methyl-pentanoylamino)-4-cyano-piperidine-1-carboxylic acid benzyl ester
	Benzyl-carbamic acid 1-(2-benzyl-4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-3-methyl-butyl ester
	Benzyl-carbamic acid 1-(2-benzyloxymethyl-4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-3-methyl-butyl ester
	Benzyl-carbamic acid 1-(5-benzyloxymethyl-3-cyano-1-methyl-pyrrolidin-3-ylcarbamoyl)-3-methyl-butyl ester
	4-(2-Benzylcarbamoxyloxy-4-methyl-pentanoylamino)-4-cyano-1-methyl-pyrrolidine-2-carboxylic acid methyl ester

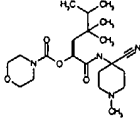
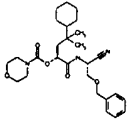
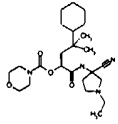
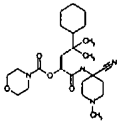
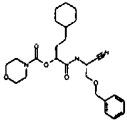
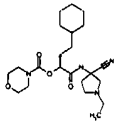
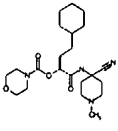
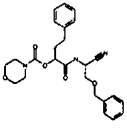
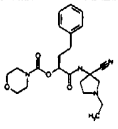
Structure	Chemical Name*
	Benzyl-carbamic acid 1-(3-cyano-5-hydroxymethyl-1-methyl-pyrrolidin-3-ylcarbamoyl)-3-methyl-butyl ester
	Benzyl-carbamic acid 1-(4-cyano-1,2,2-trimethyl-piperidin-4-ylcarbamoyl)-3-methyl-butyl ester
	Benzyl-carbamic acid 1-(4-cyano-2-hydroxymethyl-1-methyl-piperidin-4-ylcarbamoyl)-3-methyl-butyl ester
	Benzyl-carbamic acid 1-(4-cyano-1-methyl-2-methylcarbamoyl-piperidin-4-ylcarbamoyl)-3-methyl-butyl ester
	Benzyl-carbamic acid 1-(3-cyano-1-methyl-5-methylcarbamoyl-pyrrolidin-3-ylcarbamoyl)-3-methyl-butyl ester
	3-(2-Benzylcarbamoxyloxy-4-methyl-pentanoylamino)-3-cyano-pyrrolidine-1-carboxylic acid ethyl ester
	Benzyl-carbamic acid 1-(3-cyano-1-ethylcarbamoyl-pyrrolidin-3-ylcarbamoyl)-3-methyl-butyl ester
	Benzyl-carbamic acid 1-(1-benzylcarbamoxy-4-cyano-piperidin-4-ylcarbamoyl)-3-methyl-butyl ester
	Benzyl-carbamic acid 1-(4-cyano-1-cyclohexanecarbonyl-piperidin-4-ylcarbamoyl)-3-methyl-butyl ester
	Benzyl-carbamic acid 1-[4-cyano-1-(piperidine-1-carbonyl)-piperidin-4-ylcarbamoyl]-3-methyl-butyl ester

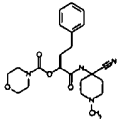
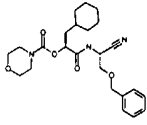
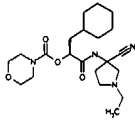
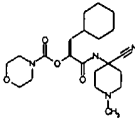
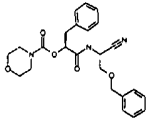
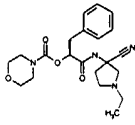
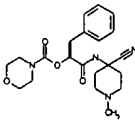
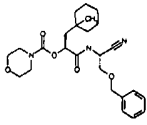
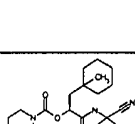
Structure	Chemical Name*
	ylcarbamoyl]-3-methyl-butyl ester
	Benzyl-carbamic acid 1-[4-cyano-1-(4-methyl-piperazine-1-carbonyl)-piperidin-4-ylcarbamoyl]-3-methyl-butyl ester
	Benzyl-carbamic acid 1-[4-cyano-1-(tetrahydro-pyran-4-carbonyl)-piperidin-4-ylcarbamoyl]-3-methyl-butyl ester
	Benzyl-carbamic acid 1-(3-cyano-1-isobutyryl-pyrrolidin-3-ylcarbamoyl)-3-methyl-butyl ester
	Benzyl-carbamic acid 1-[3-cyano-1-(2-pyridin-4-yl-acetyl)-pyrrolidin-3-ylcarbamoyl]-3-methyl-butyl ester
	Benzyl-carbamic acid 1-(3-cyano-1-phenylcarbamoyl-pyrrolidin-3-ylcarbamoyl)-3-methyl-butyl ester
	Benzyl-carbamic acid 1-(1-benzylcarbamoyl-3-cyano-pyrrolidin-3-ylcarbamoyl)-3-methyl-butyl ester
	3-(2-Benzylcarbamoxyloxy-4-methyl-pentanoylamino)-3-cyano-pyrrolidine-1-carboxylic acid benzyl ester
	Benzyl-carbamic acid 1-(3-cyano-1-ethyl-azepan-3-ylcarbamoyl)-3-methyl-butyl ester
	3-(2-Benzylcarbamoxyloxy-4-methyl-pentanoylamino)-3-cyano-azepane-1-carboxylic acid 2-methoxy-ethyl ester

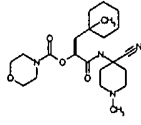
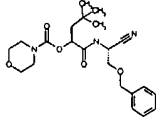
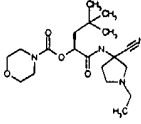
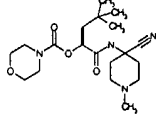
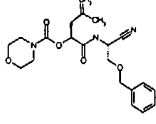
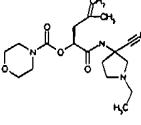
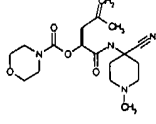
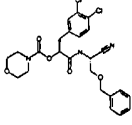
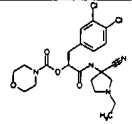
Structure	Chemical Name*
	Benzyl-carbamic acid 1-[3-cyano-1-(2-methoxy-ethylcarbamoyl)-azepan-3-ylcarbamoyl]-3-methyl-butyl ester
	Benzyl-carbamic acid 1-(3-cyano-1-phenylacetyl-azepan-3-ylcarbamoyl)-3-methyl-butyl ester
	Benzyl-carbamic acid 1-(1-benzyl-4-cyano-azepan-4-ylcarbamoyl)-3-methyl-butyl ester
	4-(2-Benzylcarbamoyloxy-4-methyl-pentanoylamino)-4-cyano-azepane-1-carboxylic acid isopropyl ester
	Benzyl-carbamic acid 1-(1-benzylcarbamoyl-4-cyano-azepan-4-ylcarbamoyl)-3-methyl-butyl ester
	Benzyl-carbamic acid 1-[4-cyano-1-(3-morpholin-4-yl-propionyl)-azepan-4-ylcarbamoyl]-3-methyl-butyl ester
	Benzyl-carbamic acid 1-(1-benzyl-4-cyano-7-oxo-azepan-4-ylcarbamoyl)-3-methyl-butyl ester
	Benzyl-carbamic acid 1-(1-benzyl-4-cyano-2-oxo-azepan-4-ylcarbamoyl)-3-methyl-butyl ester
	Benzyl-carbamic acid 1-(3-cyano-1-ethyl-2-oxo-azepan-3-ylcarbamoyl)-3-methyl-butyl ester

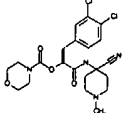
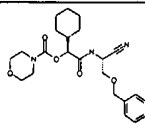
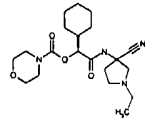
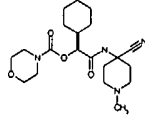
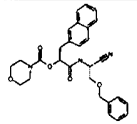
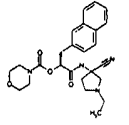
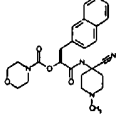
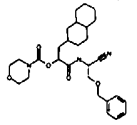
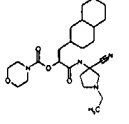
Structure	Chemical Name
	Benzyl-carbamic acid 1-(3-cyano-1-ethyl-7-oxo-azepan-3-ylcarbamoyl)-3-methyl-butyl ester
	Benzyl-carbamic acid 1-(1-benzyl-3-cyano-5-oxo-pyrrolidin-3-ylcarbamoyl)-3-methyl-butyl ester
	Benzyl-carbamic acid 1-(1-benzyl-3-cyano-2-oxo-pyrrolidin-3-ylcarbamoyl)-3-methyl-butyl ester
	Benzyl-carbamic acid 1-(1-benzyl-4-cyano-2-oxo-piperidin-4-ylcarbamoyl)-3-methyl-butyl ester
	Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-4,4-dimethyl-pentyl ester
	Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-4,4-dimethyl-pentyl ester
	Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-4,4-dimethyl-pentyl ester
	Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-4-methyl-pentyl ester
	Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-4-methyl-pentyl ester

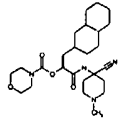
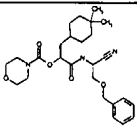
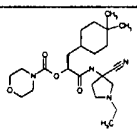
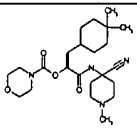
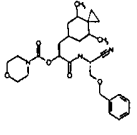
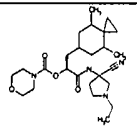
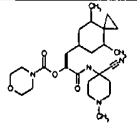
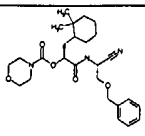
Structure	Chemical Name*
	Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbonyl)-4-methyl-pentyl ester
	Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbonyl]-3,3,4,4-tetramethyl-pentyl ester
	Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbonyl)-3,3,4,4-tetramethyl-pentyl ester
	Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbonyl)-3,3,4,4-tetramethyl-pentyl ester
	Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbonyl]-3,3-dimethyl-pentyl ester
	Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbonyl)-3,3-dimethyl-pentyl ester
	Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbonyl)-3,3-dimethyl-pentyl ester
	Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbonyl]-3,3,4-trimethyl-pentyl ester
	Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbonyl)-3,3,4-trimethyl-pentyl ester

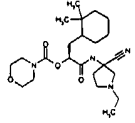
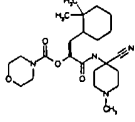
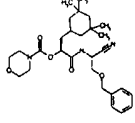
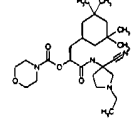
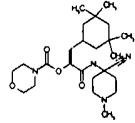
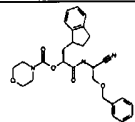
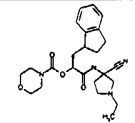
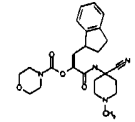
Structure	Chemical Name*
	Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-3,3,4-trimethyl-pentyl ester
	Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3-cyclohexyl-3-methyl-butyl ester
	Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-3-cyclohexyl-3-methyl-butyl ester
	Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-3-cyclohexyl-3-methyl-butyl ester
	Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3-cyclohexyl-propyl ester
	Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-3-cyclohexyl-propyl ester
	Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-3-cyclohexyl-propyl ester
	Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3-phenyl-propyl ester
	Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-3-phenyl-propyl ester

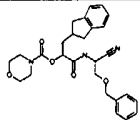
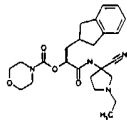
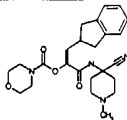
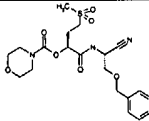
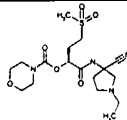
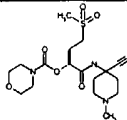
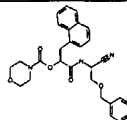
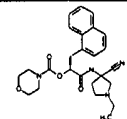
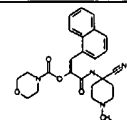
Structure	Chemical Name*
	Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-3-phenyl-propyl ester
	Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-cyclohexyl-ethyl ester
	Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-2-cyclohexyl-ethyl ester
	Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethyl ester
	Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-phenyl-ethyl ester
	Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-2-phenyl-ethyl ester
	Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-phenyl-ethyl ester
	Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-(1-methyl-cyclohexyl)-ethyl ester
	Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-2-(1-methyl-cyclohexyl)-ethyl ester

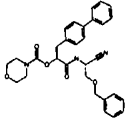
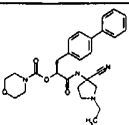
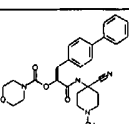
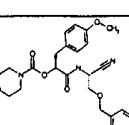
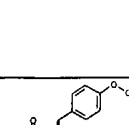
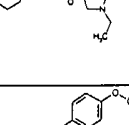
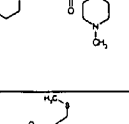
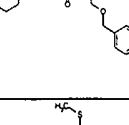
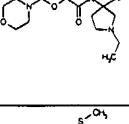
Structure	Chemical Name*
	Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-(1-methyl-cyclohexyl)-ethyl ester
	Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3,3-dimethyl-butyl ester
	Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-3,3-dimethyl-butyl ester
	Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-3,3-dimethyl-butyl ester
	Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3-methyl-but-3-enyl ester
	Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-3-methyl-but-3-enyl ester
	Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-3-methyl-but-3-enyl ester
	Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-(3,4-dichloro-phenyl)-ethyl ester
	Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-2-(3,4-dichloro-phenyl)-ethyl ester

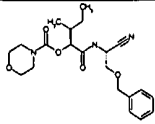
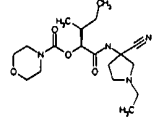
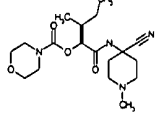
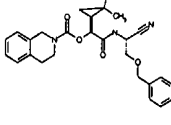
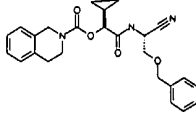
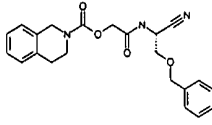
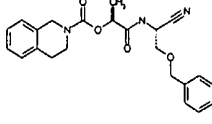
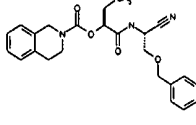
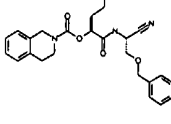
Structure	Chemical Name*
	Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-(3,4-dichloro-phenyl)-ethyl ester
	Morpholine-4-carboxylic acid [(benzyloxymethyl-cyano-methyl)-carbamoyl]-cyclohexyl-methyl ester
	Morpholine-4-carboxylic acid (3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-cyclohexyl-methyl ester
	Morpholine-4-carboxylic acid (4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-cyclohexyl-methyl ester
	Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-naphthalen-2-yl-ethyl ester
	Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-2-naphthalen-2-yl-ethyl ester
	Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-naphthalen-2-yl-ethyl ester
	Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-(decahydro-naphthalen-2-yl)-ethyl ester
	Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-2-(decahydro-naphthalen-2-yl)-ethyl ester

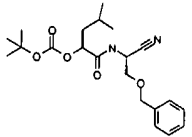
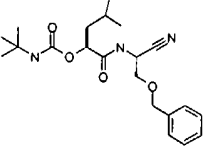
Structure	Chemical Name*
	Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-(decahydro-naphthalen-2-yl)-ethyl ester
	Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-(4,4-dimethyl-cyclohexyl)-ethyl ester
	Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-2-(4,4-dimethyl-cyclohexyl)-ethyl ester
	Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-(4,4-dimethyl-cyclohexyl)-ethyl ester
	Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-(4,8-dimethyl-spiro[2.5]oct-6-yl)-ethyl ester
	Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-2-(4,8-dimethyl-spiro[2.5]oct-6-yl)-ethyl ester
	Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-(4,8-dimethyl-spiro[2.5]oct-6-yl)-ethyl ester
	Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-(2,2-dimethyl-cyclohexyl)-ethyl ester

Structure	Chemical Name*
	Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-2-(2,2-dimethyl-cyclohexyl)-ethyl ester
	Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-(2,2-dimethyl-cyclohexyl)-ethyl ester
	Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-(3,3,5,5-tetramethyl-cyclohexyl)-ethyl ester
	Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-2-(3,3,5,5-tetramethyl-cyclohexyl)-ethyl ester
	Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-(3,3,5,5-tetramethyl-cyclohexyl)-ethyl ester
	Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-indan-1-yl-ethyl ester
	Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-2-indan-1-yl-ethyl ester
	Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-indan-1-yl-ethyl ester

Structure	Chemical Name*
	Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-indan-2-yl-ethyl ester
	Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-2-indan-2-yl-ethyl ester
	Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-indan-2-yl-ethyl ester
	Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3-methanesulfonyl-propyl ester
	Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-3-methanesulfonyl-propyl ester
	Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-3-methanesulfonyl-propyl ester
	Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-naphthalen-1-yl-ethyl ester
	Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-2-naphthalen-1-yl-ethyl ester
	Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-naphthalen-1-yl-ethyl ester

Structure	Chemical Name*
	Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-biphenyl-4-yl-ethyl ester
	Morpholine-4-carboxylic acid 2-biphenyl-4-yl-1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-ethyl ester
	Morpholine-4-carboxylic acid 2-biphenyl-4-yl-1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-ethyl ester
	Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-(4-methoxy-phenyl)-ethyl ester
	Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-2-(4-methoxy-phenyl)-ethyl ester
	Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-(4-methoxy-phenyl)-ethyl ester
	Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3-methylsulfonyl-propyl ester
	Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-3-methylsulfonyl-propyl ester
	Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-3-methylsulfonyl-propyl ester

Structure	Chemical Name*
	Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-methyl-butyl ester
	Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-2-methyl-butyl ester
	Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-methyl-butyl ester
	3,4-Dihydro-1H-isoquinoline-2-carboxylic acid [(benzyloxymethyl-cyano-methyl)-carbamoyl]-(2,2-dimethyl-cyclopropyl)-methyl ester
	3,4-Dihydro-1H-isoquinoline-2-carboxylic acid [(benzyloxymethyl-cyano-methyl)-carbamoyl]-cyclopropyl-methyl ester
	3,4-Dihydro-1H-isoquinoline-2-carboxylic acid [(benzyloxymethyl-cyano-methyl)-carbamoyl]-methyl ester
	3,4-Dihydro-1H-isoquinoline-2-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-ethyl ester
	3,4-Dihydro-1H-isoquinoline-2-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-propyl ester
	3,4-Dihydro-1H-isoquinoline-2-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-butyl ester

Structure	Chemical Name*
	Carbonic acid (S)-1-(((R)-benzyloxymethyl-cyano-methyl)-carbamoyl]-3-methyl-butyl ester tert-butyl ester
	tert-Butyl-carbamic acid (S)-1-(((R)-benzyloxymethyl-cyano-methyl)-carbamoyl]-3-methyl-butyl ester

* No stereochemistry is designated in the chemical names.

METHODS OF THERAPEUTIC USE

- 5 The compounds of the invention are useful in inhibiting the activity of cysteine proteases, such as cathepsins S, K, F, L and B. In doing so, these compounds are useful in blocking disease processes mediated by these cysteine proteases. Accordingly, the compounds of the present invention are useful in treating cysteine protease mediated disease states, i.e., those diseases in which cysteine protease activity contributes to the pathology and/or
- 10 symptomatology of the disease. A variety of such cysteine protease mediated disease states are known in the art and are disclosed, for example, in the references cited in the "Background of the Invention" section above. Examples of such diseases include chronic inflammatory disorders, emphysema, malaria, Chagas' disease, a disease characterized by bone resorption, bone loss or excessive cartilage or bone matrix degradation,
- 15 autoimmune diseases, Alzheimer's disease, atherosclerosis, endometriosis, asthma and airway inflammatory diseases.

Compounds of this invention effectively block degradation of the invariant chain to CLIP by cathepsin S, and thus inhibit antigen presentation and antigen-specific immune

20 responses. Control of antigen specific immune responses is an attractive means for treating autoimmune diseases and other undesirable T-cell mediated immune responses. Thus, there is provided methods of treatment using the compounds of this invention for such conditions. These encompass autoimmune diseases and other diseases involving

inappropriate antigen specific immune responses including, but not limited to, rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, ulcerative colitis, multiple sclerosis, Guillain-Barre syndrome, psoriasis, Grave's disease, myasthenia gravis, scleroderma, endometriosis, glomerulonephritis, atopic dermatitis, insulin-
5 dependent diabetes mellitus and asthma. The compounds of the invention can also be used to treat other disorders associated with extracellular proteolysis such as Alzheimer's disease and atherosclerosis. The compounds of the invention can also be used to treat other disorders associated with inappropriate autoimmune responses, T-cell mediated immune responses, or extracellular proteolysis mediated by cathepsin S, unrelated to
10 those listed above or discussed in the Background of the Invention. Therefore, the invention also provides methods of modulating an autoimmune disease comprising administering to a patient in need of such treatment a pharmaceutically effect amount of a compound according to the invention.

15 Compounds of the invention also inhibit cathepsin K. In doing so, they may block bone resorption, bone loss and inappropriate degradation of bone collagen and other bone matrix proteases. Thus, there is provided a method for treating diseases characterized by bone resorption, bone loss or excessive cartilage or bone matrix degradation such as osteoporosis, Paget's disease, Gaucher disease, gingivitis, periodontitis, osteoarthritis and
20 rheumatoid arthritis, or diseases characterized by increases in bone resorption and demineralization of bone, such as those associated with many cancers and with bone metastases of breast and prostate tumors. In view of their Cathepsin K inhibitory activity, the compounds of the invention may also be useful for treating disorders associated with excessive elastin degradation such as lymphangiomyomatosis, vascular inflammation,
25 and cardiovascular diseases such as atherosclerosis.. Inhibition of cathepsins F, L, and B are also within the scope of the invention due to similarity of the active sites in cysteine proteases as described above.

In addition, the compounds according to the invention can be used for the treatment of
30 any other specific disease-state or condition not specifically mentioned above which have

been treated, are being treated or will in the future be treated with compounds that are inhibitors of cathepsins S, K, F, L or B.

The activity of particular compounds disclosed herein against the various cathepsins, for example, cathepsin S and K, may be determined without undue experimentation by one
5 of ordinary skill in the art in view of the knowledge in the art, the guidance provided throughout this specification and by the screens described in the section below entitled "Assessment of Biological Properties."

10 Certain compounds of the invention have been tested for and have demonstrated cathepsin K inhibitory activity in one or more of the screens described below. Based on this testing, the following are compounds of the invention that would be expected to possess selective inhibitory activity against cathepsin K:

(3,4-Dichloro-phenyl)-carbamic acid 1-[(cyano-methyl-methyl)-carbamoyl]-3,3-dimethyl-butyl ester;

3-(2-Benzylcarbamoxyloxy-4-methyl-pentanoylamino)-3-cyano-azepane-1-carboxylic acid 2-methoxy-ethyl ester;

3-(2-Benzylcarbamoxyloxy-4-methyl-pentanoylamino)-3-cyano-pyrrolidine-1-carboxylic acid ethyl ester;

3-(2-Benzylcarbamoxyloxy-4-methyl-pentanoylamino)-3-cyano-pyrrolidine-1-carboxylic acid benzyl ester;

3,4-Dihydro-1H-isoquinoline-2-carboxylic acid [(benzyloxymethyl-cyano-methyl)-carbamoyl]-(2,2-dimethyl-cyclopropyl)-methyl ester;

3,4-Dihydro-1H-isoquinoline-2-carboxylic acid [(benzyloxymethyl-cyano-methyl)-carbamoyl]-cyclopropyl-methyl ester;

3,4-Dihydro-1H-isoquinoline-2-carboxylic acid [(benzyloxymethyl-cyano-methyl)-
carbamoyl]-methyl ester;

3,4-Dihydro-1H-isoquinoline-2-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-
carbamoyl]-3-methyl-butyl ester;

3,4-Dihydro-1H-isoquinoline-2-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-
carbamoyl]-2-cyclopropyl-ethyl ester;

3,4-Dihydro-1H-isoquinoline-2-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-
carbamoyl]-cyclohexyl ester

3,4-Dihydro-1H-isoquinoline-2-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-
carbamoyl]-3,3-difluoro-propyl ester

3,4-Dihydro-1H-isoquinoline-2-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-
carbamoyl]-3,3,3-trifluoro-propyl ester

3,4-Dihydro-1H-isoquinoline-2-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-
carbamoyl]-ethyl ester

3,4-Dihydro-1H-isoquinoline-2-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-
carbamoyl]-propyl ester

3,4-Dihydro-1H-isoquinoline-2-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-
carbamoyl]-butyl ester

3,4-Dihydro-1H-isoquinoline-2-carboxylic acid 1-{{(2-chloro-benzyloxymethyl)-
cyano-methyl}-carbamoyl}-3-methyl-butyl ester

3,4-Dihydro-1H-isoquinoline-2-carboxylic acid 1-[[{(3-carboxy-benzyloxymethyl)-cyano-methyl]-carbamoyl}-3-methyl-butyl ester

3,4-Dihydro-1H-isoquinoline-2-carboxylic acid 1-[[cyano-(4-methoxy-benzyloxymethyl)-methyl]-carbamoyl]-3-methyl-butyl ester

3-{2-[(2-Benzylcarbamoyloxy-4-methyl-pentanoyl)-methyl-amino]-2-cyano-ethoxymethyl}-benzoic acid

3-Methyl-benzofuran-2-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3-methyl-butyl ester

4-(2-Benzylcarbamoyloxy-4-methyl-pentanoylamino)-4-cyano-1-methyl-pyrrolidine-2-carboxylic acid methyl ester

4-(2-Benzylcarbamoyloxy-4-methyl-pentanoylamino)-4-cyano-azepane-1-carboxylic acid isopropyl ester

4-(2-Benzylcarbamoyloxy-4-methyl-pentanoylamino)-4-cyano-piperidine-1-carboxylic acid ethyl ester

4-(2-Benzylcarbamoyloxy-4-methyl-pentanoylamino)-4-cyano-piperidine-1-carboxylic acid cyclohexylmethyl ester

4-(2-Benzylcarbamoyloxy-4-methyl-pentanoylamino)-4-cyano-piperidine-1-carboxylic acid benzyl ester

4-(4-{1-[(Benzyl-cyano-methyl)-carbamoyl]-propoxycarbonyl}-thiazol-2-ylamino)-piperidine-1-carboxylic acid ethyl ester

4-[(4-Benzyl-piperazine-1-carbonyl)-amino]-benzoic acid 1- {[cyano-(4-methyl-benzyl)-methyl]-carbamoyl}-cyclopentyl ester

4-Ethoxycarbonylamino-benzoic acid 4-(4-cyano-tetrahydro-pyran-4-ylcarbamoyl)-tetrahydro-pyran-4-yl ester

4-Phenyl-piperazine-1-carboxylic acid [(cyano-dimethyl-methyl)-carbamoyl]-phenyl-methyl ester

5-(2-Morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3-methyl-butyl ester

5-Pyridin-4-yl-thiophene-2-carboxylic acid (1-cyano-3-methanesulfonyl-propylcarbamoyl)-pyridin-3-yl-methyl ester

5-Pyridin-4-yl-thiophene-2-carboxylic acid (1-cyano-3-methanesulfonyl-propylcarbamoyl)-pyridin-3-yl-methyl ester

Benzo[b]thiophene-2-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3-methyl-butyl ester

Benzofuran-2-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3-methyl-butyl ester

Benzyl-carbamic acid 1-(1-benzyl-3-cyano-2-oxo-pyrrolidin-3-ylcarbamoyl)-3-methyl-butyl ester

Benzyl-carbamic acid 1-(1-benzyl-3-cyano-5-oxo-pyrrolidin-3-ylcarbamoyl)-3-methyl-butyl ester

Benzyl-carbamic acid 1-(1-benzyl-4-cyano-2-oxo-azepan-4-ylcarbamoyl)-3-methyl-butyl ester

Benzyl-carbamic acid 1-(1-benzyl-4-cyano-2-oxo-piperidin-4-ylcarbamoyl)-3-methyl-butyl ester

Benzyl-carbamic acid 1-(1-benzyl-4-cyano-7-oxo-azepan-4-ylcarbamoyl)-3-methyl-butyl ester

Benzyl-carbamic acid 1-(1-benzyl-4-cyano-azepan-4-ylcarbamoyl)-3-methyl-butyl ester

Benzyl-carbamic acid 1-(1-benzylcarbamoyl-3-cyano-pyrrolidin-3-ylcarbamoyl)-3-methyl-butyl ester

Benzyl-carbamic acid 1-(1-benzylcarbamoyl-4-cyano-azepan-4-ylcarbamoyl)-3-methyl-butyl ester

Benzyl-carbamic acid 1-(1-benzylcarbamoyl-4-cyano-piperidin-4-ylcarbamoyl)-3-methyl-butyl ester

Benzyl-carbamic acid 1-(1-cyano-3-methyl-butylcarbamoyl)-2-cyclopropyl-ethyl ester

Benzyl-carbamic acid 1-(1-cyano-3-methyl-butylcarbamoyl)-3-methyl-butyl ester

Benzyl-carbamic acid 1-(1-cyano-3-methyl-butylcarbamoyl)-cyclohexyl ester

Benzyl-carbamic acid 1-(1-cyano-3-phenyl-propylcarbamoyl)-2-cyclopropyl-ethyl ester

Benzyl-carbamic acid 1-(1-cyano-3-phenyl-propylcarbamoyl)-3-methyl-butyl ester

Benzyl-carbamic acid 1-(1-cyano-3-phenyl-propylcarbamoyle)-cyclohexyl ester

Benzyl-carbamic acid 1-(1-cyano-cyclopropylcarbamoyle)-2-cyclopropyl-ethyl ester

Benzyl-carbamic acid 1-(1-cyano-cyclopropylcarbamoyle)-3-methyl-butyl ester

Benzyl-carbamic acid 1-(1-cyano-cyclopropylcarbamoyle)-cyclohexyl ester

Benzyl-carbamic acid 1-(2-benzyl-4-cyano-1-methyl-piperidin-4-ylcarbamoyle)-3-methyl-butyl ester

Benzyl-carbamic acid 1-(2-benzyloxymethyl-4-cyano-1-methyl-piperidin-4-ylcarbamoyle)-3-methyl-butyl ester

Benzyl-carbamic acid 1-(3-cyano-1-ethyl-2-oxo-azepan-3-ylcarbamoyle)-3-methyl-butyl ester

Benzyl-carbamic acid 1-(3-cyano-1-ethyl-7-oxo-azepan-3-ylcarbamoyle)-3-methyl-butyl ester

Benzyl-carbamic acid 1-(3-cyano-1-ethyl-azepan-3-ylcarbamoyle)-3-methyl-butyl ester

Benzyl-carbamic acid 1-(3-cyano-1-ethylcarbamoyle-pyrrolidin-3-ylcarbamoyle)-3-methyl-butyl ester

Benzyl-carbamic acid 1-(3-cyano-1-isobutyryl-pyrrolidin-3-ylcarbamoyle)-3-methyl-butyl ester

Benzyl-carbamic acid 1-(3-cyano-1-methyl-5-methylcarbamoyle-pyrrolidin-3-ylcarbamoyle)-3-methyl-butyl ester

Benzyl-carbamic acid 1-(3-cyano-1-phenylacetyl-azepan-3-ylcarbamoyle)-3-methyl-butyl ester

Benzyl-carbamic acid 1-(3-cyano-1-phenylcarbamoyle-pyrrolidin-3-ylcarbamoyle)-3-methyl-butyl ester

Benzyl-carbamic acid 1-(3-cyano-5-hydroxymethyl-1-methyl-pyrrolidin-3-ylcarbamoyle)-3-methyl-butyl ester

Benzyl-carbamic acid 1-(4-cyano-1,2,2,6,6-pentamethyl-piperidin-4-ylcarbamoyle)-3-methyl-butyl ester

Benzyl-carbamic acid 1-(4-cyano-1,2,2-trimethyl-piperidin-4-ylcarbamoyle)-3-methyl-butyl ester

Benzyl-carbamic acid 1-(4-cyano-1-cyclohexanecarbonyl-piperidin-4-ylcarbamoyle)-3-methyl-butyl ester

Benzyl-carbamic acid 1-(4-cyano-1-methyl-2,6-dioxo-piperidin-4-ylcarbamoyle)-3-methyl-butyl ester

Benzyl-carbamic acid 1-(4-cyano-1-methyl-2-methylcarbamoyle-piperidin-4-ylcarbamoyle)-3-methyl-butyl ester

Benzyl-carbamic acid 1-(4-cyano-2-hydroxymethyl-1-methyl-piperidin-4-ylcarbamoyle)-3-methyl-butyl ester

Benzyl-carbamic acid 1-(5-benzyloxymethyl-3-cyano-1-methyl-pyrrolidin-3-ylcarbamoyle)-3-methyl-butyl ester

Benzyl-carbamic acid 1-(cyanomethyl-carbamoyl)-2-cyclopropyl-ethyl ester

Benzyl-carbamic acid 1-(cyanomethyl-carbamoyl)-3-methyl-butyl ester

Benzyl-carbamic acid 1-(cyanomethyl-carbamoyl)-cyclohexyl ester

Benzyl-carbamic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-cyclopropyl-ethyl ester

Benzyl-carbamic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3-methyl-butyl ester

Benzyl-carbamic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-cyclohexyl ester

Benzyl-carbamic acid 1-[(benzyloxymethyl-cyano-methyl)-methyl-carbamoyl]-3-methyl-butyl ester

Benzyl-carbamic acid 1-[(benzyloxymethyl-cyano-methyl)-methyl-carbamoyl]-2-cyclopropyl-ethyl ester

Benzyl-carbamic acid 1-[(benzyloxymethyl-cyano-methyl)-methyl-carbamoyl]-cyclohexyl ester

Benzyl-carbamic acid 1-[(benzyloxymethyl-cyano-methyl-methyl)-carbamoyl]-3-methyl-butyl ester

Benzyl-carbamic acid 1-[(benzyloxymethyl-cyano-methyl-methyl)-carbamoyl]-2-cyclopropyl-ethyl ester

Benzyl-carbamic acid 1-[(benzyloxymethyl-cyano-methyl-methyl)-carbamoyl]-cyclohexyl ester

Benzyl-carbamic acid 1-[3-cyano-1-(2-methoxy-ethylcarbamoyl)-azepan-3-ylcarbamoyl]-3-methyl-butyl ester

Benzyl-carbamic acid 1-[3-cyano-1-(2-pyridin-4-yl-acetyl)-pyrrolidin-3-ylcarbamoyl]-3-methyl-butyl ester

Benzyl-carbamic acid 1-[4-cyano-1-(3-morpholin-4-yl-propionyl)-azepan-4-ylcarbamoyl]-3-methyl-butyl ester

Benzyl-carbamic acid 1-[4-cyano-1-(4-methyl-piperazine-1-carbonyl)-piperidin-4-ylcarbamoyl]-3-methyl-butyl ester

Benzyl-carbamic acid 1-[4-cyano-1-(piperidine-1-carbonyl)-piperidin-4-ylcarbamoyl]-3-methyl-butyl ester

Benzyl-carbamic acid 1-[4-cyano-1-(tetrahydro-pyran-4-carbonyl)-piperidin-4-ylcarbamoyl]-3-methyl-butyl ester

Benzyl-carbamic acid 1-{{(2-chloro-benzyloxymethyl)-cyano-methyl}-carbamoyl}-2-cyclopropyl-ethyl ester

Benzyl-carbamic acid 1-{{cyano-(4-methoxy-benzyloxymethyl)-methyl}-carbamoyl}-2-cyclopropyl-ethyl ester

Carbonic acid (S)-1-(((R)-benzyloxymethyl-cyano-methyl)-carbamoyl]-3-methyl-butyl ester tert-butyl ester

Carbonic acid benzyl ester 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3-methyl-butyl ester

Carbonic acid benzyl ester 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-cyclopropyl-ethyl ester

Carbonic acid benzyl ester 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-cyclohexyl ester

Naphthalen-2-yl-carbamic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-cyclohexyl ester

Naphthalen-2-yl-carbamic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3-methyl-butyl ester

Naphthalen-2-yl-carbamic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-cyclopropyl-ethyl ester

Naphthalen-2-yl-carbamic acid 1-{{(2-chloro-benzyloxymethyl)-cyano-methyl}-carbamoyl}-cyclohexyl ester

Naphthalen-2-yl-carbamic acid 1-{{cyano-(4-methoxy-benzyloxymethyl)-methyl}-carbamoyl}-cyclohexyl ester

Naphthalene-2-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3-methyl-butyl ester

Naphthalene-2-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-cyclopropyl-ethyl ester

Naphthalene-2-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-cyclohexyl ester

Phenyl-carbamic acid 1-(cyanomethyl-carbamoyl)-2-dimethylamino-ethyl ester

Quinolin-2-yl-carbamic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-methyl-butyl ester; and

tert-Butyl-carbamic acid (S)-1-[(R)-benzyloxymethyl-cyano-methyl)-carbamoyl]-3-methyl-butyl ester

Certain compounds of the invention have been tested for and have demonstrated cathepsin S inhibitory activity in one or more of the screens described below. Based on
5 this testing, the following are compounds of the invention that would be expected to possess selective inhibitory activity against cathepsin S:

Morpholine-4-carboxylic acid (3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-cyclohexyl-methyl ester

Morpholine-4-carboxylic acid (4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-cyclohexyl-methyl ester

Morpholine-4-carboxylic acid [(benzyloxymethyl-cyano-methyl)-carbamoyl]-cyclohexyl-methyl ester

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-4,4-dimethyl-pentyl ester

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-4-methyl-pentyl ester

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-3,3,4,4-tetramethyl-pentyl ester

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-3,3-dimethyl-pentyl ester

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-3,3,4-trimethyl-pentyl ester

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-3-cyclohexyl-3-methyl-butyl ester

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-3-cyclohexyl-propyl ester

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-3-phenyl-propyl ester

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-2-cyclohexyl-ethyl ester

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-2-phenyl-ethyl ester

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-2-(1-methyl-cyclohexyl)-ethyl ester

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-3,3-dimethyl-butyl ester

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-3-methyl-but-3-enyl ester

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyle)-2-(3,4-dichloro-phenyl)-ethyl ester

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyle)-2-naphthalen-2-yl-ethyl ester

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyle)-2-(decahydro-naphthalen-2-yl)-ethyl ester

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyle)-2-(4,4-dimethyl-cyclohexyl)-ethyl ester

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyle)-2-(4,8-dimethyl-spiro[2.5]oct-6-yl)-ethyl ester

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyle)-2-(2,2-dimethyl-cyclohexyl)-ethyl ester

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyle)-2-(3,3,5,5-tetramethyl-cyclohexyl)-ethyl ester

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyle)-2-indan-1-yl-ethyl ester

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyle)-2-indan-2-yl-ethyl ester

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyle)-3-methanesulfonyl-propyl ester

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-2-naphthalen-1-yl-ethyl ester

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-2-(4-methoxy-phenyl)-ethyl ester

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-3-methylsulfanyl-propyl ester

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-2-methyl-butyl ester

Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-4,4-dimethyl-pentyl ester

Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-4-methyl-pentyl ester

Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-3,3,4,4-tetramethyl-pentyl ester

Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-3,3-dimethyl-pentyl ester

Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-3,3,4-trimethyl-pentyl ester

Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-3-cyclohexyl-3-methyl-butyl ester

Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-3-cyclohexyl-propyl ester

Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-3-phenyl-propyl ester

Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethyl ester

Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-phenyl-ethyl ester;

Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-(1-methyl-cyclohexyl)-ethyl ester;

Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-3,3-dimethyl-butyl ester;

Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-3-methyl-but-3-enyl ester;

Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-(3,4-dichloro-phenyl)-ethyl ester;

Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-naphthalen-2-yl-ethyl ester;

Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-(decahydro-naphthalen-2-yl)-ethyl ester;

Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-(4,4-dimethyl-cyclohexyl)-ethyl ester;

Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-(4,8-dimethyl-spiro[2.5]oct-6-yl)-ethyl ester;

Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-(2,2-dimethyl-cyclohexyl)-ethyl ester;

Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-(3,3,5,5-tetramethyl-cyclohexyl)-ethyl ester;

Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-indan-1-yl-ethyl ester;

Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-indan-2-yl-ethyl ester;

Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-3-methanesulfonyl-propyl ester;

Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-naphthalen-1-yl-ethyl ester;

Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-(4-methoxy-phenyl)-ethyl ester;

Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-3-methylsulfanyl-propyl ester;

Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-methyl-butyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3-methyl-butyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-cyclopropyl-ethyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-cyclohexyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-4,4-dimethyl-pentyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-4-methyl-pentyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3,3,4,4-tetramethyl-pentyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3,3-dimethyl-pentyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3,3,4-trimethyl-pentyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3-cyclohexyl-3-methyl-butyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3-cyclohexyl-propyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3-phenyl-propyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-cyclohexyl-ethyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-phenyl-ethyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-(1-methyl-cyclohexyl)-ethyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3,3-dimethyl-butyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3-methyl-but-3-enyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-(3,4-dichloro-phenyl)-ethyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-naphthalen-2-yl-ethyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-(decahydro-naphthalen-2-yl)-ethyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-(4,4-dimethyl-cyclohexyl)-ethyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-(4,8-dimethyl-spiro[2.5]oct-6-yl)-ethyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-(2,2-dimethyl-cyclohexyl)-ethyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-(3,3,5,5-tetramethyl-cyclohexyl)-ethyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-indan-1-yl-ethyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-indan-2-yl-ethyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3-methanesulfonyl-propyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-naphthalen-1-yl-ethyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-biphenyl-4-yl-ethyl ester

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-(4-methoxy-phenyl)-ethyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3-methylsulfanyl-propyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-methyl-butyl ester;

Morpholine-4-carboxylic acid 2-biphenyl-4-yl-1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-ethyl ester; and

Morpholine-4-carboxylic acid 2-biphenyl-4-yl-1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-ethyl ester.

For therapeutic use, the compounds of the invention may be administered in any conventional dosage form in any conventional manner to a patient, e.g. a mammal, in need of such treatment. Routes of administration include, but are not limited to,
5 intravenously, intramuscularly, subcutaneously, intrasynovially, by infusion, sublingually, transdermally, orally, topically or by inhalation. The preferred modes of administration are oral and intravenous.

The compounds of this invention may be administered alone or in combination with
10 adjuvants that enhance stability of the inhibitors, facilitate administration of pharmaceutical compositions containing them in certain embodiments, provide increased dissolution or dispersion, increase inhibitory activity, provide adjunct therapy, and the like, including other active ingredients. Advantageously, such combination therapies utilize lower dosages of the conventional therapeutics, thus avoiding possible toxicity and
15 adverse side effects incurred when those agents are used as monotherapies. Compounds of the invention may be physically combined with the conventional therapeutics or other adjuvants into a single pharmaceutical composition. Advantageously, the compounds may then be administered together in a single dosage form. In some embodiments, the pharmaceutical compositions comprising such combinations of compounds contain at

least about 15%, but more preferably at least about 20%, of a compound of the invention (w/w) or a combination thereof. Alternatively, the compounds may be administered separately (either serially or in parallel). Separate dosing allows for greater flexibility in the dosing regime.

5

As mentioned above, dosage forms of the compounds of this invention include pharmaceutically acceptable carriers and adjuvants known to those of ordinary skill in the art. These carriers and adjuvants include, for example, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, buffer substances, water, salts or electrolytes
10 and cellulose-based substances. Preferred dosage forms include, tablet, capsule, caplet, liquid, solution, suspension, emulsion, lozenges, syrup, reconstitutable powder, granule, suppository and transdermal patch. Methods for preparing such dosage forms are known (see, for example, H.C. Ansel and N.G. Popovich, *Pharmaceutical Dosage Forms and Drug Delivery Systems*, 5th ed., Lea and Febiger (1990)). Dosage levels and
15 requirements are well-recognized in the art and may be selected by those of ordinary skill in the art from available methods and techniques suitable for a particular patient. In some embodiments, dosage levels range from about 10-1000 mg/dose for a 70 kg patient. Although one dose per day may be sufficient, up to 5 doses per day may be given. For oral doses, up to 2000 mg/day may be required. As the skilled artisan will appreciate,
20 lower or higher doses may be required depending on particular factors. For instance, specific dosage and treatment regimens will depend on factors such as the patient's general health profile, the severity and course of the patient's disorder or disposition thereto, and the judgment of the treating physician.

25

ASSESSMENT OF BIOLOGICAL PROPERTIES

Expression and Purification of recombinant human Cathepsin S

Cloning of human cathepsin S:

30

U937 RNA was subjected to reverse transcriptase / polymerase chain reaction with primer A (5'cacaatgaaacggctggttg 3') and primer B (5'ctagatttctgggtaagaggg 3')

designed to specifically amplify the cathepsin S cDNA. The resulting 900 bp DNA fragment was subcloned into pGEM-T (Promega) and sequenced to confirm its identity. This construct was used for all subsequent manipulations. This procedure is typical for cloning of known genes and is established in its field.

5

Human Pre-Pro-Cat S was removed from pGem-T vector (Promega, 2800 Woods Hollow Rd, Madison, WI 53711) by digestion with restriction enzyme SacII, followed by treatment with T4 DNA polymerase to generate a blunt end, and a second restriction enzyme digest with Sall. It was subcloned into pFastBac1 donor plasmid (GibcoBRL, 10 8717 Grovemont Cr., Gaithersburg, MD 20884) which had been cut with restriction enzyme BamHI and blunt-ended and then cut with restriction enzyme Sall. The ligation mixture was used to transform DH5a competent cells (GibcoBRL) and plated on LB plates containing 100ug/ml ampicillin. Colonies were grown in overnight cultures of LB media containing 50ug/ml Ampicillin, plasmid DNA isolated and correct insert 15 confirmed by restriction enzyme digestion. Recombinant pFastBac donor plasmid was transformed into DH10Bac competent cells (GibcoBRL). Large white colonies were picked from LB plates containing 50ug/ml kanamycin, 7ug/ml gentamicin, 10ug/ml tetracycline, 100ug/ml Bluo-gal, and 40ug/ml IPTG. DNA was isolated and used to transfect Sf9 insect cells using CellFECTIN reagent (GibcoBRL). Cells and supernatant 20 were harvested after 72 hours. Viral supernatant was passaged twice and presence of Cat S confirmed by PCR of the supernatant.

SF9 cells were infected with recombinant baculovirus at a MOI of 5 for 48-72 hrs. Cell pellet was lysed and incubated in buffer at pH 4.5 at 37 for 2 hours to activate Cat S from 25 pro-form to active mature form (Bromme, D & McGrath, M., Protein Science, 1996, 5:789-791.) Presence of Cat S was confirmed by SDS-PAGE and Western blot using rabbit anti-human proCat S.

Inhibition of Cathepsin S

Human recombinant cathepsin S expressed in Baculovirus is used at a final concentration of 10 nM in buffer. Buffer is 50 mM Na Acetate, pH 6.5, 2.5 mM EDTA, 2.5 mM TCEP.
5 Enzyme is incubated with either compound or DMSO for 10 min at 37°C. Substrate 7-amino-4-methylcoumarin, CBZ-L-valyl-L-valyl-L-arginineamide (custom synthesis by Molecular Probes) is diluted to 20uM in water (final concentration of 5uM), added to assay and incubated for additional 10 minutes at 37°C. Compound activity is measured by diminished fluorescence compared to DMSO control when read at 360nm excitation
10 and 460nm emission.

Another assay for Cathepsin S inhibitory activity is the cell based assay described in Riese, R.J. et al., Immunity, 1996, 4, 357-366, incorporated herein by reference.

15 Preferred compounds for the inhibition of Cathepsin S are those that will exhibit an IC₅₀ of 10 micromolar or below in the above assays.

Inhibition of Cathepsin K, F, L and B:

20 Inhibition of these enzymes by particular compounds of the invention may be determined without undue experimentation by using art recognized methods as provided in the references cited hereinbelow each of which is incorporated herein by reference:

A Cathepsin K bone resorption cellular assay can be carried out as follows:

25

In vitro culturing of murine osteoclasts can be accomplished by a modification of previous published protocols (1-6). Briefly, tibiae and femur are removed from 6-10 week-old C57BL/6 male mice. Marrow is flushed from the bones and placed into MEM-alpha media (Gibco) supplemented with 10% FCS (Gibco). After washing, 100 mm
30 tissue culture dishes is seeded at 1×10^6 cells/cm² (at 2×10^6 cells/mL) and supplemented with 10 nM 1,25-dihydroxyvitamin D3 (Sigma) and cultured at 37°C and 5% CO₂.

Cultures are fed every 3 days by removing 80% of the media and replacement with fresh media and vitamin D₃. *In vitro* bone resorption assays can be carried out similar to those previously described (1, 7-9) with modifications: After 7 days in culture, osteoclasts are trypsinized and scraped off 100 mm dishes and split into 96 well plates containing bovine
5 cortical bone slices. After 2 hours at 37°C, non-adherent cells are removed by washing and MEM-alpha media containing 0.7 g sodium bicarbonate/liter is added to the wells and media is supplemented with 100 ng/mL sRANKL (R&D Systems). After 3-4 days, supernatants are removed and analyzed for the presence of C-terminal peptides from type I collagen using a one-step ELISA (Osteometer Biotech) originally described by Foged et
10 al. (10).

1. S.K. Lee, S.R. Goldring, and J.A. Lorenzo. (1995) *Endocrinology* 136: 4572.
2. N. Takahashi et al. (1988) *Endocrinology* 122: 1373.
3. N. Takahashi et al. (1988) *Endocrinology* 123:1504.
- 15 4. T. Akatsu et al. (1992) *J. Bone Miner. Res.* 7: 1297.
5. T. Akatsu et al. (1989) *J. Bone Miner. Res.* 4: 29.
6. T. Shuto et al. (1994) *Endocrinology* 134:1121.
7. A. Boyde, N.N. Ali, and S.J. Jones. (1984) *Br. Dent. J.* 156: 216.
8. D.W. Dempster et al. (1987) *J. Bone Miner. Res.* 2: 443.
- 20 9. R.J. Murrills et al. (1989) *J. Bone Miner. Res.* 4: 259.
10. N.T. Foged et al. (1996) *J. Bone Miner. Res.* 11: 226.

Preferred compounds for the inhibition of Cathepsin K are those that will exhibit an IC₅₀ of 50 micromolar or below in the above cellular assay.

25

A Cathepsin K enzymatic assay is disclosed in the following reference:

- Bromme, D., Okamoto, K., Wang, B. B., and Biroc, S. (1996) *J. Biol. Chem.* **271**,
30 2126-2132.

Preferred compounds for the inhibition of Cathepsin K are those that will exhibit an IC₅₀ of 10 micromolar or below in the above enzymatic assay.

5 Cathepsins B and L assays are to be found in the following reference:

Methods in Enzymology, Vol.244, Proteolytic Enzymes: Serine and Cysteine Peptidases, Alan J. Barrett, ed.

10

Cathepsin F assays are to be found in the following references:

Wang, B., Shi, G.P., Yao, P.M., Li, Z., Chapman, H.A., and Bromme, D. (1998) *J. Biol. Chem.* **273**, 32000-32008.

15

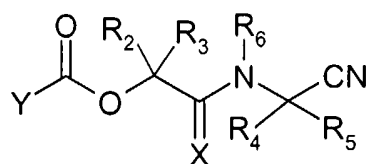
Santamaria, I., Velasco, G., Pendas, A.M., Paz, A., and Lopez-Otin, C (1999) *J. Biol. Chem.* **274**, 13800-13809.

20 Preferred compounds for the inhibition of Cathepsins B, L and F are those that will exhibit an IC₅₀ of 10 micromolar or below in the above assays.

What is claimed is

1. A compound of the following formula (I):

5



(I)

10

wherein:

Y is R₁, R₁O-, R₁S-, (R₁)₂N-, (R₁)₃C-;

15

Each R₁ is independently hydrogen, C1-10 alkyl, C3-8 cycloalkyl, aryl, benzyl, tetrahydronaphthyl, indenyl, indanyl, C1-10alkylsulfonylC1-10alkyl, C3-8cycloalkylsulfonylC1-10alkyl, arylsulfonylC1-10alkyl, a heterocyclyl or heteroaryl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indoliny, pyranyl, tetrahydropyranyl, tetrahydrothiopyranyl, thiopyranyl, furanyl, tetrahydrofuranly, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, tetrazolyl, pyrazolyl, indolyl, benzofuranly, benzothienyl, dihydrobenzofuranly, dihydrobenzothienyl, benzimidazolyl, benzothiazolyl, benzisoxazolyl, benzisothiazolyl, quinolinyl, tetrahydroquinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, quinazolinyl, tetrahydroquinazolinyl, benzoxazolyl, 2*H*-benzo[e][1,3]oxazine and quinoxalinyl, wherein each R₁ is optionally substituted by one or more R_a; or R₁ is R_a or R_b;

20

25

Each R_a is independently hydrogen, C1-10 alkyl, C3-8 cycloalkyl, aryl, tetrahydronaphthyl, indenyl, indanyl, a heterocycle or heteroaryl selected from the group consisting of pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, thienyl, pyrrolyl, oxazolyl, dihydro-oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, dihydrobenzofuranyl, dihydrobenzothienyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, benzisoxazolyl, quinolinyl, isoquinolinyl, quinazolinyl, and quinoxalinyl, C1-10 alkoxy, C1-10alkanoyl, C1-10alkanoyloxy, aryloxy, benzyloxy, aroyl, C1-10 alkoxycarbonyl, aryloxycarbonyl, aroyloxy, heterocyclyloxy, heterocyclyl-C1-6alkoxy, heteroaryloxy or heteroaryl-C1-6alkoxy, wherein the heterocyclyl or heteroaryloxy moiety is selected from those described in this paragraph, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-10 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, dihydrobenzofuranyl, dihydrobenzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or quinoxalinyl, or R_a is C1-10 mono- or dialkyl amino, C1-10 alkanoylamino, aroylamino, C1-10 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, arylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by one or more C1-10 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, dihydrobenzofuranyl, dihydrobenzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or quinoxalinyl, or R_a is C1-10 alkoxycarbonylamino, aryloxycarbonylamino, heterocyclylcarbonylamino, heteroarylcarbonylamino, C1-10 alkylcarbamoyloxy, arylcarbamoyloxy, C1-10 alkylsulfonylamino, arylsulfonylamino, C1-10

alkylaminosulfonyl, arylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-10 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, dihydrobenzofuranyl, dihydrobenzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or quinoxalinyl, or R_a is halogen, hydroxy, oxo, carboxy, cyano, nitro, carboxamide, amidino or guanidino, wherein R_a may be further optionally substituted by one or more R_b;

R_b is a C1-6 saturated or unsaturated alkyl group wherein one or more carbon atoms are optionally replaced by O, N, S(O), S(O)₂ or S and wherein said alkyl group is optionally independently substituted with one or two oxo groups, and/or one or more: -NH₂, C1-4 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, dihydrobenzofuranyl, dihydrobenzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or quinoxalinyl;

or R_b is C3-6 cycloalkyl, C1-6 alkoxy, aryl, aryloxy, benzyloxy, halogen, hydroxy, oxo, carboxy, cyano, nitro, mono-C1-5alkylamino, di-C1-5alkylamino, carboxamide, amidino or guanidino;

R₂ and R₃ are each independently a hydrogen, C3-8 cycloalkyl, arylC1-5alkyl, aryl, or a C1-10 saturated or unsaturated alkyl group wherein one or more C atoms are optionally replaced by O, NH, S(O), S(O)₂ or S and wherein said alkyl group is optionally independently substituted with one or two oxo groups, and/or one or more: -NH₂, C₁₋₄ alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl,

pyranyl, thiopyranyl, furanyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, dihydrobenzofuranyl, dihydrobenzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, quinazolinyl, benzoxazolyl or quinoxalinyl; wherein each R₂ and R₃ is
5 independently optionally substituted by one or more R_c; or R₂ and R₃ are each independently R_c;

R_c is C1-10 alkyl, C3-8 cycloalkyl, aryl, indanyl, indenyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, bicyclo[4.1.0]heptanyl, bicyclo[3.1.0]hexanyl,
10 bicyclo[1.1.1]pentanyl, spiro[2.5]octanyl, cubanyl, tetrahydronaphthyl, decahydronaphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, tetrahydrofuranyl, pyranyl, tetrahydropyranyl, tetrahydrothiopyranyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl,
15 dihydrobenzofuranyl, octahydrobenzofuranyl, benzofuranyl, benzothienyl, dihydrobenzofuranyl, dihydrobenzothienyl, benzimidazolyl, benzothiazolyl, tetrahydroquinolinyl, quinolinyl, tetrahydroisoquinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, C1-10 alkoxy, aryloxy, C1-10 alkanoyl, aroyl, C1-10 alkoxy-carbonyl, aryloxy-carbonyl, C1-10 alkanoyloxy, aroyloxy, carbamoyl
20 wherein the nitrogen atom may be independently mono or di-substituted by C1-10 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, dihydrobenzofuranyl, dihydrobenzothienyl, benzimidazolyl, benzothiazolyl,
25 quinolinyl, isoquinolinyl, quinazolinyl or quinoxalinyl, or R_c is C1-10 alkanoylamino, aroylamino, C1-10 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, arylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-10 alkyl, aryl, pyrrolidinyl, piperidinyl,
30 morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl,

pyrazinyl, indolyl, benzofuranyl, benzothienyl, dihydrobenzofuranyl,
dihydrobenzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl,
quinazolinyl or quinoxalinyl,
or R_c is C1-10 alkoxy-carbonylamino, aryloxy-carbonylamino, C1-10
5 alkyl-carbamoyloxy, aryl-carbamoyloxy, C1-10 alkyl-sulfonylamino,
arylsulfonylamino, C1-10 alkyl-aminosulfonyl, aryl-aminosulfonyl, amino wherein
the nitrogen atom may be independently mono or di-substituted by C1-10 alkyl,
aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl,
indolinyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl,
10 tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl,
dihydrobenzofuranyl, dihydrobenzothienyl, benzimidazolyl, benzothiazolyl,
quinolinyl, isoquinolinyl, quinazolinyl or quinoxalinyl,
or R_c is halogen, hydroxy, oxo, carboxy, cyano, nitro, amidino or guanidino;
Each R_c may be further optionally substituted by one or more R_d;

15

R_d is C1-5 alkyl, C3-6 cycloalkyl, aryl, arylC1-5alkyl, C1-5 alkoxy,
aryloxy, arylC1-5alkoxy, aroyl, amino, halogen, hydroxy, oxo, carboxy,
cyano, nitro, amidino or guanidino; or

20 R₂ and R₃ together with the carbon they are attached optionally form a nonaromatic 3-10
membered mono- or bicyclic optionally partially unsaturated cycloalkyl or a 3-10
membered mono- or bicyclic heterocycle each in turn optionally substituted by one or
more R_c as described hereinabove;

R₄ and R₅ are each independently a hydrogen, or a C1-10 saturated or unsaturated alkyl
25 group wherein one or more C atoms are optionally replaced by O, NH, S(O), S(O)₂ or S
and wherein said alkyl group is optionally independently substituted with one or two oxo
groups, and/or one or more: -NH₂, C₁₋₄ alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl,
thiomorpholinyl, piperazinyl, indolinyl, pyranyl, thiopyranyl, furanyl, thienyl, pyrrolyl,
oxazolyl, isoxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl,
30 benzofuranyl, benzothienyl, dihydrobenzofuranyl, dihydrobenzothienyl, benzimidazolyl,
benzothiazolyl, quinolinyl, isoquinolinyl, quinazolinyl, benzoxazolyl or quinoxalinyl;

or R₄ and R₅ are each independently C1-10alkoxyC1-10alkyl, C1-10alkylaminoC1-10alkyl, C1-10alkylthioC1-10alkyl wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, C3-8 cycloalkyl, aryl, tetrahydronaphthyl, indenyl, indanyl, C3-7cycloalkylsulfonylC1-5alkyl, arylsulfonylC1-5alkyl, heterocyclyl selected from

5 pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, pyranyl, tetrahydropyranyl, thiopyranyl, tetrahydrothiopyranyl, furanyl, tetrahydrofuranyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridiziny, tetrazolyl, triazolyl, pyrazolyl, indolyl, benzofuranyl, benzothienyl, dihydrobenzofuranyl, dihydrobenzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl,

10 tetrahydroquinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, quinazoliny, tetrahydroquinazoliny, benzoxazolyl and quinoxaliny, C1-10alkanoyl, aroyl, C1-10alkoxycarbonyl, arylC1-5alkoxycarbonyl, aryloxycarbonyl, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-10 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl,

15 thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, dihydrobenzofuranyl, dihydrobenzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, quinazoliny or quinoxaliny,

or R₄ and R₅ are each independently C1-10 alkanoylamino, aroylamino, C1-10 alkylthio

20 wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, arylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-10 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl,

25 benzofuranyl, benzothienyl, dihydrobenzofuranyl, dihydrobenzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, quinazoliny or quinoxaliny,

or R₄ and R₅ are each independently C1-10 alkoxy-carbonylamino, aryloxycarbonylamino, C1-10 alkylcarbamoxy, arylcarbamoxy, C1-10 alkylsulfonylamino, arylsulfonylamino, C1-10 alkylaminosulfonyl, arylaminosulfonyl, amino wherein the

30 nitrogen atom may be independently mono or di-substituted by C1-10 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl,

thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, dihydrobenzofuranyl, dihydrobenzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or quinoxalinyl,

5 or R₄ and R₅ are each independently halogen, hydroxy, carboxy, cyano, nitro, carboxamide, amidino or guanidino;

wherein each R₄ and R₅ may be further optionally independently substituted by one or more R_e;

10 or R₄ and R₅ together with the carbon they are attached to optionally form a heterocyclic ring said heterocyclic ring being selected from:

azepanyl, piperidinyl, pyrrolidinyl, azetidiny, oxepanyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrofuranyl, oxetanyl, azocanyl, oxocanyl, 1,3-diazocanyl, 1,4-diazocanyl, 1,5-diazocanyl, 1,3-dioxocanyl, 1,4-dioxocanyl, 1,5-dioxocanyl, 1,3-oxazocanyl, 1,4-oxazocanyl, 1,5-oxazocanyl, 1,3-diazepanyl, 1,4-diazepanyl, 1,3-dioxepanyl, 1,4-dioxepanyl, 1,3-oxazepanyl, 1,4-oxazepanyl, 1,2-thiazocanyl-1,1-dioxide, 1,2,8-thiadiazocanyl-1,1-dioxide, 1,2-thiazepanyl-1,1-dioxide, 1,2,7-thiadiazepanyl-1,1-dioxide, tetrahydrothiophenyl, hexahydropyrimidinyl, hexahydropyridazinyl, piperazinyl, 1,4,5,6-tetrahydropyrimidinyl, pyrazolidinyl, dihydro-oxazolyl, dihydrothiazolyl, dihydroimidazolyl, isoxazolinyl, oxazolidinyl, 1,2-thiazinanyl-1,1-dioxide, 1,2,6-thiadiazinanyl-1,1-dioxide, isothiazolidinyl-1,1-dioxide, imidazolidinyl-2,4-dione, imidazolidinyl, morpholinyl, dioxanyl, tetrahydropyridinyl, thiomorpholinyl, thiazolidinyl, dihydropyranyl, dithianyl, decahydro-quinolinyl, decahydro-isoquinolinyl, 1,2,3,4-tetrahydro-quinolinyl, indolinyl, octahydro-quinoliziny, dihydro-indoliziny, octahydro-indoliziny, octahydro-indolyl, decahydroquinazolinyl, decahydroquinoxalinyl, 1,2,3,4-tetrahydroquinazolinyl or 1,2,3,4-tetrahydroquinoxalinyl;

25 or R₄ and R₅ together with the carbon they are attached to optionally form a C₆-C₁₀ bridged bicyclic ring group wherein one or more carbon atoms are optionally replaced by a heteroatom chosen from N, O, S, S(O) or S(O)₂;

30

or R₄ and R₅ together with the carbon they are attached to optionally form a carbocyclic ring group, said carbocyclic ring group being selected from:
cyclopropanyl, cyclobutanyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, cyclooctanyl, cyclononyl, cyclodecanyl, cubanyl, bicyclo[1.1.0]propanyl, bicyclo[2.1.0]butanyl,
5 bicyclo[3.1.0]hexanyl, bicyclo[4.1.0]heptanyl, bicyclo[5.1.0]octanyl,
bicyclo[2.2.0]hexanyl, bicyclo[3.2.0]heptanyl, bicyclo[4.2.0]octanyl,
bicyclo[5.2.0]nonanyl, bicyclo[3.3.0]octanyl, bicyclo[4.3.0]nonanyl,
bicyclo[5.3.0]decanyl, bicyclo[4.4.0]decanyl, bicyclo[5.4.0]undecanyl,
bicyclo[1.1.1]pentanyl, bicyclo[2.1.1]hexanyl, bicyclo[3.1.1]heptanyl,
10 bicyclo[4.1.1]octanyl, bicyclo[5.1.1]nonanyl, bicyclo[2.2.1]heptanyl,
bicyclo[3.2.1]octanyl, bicyclo[4.2.1]nonanyl, bicyclo[5.2.1]decanyl,
bicyclo[2.2.2]octanyl, bicyclo[3.2.2]nonanyl, bicyclo[4.2.2]decanyl,
bicyclo[5.2.2]undecanyl, bicyclo[3.3.2]decanyl, bicyclo[4.3.2]undecanyl,
bicyclo[5.3.2]dodecanyl, bicyclo[3.3.3]undecanyl, bicyclo[4.3.3]dodecanyl,
15 bicyclo[5.3.3]tridecanyl;

each of the above ring groups formed by the combination of R₄ and R₅ being optionally
20 substituted with one or more R_e; or R₄ and R₅ are each independently R_e;

R_e is a C1-10 saturated or unsaturated alkyl group wherein one or more C atoms are optionally replaced by O, NH, S(O), S(O)₂ or S and wherein said alkyl group is optionally independently substituted with one or two oxo groups, and/or one or
25 more: -NH₂, C₁₋₄ alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, pyranyl, thiopyranyl, furanyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, dihydrobenzofuranyl, dihydrobenzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl,
30 quinazoliny, benzoxazolyl or quinoxalinyl;

or R_e is a C1-10alkoxy, C1-10alkoxyC1-10alkyl, C1-10alkylaminoC1-10alkyl, C1-10alkylthioC1-10alkyl wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, C3-8 cycloalkyl, C3-8 cycloalkyloxy, aryl, tetrahydronaphthyl, indenyl, indanyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, 5 piperazinyl, indolinyl, thiopyranyl, tetrahydrothiopyranyl, pyranyl, tetrahydropyranyl, tetrahydrofuranyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, dihydrobenzofuranyl, dihydrobenzothienyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, benzisoxazolyl, quinolinyl, 10 isoquinolinyl, quinazoliny, quinoxaliny, C1-10alkanoyl, aroyl, C1-10alkanoyloxy, aryloxy, benzyloxy, C1-10alkoxycarbonyl, arylC1-3alkoxycarbonyl, aryloxycarbonyl, aroyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-10 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, 15 furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, dihydrobenzofuranyl, dihydrobenzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, quinazoliny or quinoxaliny,

or R_e is ureido wherein either nitrogen atom may be independently substituted by 20 C1-10 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, dihydrobenzofuranyl, dihydrobenzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, quinazoliny or quinoxaliny,

or R_e is amino wherein the nitrogen atom may be independently mono or di- 25 substituted by C1-10 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, dihydrobenzofuranyl, dihydrobenzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, quinazoliny or 30 quinoxaliny,

or R_e is halogen, hydroxy, oxo, carboxy, cyano, nitro, carboxamide, amidino or guanidino,

wherein R_e may be further optionally substituted by one or more R_f;

5 R_f is C1-5 alkyl, C3-6 cycloalkyl, tolylsulfonyl, C1-5 alkoxy, aryl, aryloxy, benzyloxy, halogen, hydroxy, oxo, carboxy, cyano, nitro, carboxamide, amidino or guanidino;
or R_f is aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl,
10 imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, dihydrobenzofuranyl, dihydrobenzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, quinazoliny or quinoxaliny,
or R_f is amino wherein the nitrogen atom may be independently mono or
15 di-substituted by C1-10 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, dihydrobenzofuranyl, dihydrobenzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl,
20 isoquinolinyl, quinazoliny or quinoxaliny;
or R_f is a C1-10 saturated or unsaturated alkyl group wherein one or more C atoms are optionally replaced by O, NH, S(O), S(O)₂ or S and wherein said alkyl group is optionally independently substituted with one or two oxo groups, and/or one or more: -NH₂, C₁₋₄ alkyl, aryl, pyrrolidinyl,
25 piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, pyranyl, thiopyranyl, furanyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, dihydrobenzofuranyl, dihydrobenzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, quinazoliny, benzoxazolyl or
30 quinoxaliny;

R₆ is hydrogen, hydroxy, C1-3 alkyl, or C3-6 cycloalkyl;

5

X is O or S; or

the pharmaceutically acceptable derivatives thereof;

with the provisos that:

- (1) when R₂ is hydrogen; and R₃ is hydrogen, propyl or phenyl; and R₄ is hydrogen,
10 methyl, ethyl or benzyl; and R₅ is alkoxy carbonyl; and R₆ is hydrogen; then Y is not
methyl or chloromethyl;
- (2) when R₂ is hydrogen; and R₃ is phenyl; and R₄ is phenyl; and R₅ is trifluoromethyl;
and R₆ is hydrogen; then Y is not methyl; and
- (3) when R₂ is hydrogen or alkyl; and R₃ is hydrogen, alkyl or benzyl; and R₄ is
15 hydrogen, alkyl or cycloalkyl; and R₅ is hydrogen, alkyl or cycloalkyl; or R₄ and R₅
together with the carbon atom they are attached to form cyclopentanyl, cyclohexanyl
or cycloheptanyl; and R₆ is hydrogen; then Y is not methyl or phenyl substituted by
optionally substituted pyrimidinyl.

20 2. The compound according to claim 1, wherein:

Y is R₁, R₁O-, (R₁)₂N- or (R₁)₃C-;

Each R₁ is independently hydrogen, C1-7 alkyl, C3-7 cycloalkyl, phenyl, naphthyl,
25 benzyl, tetrahydronaphthyl, C1-7alkylsulfonylC1-7alkyl, C3-7cycloalkylsulfonylC1-
7alkyl, arylsulfonylC1-7alkyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl,
piperazinyl, indolinyl, pyranyl, thiopyranyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl,
imidazolyl, pyridinyl, isoxazolyl, pyrimidinyl, pyrazinyl, pyridazinyl, indolyl, quinolinyl,
isoquinolyl, tetrahydroisoquinolyl, benzofuranyl, benzothienyl, benzimidazolyl,
30 benzothiazolyl, benzoisoxazolyl, benzoisothiazolyl, benzoxazolyl, or 2*H*-

benzo[e][1,3]oxazine; wherein each R₁ is optionally substituted by one or more R_a; or R₁ is R_a or R_b;

Each R_a is independently hydrogen, C1-7 alkyl, C3-6 cycloalkyl, phenyl,
5 naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl,
furanyl, thienyl, oxazolyl, dihydro-oxazolyl, thiazolyl, imidazolyl, triazolyl,
tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl,
benzimidazolyl, benzothiazolyl, benzoxazolyl, quinolinyl, isoquinolinyl,
10 quinazoliny, quinoxaliny, C1-7 alkoxy, C1-7alkanoyl, C1-7alkanoyloxy,
aryloxy, benzyloxy, aroyl, C1-7 alkoxycarbonyl, aryloxycarbonyl, aroyloxy,
carbamoyl wherein the nitrogen atom may be independently mono or di-
substituted by C1-7 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl,
thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl,
15 triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl,
benzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl,
quinazoliny or quinoxaliny,
or R_a is C1-7 alkanoylamino, aroylamino, C1-7 alkylthio wherein the sulfur atom
may be oxidized to a sulfoxide or sulfone, arylthio wherein the sulfur atom may
be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be
20 independently substituted by C1-7 alkyl, aryl, pyrrolidinyl, piperidinyl,
morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl, thiazolyl,
imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl,
benzofuranyl, benzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl,
isoquinolinyl, quinazoliny or quinoxaliny,
25 or R_a is C1-7 alkoxycarbonylamino, aryloxycarbonylamino,
heterocyclylcarbonylamino, heteroarylcarbonylamino, C1-7 alkylcarbamoyloxy,
arylcarbamoyloxy, C1-7 alkylsulfonylamino, arylsulfonylamino, C1-7
alkylaminosulfonyl, arylaminosulfonyl, amino wherein the nitrogen atom may be
independently mono or di-substituted by C1-7 alkyl, aryl, pyrrolidinyl,
30 piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl,
thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl,

indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or quinoxaliny,

or R_a is halogen, hydroxy, oxo, carboxy, cyano, nitro, carboxamide, amidino or guanidino,

5 wherein R_a may be further optionally substituted by one or more R_b;

R_b is a C1-6 saturated alkyl group wherein one or two carbon atoms are optionally replaced by O or S and wherein said alkyl group is optionally independently substituted with one or two oxo groups and/or one or more: C1-4 alkyl, aryl, piperidinyl, morpholinyl, thiomorpholinyl or piperazine;

10

or R_b is C3-6 cycloalkyl, aryl, C1-6 alkoxy, aryloxy, benzyloxy, halogen, hydroxy, oxo, carboxy, cyano, nitro, carboxamide, amidino or guanidino;

15 R₂ is hydrogen or methyl or ethyl;

R₃ is a hydrogen, C2-5alkylene, C3-7 cycloalkyl, arylC1-3alkyl, aryl or a C1-6 saturated alkyl group wherein one or two of the C atoms are optionally replaced by O, NH or S; wherein R₃ is optionally substituted by one or more R_c; or R₃ is R_c;

20

R_c is C1-5 alkyl, C3-7 cycloalkyl, aryl, indanyl, indenyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, bicyclo[4.1.0]heptanyl, bicyclo[3.1.0]hexanyl, bicyclo[1.1.1]pentanyl, spiro[2.5]octanyl, cubanyl, 1,2,3,4-tetrahydronaphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, tetrahydrofuranyl, pyranyl, tetrahydropyranyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxaliny, C1-5 alkoxy, aryloxy, C1-5 alkanoyl, aroyl, C1-5 alkoxy carbonyl, aryloxy carbonyl, C1-5 alkanoyloxy, aroyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-5 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl,

25
30

thiomorpholinyl, piperazinyl, indolinyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, quinazolinyll or quinoxalinyll,

5 or R_c is C1-5 alkanoylamino, aroylamino, C1-5 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, arylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-5 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, quinazolinyll or quinoxalinyll,

10 or R_c is C1-5 alkoxy-carbonylamino, aryloxy-carbonylamino, C1-5 alkyl-carbamoyloxy, aryl-carbamoyloxy, C1-5 alkyl-sulfonylamino, aryl-sulfonylamino, C1-5 alkyl-aminosulfonyl, aryl-aminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-5 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, quinazolinyll or quinoxalinyll,

15 or R_c is halogen, hydroxy, oxo, carboxy, cyano, nitro, amidino or guanidino; Each R_c may be further optionally substituted by one or more R_d;

25 R_d is C1-5 alkyl, C3-6 cycloalkyl, aryl, arylC1-4-alkyl, C1-5 alkoxy, aryloxy, arylC1-5alkoxy, aroyl, halogen, hydroxy, oxo or cyano;

or R₂ and R₃ together with the carbon they are attached optionally form a nonaromatic 5-7 membered cycloalkyl or a 5-7 membered heterocycle, each optionally substituted by R_c as described hereinabove;

30

R₄ and R₅ are each independently hydrogen, or a C1-8 saturated alkyl group wherein one or two C atoms are optionally replaced by O, S(O), S(O)₂ or S and wherein said alkyl group is optionally substituted with one or two oxo groups and/or one or more: aryl, indolyl or indolinyl;

5

or R₄ and R₅ are each independently C1-8alkoxyC1-8alkyl, C1-8alkylaminoC1-8alkyl, C1-8alkylthioC1-8alkyl wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, , C3-7 cycloalkyl, aryl, tetrahydronaphthyl, indanyl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, pyranyl, tetrahydropyranyl, thiopyranyl, tetrahydrothiopyranyl, furanyl, tetrahydrofuranyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, tetrazolyl, triazolyl, pyrazolyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, quinazolinyl, benzoxazolyl and quinoxalinyl, C1-7alkanoyl, aroyl, C1-7 alkoxy carbonyl, arylC1-4alkoxy carbonyl, aryloxy carbonyl, carbamoyl

10 tetrahydropyranyl, thiopyranyl, tetrahydrothiopyranyl, furanyl, tetrahydrofuranyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, tetrazolyl, triazolyl, pyrazolyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, quinazolinyl, benzoxazolyl and quinoxalinyl, C1-7alkanoyl, aroyl, C1-7 alkoxy carbonyl, arylC1-4alkoxy carbonyl, aryloxy carbonyl, carbamoyl

15 wherein the nitrogen atom may be independently mono or di-substituted by C1-7 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or quinoxalinyl,

20

or R₄ and R₅ are each independently C1-7 alkanoylamino, aroylamino, C1-7 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, arylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-7 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or quinoxalinyl,

25 morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or quinoxalinyl,

or R₄ and R₅ are each independently C1-7 alkoxy carbonylamino, aryloxy carbonylamino, C1-7 alkyl carbamoyloxy, aryl carbamoyloxy, C1-7 alkyl sulfonylamino, aryl sulfonylamino, C1-7 alkyl aminosulfonyl, aryl aminosulfonyl, amino wherein the

30 C1-7 alkyl carbamoyloxy, aryl carbamoyloxy, C1-7 alkyl sulfonylamino, aryl sulfonylamino, C1-7 alkyl aminosulfonyl, aryl aminosulfonyl, amino wherein the

nitrogen atom may be independently mono or di-substituted by C1-7 alkyl, aryl,
pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl,
pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl,
benzofuranyl, benzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl,
5 quinazolinyl or quinoxalinyl,

or R₄ and R₅ are each independently halogen, hydroxy, carboxy, cyano, nitro or
carboxamide,

wherein each R₄ and R₅ may be further optionally independently substituted by one or
more R_e;

10

or R₄ and R₅ together with the carbon they are attached optionally form a heterocyclic
ring said heterocyclic ring being selected from:

piperidinyl, pyrrolidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, azetidiny, azepanyl,
oxepanyl, tetrahydrofuranyl, oxetanyl, hexahydropyrimidinyl, hexahydropryridazinyl,
15 piperazinyl, 1,4,5,6-tetrahydropyrimidinyl, octahydro-indoliziny, octahydro-quinoliziny,
decahydro-quinolinyl, 1,2,3,4-tetrahydro-quinolinyl, dihydro-oxazolyl, 1,2-thiazinanyl-
1,1-dioxide, 1,2,6-thiadiazinanyl-1,1-dioxide, isothiazolidinyl-1,1-dioxide,
imidazolidinyl, pyrazolidinyl or

20 R₄ and R₅ together with the carbon atom they are attached to form a cyclopropanyl,
cyclobutanyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, or a bridged bicyclo group
chosen from aza-bicyclo[3.2.1]octane, aza-bicyclo[2.2.1]heptane, aza-
bicyclo[2.2.2]octane, aza-bicyclo[3.2.2]nonane, aza-bicyclo[2.1.1]hexane, aza-
bicyclo[3.1.1]heptane, aza-bicyclo[3.3.2]decane and 2-oxa or 2-thia-5-aza-
25 bicyclo[2.2.1]heptane;

each ring being substituted with one or more R_e;

R_e is C1-8 saturated alkyl group wherein one or two of the C atoms are optionally
30 replaced by O, S(O), S(O)₂ or S, and wherein said alkyl group is optionally

independently substituted with one or two oxo groups and/or one or more: C₁₋₄alkyl or aryl;
or R_e is C1-7alkoxy, C1-7alkoxyC1-7alkyl, C1-7alkylaminoC1-7alkyl, C1-7alkylthioC1-7alkyl wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, C3-7 cycloalkyl, aryl, tetrahydronaphthyl, indanyl, pyrrolidinyl,
5 piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, thiopyranyl, tetrahydrothiopyranyl, tetrahydropyranyl, tetrahydrofuranyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, quinolinyl, isoquinolinyl, quinazoliny, quinoxaliny, C1-5 alkanoyl, aroyl, C1-5alkanoyloxy, aryloxy, benzyloxy, C1-5 alkoxy carbonyl, aryloxy carbonyl, aroyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-5 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, quinazoliny or quinoxaliny,
15 or R_e is ureido wherein either nitrogen atom may be independently substituted by C1-5 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, quinazoliny or quinoxaliny,
20 or R_e is amino wherein the nitrogen atom may be independently mono or di-substituted by C1-5 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl, quinazoliny or quinoxaliny,
25 or R_e is halogen, hydroxy, oxo, carboxy, cyano, nitro, carboxamide, amidino or guanidino,
30

wherein R_e may be further optionally substituted by one or more R_f;

R_f is methyl, ethyl, t-butyl, tolylsulfonyl, C1-3 alkoxy, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, naphthyl, phenoxy, benzyloxy, fluoro, chloro, bromo, hydroxy, oxo, carboxy, cyano, nitro amino or carboxamide;

R₆ is hydrogen or methyl;

and

X is O.

3. The compound according to claim 2, wherein:

Each R₁ is independently hydrogen, C1-5 alkyl, C3-6 cycloalkyl, phenyl, benzyl, naphthyl, C1-3alkylsulfonylC1-3alkyl, C3-6cycloalkylsulfonylC1-3alkyl, arylsulfonylC1-3alkyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, isoxazolyl, pyrimidinyl, pyrazinyl, pyridazinyl, indolyl, quinolinyl, tetrahydroisoquinolyl, benzofuranyl, benzthienyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, 2H-benzo[e][1,3]oxazine; wherein each R₁ is optionally substituted by one or more R_a; or R₁ is R_a or R_b;

Each R_a is independently hydrogen, C1-3 alkyl, cyclopropyl, cyclopentyl, cyclohexyl, phenyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl, dihydro-oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, C1-3 alkoxy, C1-3alkanoyl, C1-3alkanoyloxy, aryloxy, benzyloxy, aroyl, C1-3 alkoxy-carbonyl, aryloxy-carbonyl, aroyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-3 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, thienyl,

oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, benzimidazolyl or benzothiazolyl,

or R_a is C1-3 alkanoylamino, aroylamino, C1-3 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, arylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-3 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl or piperazinyl,

or R_a is C1-5 alkoxy-carbonylamino, aryloxy-carbonylamino,

heterocyclyl-carbonylamino, heteroaryl-carbonylamino, C1-5 alkyl-carbamoyloxy, aryl-carbamoyloxy, C1-5 alkyl-sulfonylamino, aryl-sulfonylamino, C1-5 alkyl-aminosulfonyl, aryl-aminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-6 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl or piperazinyl,

or R_a is halogen, hydroxy, oxo, carboxy, cyano, nitro, carboxamide, amidino or guanidino,

wherein R_a may be further optionally substituted by one or more R_b;

R_b is a C1-6 saturated alkyl group wherein one or two carbon atoms are optionally replaced by O or S and wherein said alkyl group is optionally independently substituted with an oxo group and/or one or more: C1-4 alkyl, aryl, piperidinyl, morpholinyl, thiomorpholinyl or piperazine;

or R_b is C3-6 cycloalkyl, aryl, C1-3 alkoxy, aryloxy, benzyloxy, halogen, hydroxy, oxo, carboxy, cyano, nitro, carboxamide, amidino or guanidino;

R₂ is hydrogen or methyl;

R₃ is hydrogen, C2-5 alkylene, C3-6 cycloalkyl or aryl-C1-2 alkyl, phenyl, naphthyl, or a C1-6 saturated alkyl group wherein one or two of the C atoms are optionally replaced by O, NH or S; wherein R₃ is optionally substituted by one or more R_c; or R₃ is R_c;

R_c is C1-4 alkyl, C5-6 cycloalkyl, phenyl, naphthyl, indanyl,
bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, bicyclo[4.1.0]heptanyl,
bicyclo[3.1.0]hexanyl, bicyclo[1.1.1]pentanyl, spiro[2.5]octanyl, cubanyl, 1,2,3,4-
5 tetrahydronaphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl,
indolinyl, furanyl, tetrahydrofuranyl, pyranyl, tetrahydropyranyl, thienyl, pyrrolyl,
oxazolyl, thiazolyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl,
indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl,
isoquinolinyl, quinazolinyl, quinoxalinyl, C1-4 alkoxy, phenoxy, naphthyloxy,
10 C1-3 alkanoyl, benzoyl, C1-3 alkoxy carbonyl, phenoxy carbonyl, C1-3
alkanoyloxy, benzoyloxy, carbamoyl wherein the nitrogen atom may be
independently mono or di-substituted by C1-5 alkyl or aryl,
or R_c is C1-3 alkanoylamino, benzoylamino, C1-3 alkylthio wherein the sulfur
atom may be oxidized to a sulfoxide or sulfone, phenylthio wherein the sulfur
15 atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen
atom may be independently substituted by C1-5 alkyl or aryl,
or R_c is C1-3 alkoxy carbonylamino, aryloxy carbonylamino, C1-3
alkyl carbamoyloxy, aryl carbamoyloxy, C1-3 alkyl sulfonylamino,
arylsulfonylamino, C1-3 alkyl aminosulfonyl, aryl aminosulfonyl, amino wherein
20 the nitrogen atom may be independently mono or di-substituted by C1-5 alkyl or
aryl,
or R_c is halogen, hydroxy, oxo, carboxy, cyano, nitro, amidino or guanidino,
wherein each R_c may be further optionally substituted by one or more R_d;

25 R_d is C1-3 alkyl, C3-6 cycloalkyl, phenyl, benzyl, C1-3 alkoxy, phenoxy,
phenyl C1-3 alkoxy, benzoyl, halogen, hydroxy, oxo or cyano;

R₂ and R₃ together with the carbon they are attached optionally form a nonaromatic 5-6
membered cycloalkyl or a 5-6 membered heterocycle, each optionally substituted by R_c
30 as described hereinabove;

R₄ and R₅ are each independently hydrogen, or a C1-5 saturated alkyl group wherein one or two C atoms are optionally replaced by O, S(O), S(O)₂ or S and wherein said alkyl group is optionally substituted with one oxo group and/or one or more: phenyl, naphthyl or indolyl;

5

or R₄ and R₅ are each independently C1-6alkoxyC1-6alkyl, C1-6alkylaminoC1-6alkyl, C1-6alkylthioC1-6alkyl wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, C3-6 cycloalkyl, phenyl, naphthyl, indanyl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, tetrahydropyranyl, tetrahydrothiopyranyl, furanyl, tetrahydrofuranyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzothiazolyl, quinolinyl, isoquinolinyl and benzoxazolyl, C1-3alkanoyl, benzoyl, naphthoyl, C1-4 alkoxy carbonyl, arylC1-2alkoxy carbonyl, phenoxy carbonyl, benzoyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-

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substituted by C1-3 alkyl, phenyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl or pyrimidinyl, or R₄ and R₅ are each independently C1-4 alkanoylamino, aroylamino, C1-4 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, arylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-3 alkyl, phenyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl or benzothiazolyl,

15

or R₄ and R₅ are each independently C1-4 alkoxy carbonylamino, phenoxy carbonylamino, C1-4 alkyl carbamoyloxy, phenyl carbamoyloxy, C1-4 alkyl sulfonylamino, phenyl sulfonylamino, C1-3 alkyl aminosulfonyl, phenyl aminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-4 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, benzimidazolyl or benzothiazolyl, or R₄ and R₅ are each independently halogen, hydroxy, carboxy, cyano, nitro or carboxamide,

20

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wherein each R₄ and R₅ may be further optionally indenpendtly substituted by one or more R_e;

5 or R₄ and R₅ together with the carbon they are attached optionally form cyclopropanyl, cyclopentanyl, cyclohexanyl, or a heterocyclic ring said heterocyclic ring being selected from: piperidinyl, pyrrolidinyl, azetidiny, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrofuranly, each ring being optionally substituted with one or more R_e;

10 R_e is C1-5 saturated alkyl group wherein one or two of the C atoms are optionally replaced by O, S(O), S(O)₂ or S, and wherein said alkyl group is optionally independently substituted with one oxo group and/or one or more: C₁₋₄alkyl, phenyl or naphthyl;

or R_e is C1-4 alkoxy, C3-7 cycloalkyl, phenyl, naphthyl, indanyl, pyrrolidinyl, 15 piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, tetrahydrothiopyranyl, tetrahydropyranyl, tetrahydrofuranly, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, quinolinyl, isoquinolinyl, quinazoliny, quinoxaliny, C1-4 alkanoyl, aroyl, C1-4alkanoyloxy, phenoxy, naphthyloxy, benzyloxy, C1-4 20 alkoxy carbonyl, phenoxy carbonyl, benzoyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-3 alkyl, phenyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, benzimidazolyl, or benzothiazolyl,

25 or R_e is ureido wherein either nitrogen atom may be independently substituted by C1-3 alkyl, phenyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, benzimidazolyl or benzothiazolyl,

30 or R_e is amino wherein the nitrogen atom may be independently mono or di-substituted by C1-3 alkyl, phenyl, naphthyl, pyrrolidinyl, piperidinyl,

morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, benzimidazolyl or benzothiazolyl, or R_e is halogen, hydroxy, oxo, carboxy, cyano, nitro or carboxamide, wherein R_e may be further optionally substituted by one or more R_f;

5

R_f is methyl, ethyl, t-butyl, tolylsulfonyl, methoxy, cyclopropyl, cyclopentyl, cyclohexyl, phenyl, phenoxy, benzyloxy, fluoro, chloro, bromo, hydroxy, oxo, carboxy or carboxamide;

and

10 R₆ is hydrogen.

4. The compound according to claim 3, wherein:

Each R₁ is independently hydrogen, C1-5 alkyl, C3-6 cycloalkyl, phenyl, benzyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, indolyl, quinolinyl, tetrahydroisoquinolyl; benzofuranyl, benzthienyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, 2-*H*-benzo[e][1,3]oxazine ; wherein each R₁ is optionally substituted by one or more R_a; or R₁ is R_a or R_b;

20

Each R_a is independently C1-3 alkyl, cyclopropyl, cyclohexyl, phenyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, thienyl, oxazolyl, dihydro-oxazolyl, imidazolyl, pyridinyl, C1-3 alkoxy, C1-3alkanoyl, C1-3alkanoyloxy, aryloxy, benzyloxy, benzoyl, C1-3 alkoxy carbonyl, aryloxy carbonyl, aroyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-3 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl or piperazinyl, or R_a is C1-3 alkanoylamino, aroylamino, C1-3 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, arylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be

30

independently substituted by C1-3 alkyl, aryl, pyrrolidinyl, piperidinyl,
morpholinyl, thiomorpholinyl or piperazinyl,
or R_a is C1-3 alkoxy-carbonylamino, aryloxy-carbonylamino,
heterocyclyl-carbonylamino, C1-3 alkyl-carbamoyloxy, aryl-carbamoyloxy, C1-3
5 alkyl-sulfonylamino, aryl-sulfonylamino, C1-3 alkyl-aminosulfonyl,
aryl-aminosulfonyl, amino wherein the nitrogen atom may be independently mono
or di-substituted by C1-3 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl,
thiomorpholinyl or piperazinyl,
or R_a is halogen, hydroxy, oxo, carboxy, cyano, nitro, carboxamide, amidino or
10 guanidino,
wherein R_a may be further optionally substituted by one or more R_b;

R_b is C1-4 saturated alkyl wherein one carbon atom is optionally replaced
by O and wherein said alkyl group is optionally independently substituted
15 with an oxo group and/or one or two: C1-4 alkyl, phenyl, morpholinyl or
thiomorpholinyl;

or R_b is cyclopropyl, cyclopentyl, cyclohexyl, phenyl, methoxy, ethoxy, n-
propoxy, i-propoxy, phenoxy, benzyloxy, fluoro, chloro, bromo, iodo,
20 hydroxy, oxo, carboxy, cyano, nitro or carboxamide;

R₂ is hydrogen;

R₃ is a hydrogen, C2-4alkylene, C5-6 cycloalkyl, benzyl or naphthylmethyl, phenyl, or a
25 C1-4 saturated alkyl group wherein one of the C atoms is optionally replaced by O, NH
or S; wherein R₃ is optionally substituted by one or more R_c; or R₃ is R_c;

R_c is C1-3 alkyl, C3-6 cycloalkyl, phenyl, naphthyl, indanyl,
bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, bicyclo[4.1.0]heptanyl,
30 bicyclo[3.1.0]hexanyl, bicyclo[1.1.1]pentanyl, spiro[2.5]octanyl, cubanyl, 1,2,3,4-
tetrahydronaphthyl, furanyl, tetrahydropyranyl, thienyl, oxazolyl, thiazolyl,

imidazolyl, pyridinyl, pyrimidinyl, indolyl, benzofuranyl, benzothienyl,
benzothiazolyl, C1-3 alkoxy, phenoxy, naphthyloxy, C1-2 alkanoyl, benzoyl, C1-
2 alkoxy-carbonyl, phenoxy-carbonyl, C1-2-alkanoyloxy, benzoyloxy, carbamoyl
wherein the nitrogen atom may be independently mono or di-substituted by C1-3
5 alkyl or aryl,
or R_c is C1-2 alkanoylamino, benzoylamino, C1-2 alkylthio wherein the sulfur
atom may be oxidized to a sulfoxide or sulfone, phenylthio wherein the sulfur
atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen
atom may be independently substituted by C1-3 alkyl or aryl,
10 or R_c is C1-2 alkoxy-carbonylamino, phenoxy-carbonylamino, C1-2
alkyl-carbamoyloxy, aryl-carbamoyloxy, C1-2 alkyl-sulfonylamino,
phenyl-sulfonylamino, C1-2-alkyl-aminosulfonyl, phenyl-aminosulfonyl, amino
wherein the nitrogen atom may be independently mono or di-substituted by C1-3
alkyl or phenyl,
15 or R_c is halogen, hydroxy, oxo, carboxy or cyano,
wherein each R_c may be further optionally substituted by one or more R_d;

R_d is methyl, cyclopropyl, cyclohexyl, phenyl, benzyl, methoxy, phenoxy,
benzyloxy, benzoyl, fluoro, chloro, oxo or cyano;

20

R₂ and R₃ together with the carbon they are attached optionally form cyclohexyl
optionally substituted by R_c as described hereinabove;

R₄ and R₅ are each independently hydrogen, or a C1-5 saturated alkyl group wherein one
25 C atom is optionally replaced by O, S or S(O)₂ and wherein said alkyl group is optionally
substituted with phenyl or indolyl;

or R₄ and R₅ are each independently C1-5-alkoxy-C1-5-alkyl, C1-5-alkyl-amino-C1-5-alkyl,
C1-5-alkyl-thio-C1-5-alkyl wherein the sulfur atom may be oxidized to a sulfoxide or
30 sulfone, C3-6 cycloalkyl, phenyl, naphthyl, indanyl, heterocyclyl selected from
pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, tetrahydropyranyl,

oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, benzimidazolyl and
benzothiazolyl, C1-3alkanoyl, benzoyl, naphthoyl, C1-3 alkoxy carbonyl,
benzyloxycarbonyl, phenoxycarbonyl, carbamoyl wherein the nitrogen atom may be
independently mono or di-substituted by C1-3 alkyl, phenyl, pyrrolidinyl, piperidinyl,
5 morpholinyl, piperazinyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl or pyrimidinyl,

or R₄ and R₅ are each independently C1-3 alkanoylamino, aroylamino, C1-3 alkylthio
wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, phenylthio wherein
the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen
10 atom may be independently substituted by C1-3 alkyl, phenyl, pyrrolidinyl, piperidinyl,
morpholinyl, piperazinyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl,
benzofuranyl, benzothienyl, benzimidazolyl or benzothiazolyl,

or R₄ and R₅ are each independently is C1-3 alkoxy carbonylamino,
phenoxycarbonylamino, C1-3 alkyl carbamoyloxy, phenyl carbamoyloxy, C1-3
15 alkylsulfonylamino, phenylsulfonylamino, C1-3 alkylaminosulfonyl,
phenylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or
di-substituted by C1-3 alkyl, phenyl, pyrrolidinyl, piperidinyl, morpholinyl,
thiomorpholinyl, piperazinyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl,
benzimidazolyl or benzothiazolyl,

20 or R₄ and R₅ are each independently halogen, hydroxy, oxo, carboxy, cyano or
carboxamide, each R₄ and R₅ may be further optionally independently substituted by one
or more R_e;

or R₄ and R₅ together with the carbon they are attached optionally form a cyclopropanyl
25 or a heterocyclic ring said heterocyclic ring being selected from:
piperidinyl, pyrrolidinyl and tetrahydropyranyl, each ring being optionally substituted
with one or more R_e;

R_e is C1-5 saturated alkyl group wherein one of the C atoms is optionally replaced
30 by O, S(O), S(O)₂ or S, and wherein said alkyl group is optionally independently
substituted with one oxo group and/or a C₁₋₄alkyl or phenyl;

or R_e is C1-3 alkoxy, C3-7 cycloalkyl, phenyl, naphthyl, indanyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, tetrahydropyranyl, indolyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, C1-3 alkanoyl, aroyl, C1-3alkanoyloxy, phenoxy, benzyloxy, C1-3 alkoxy carbonyl, phenoxy carbonyl, benzoyloxy, carbamoyl
5 wherein the nitrogen atom may be independently mono or di-substituted by C1-3 alkyl, phenyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, benzimidazolyl or benzothiazolyl, or R_e is ureido wherein either nitrogen atom may be independently substituted by
10 C1-3 alkyl, phenyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, benzimidazolyl or benzothiazolyl, or R_e is amino wherein the nitrogen atom may be independently mono or di-substituted by C1-3 alkyl, phenyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl,
15 benzimidazolyl or benzothiazolyl, or R_e is halogen, hydroxy, oxo, carboxy, cyano or carboxamide, wherein R_e may be further optionally substituted by one or more R_f;
and

R_f is methyl, cyclopentyl, cyclohexyl, phenyl, tolylsulfonyl, methoxy, phenoxy, benzyloxy, fluoro, chloro, bromo, hydroxy, oxo, carboxy or
20 carboxamide.

5. The compound according to claim 4, wherein:

25 Each R₁ is independently a hydrogen, methyl, ethyl, i-propyl, cyclopropyl, cyclopentyl, cyclohexyl, phenyl, benzyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, thiazolyl, quinolyl, tetrahydroisoquinolyl, imidazolyl, pyridinyl, pyrazinyl, or 2*H*-benzo[e][1,3]oxazine; wherein each R₁ is optionally substituted by one or more R_a; or R₁ is R_a or R_b;

30

Each R_a is independently methyl, ethyl, cyclopropyl, phenyl, pyrrolidinyl,
piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, thienyl, dihyrdo-oxazolyl,
imidazolyl, pyridinyl, methoxy, acetyl, acetoxy, phenoxy, benzyloxy, benzoyl,
methoxycarbonyl, phenoxycarbonyl, benzoyloxy, carbamoyl wherein the nitrogen
5 atom may be independently mono or di-substituted by methyl, ethyl or phenyl,
or R_a is acetylamino, benzoylamino, methylthio, phenylthio wherein the sulfur
atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen
atom may be independently substituted by methyl, ethyl or phenyl,
or R_a is C1-3alkoxycarbonylamino, phenoxycarbonylamino,
10 piperazinylcarbonylamino, methylcarbamoyloxy, phenylcarbamoyloxy,
methylsulfonylamino, phenylsulfonylamino, methylaminosulfonyl,
phenylaminosulfonyl, amino wherein the nitrogen atom may be independently
mono or di-substituted by methyl, phenyl, or piperidinyl,
or R_a is fluoro, chloro, bromo, iodo, hydroxy, oxo, carboxy, cyano, nitro or
15 carboxamide,
wherein R_a may be further optionally substituted by one or more R_b;

R_b is C1-4 saturated alkyl group, wherein one carbon atom is optionally
replaced by O and wherein said alkyl group is optionally independently
20 substituted with an oxo group and/or a C1-4 alkyl, phenyl or morpholinyl;

or R_b is cyclopropyl, phenyl, methoxy, phenoxy, benzyloxy, fluoro,
chloro, hydroxy, oxo, carboxy or carboxamide;

25 R₃ is a hydrogen, C2-4alkylene, C5-6 cycloalkyl, phenyl, benzyl or naphthylmethyl or a
C1-4 saturated alkyl group wherein one of the C atoms is optionally replaced by O or S;
wherein R₃ is optionally substituted by one or more R_c; or R₃ is R_c;

R_c is methyl, ethyl, n-propyl, i-propyl, C3-6 cycloalkyl, phenyl, indanyl,
30 bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, bicyclo[4.1.0]heptanyl,
bicyclo[3.1.0]hexanyl, bicyclo[1.1.1]pentanyl, spiro[2.5]octanyl, cubanyl, 1,2,3,4-

5 tetrahydronaphthyl, thienyl, oxazolyl, thiazolyl, pyridinyl, indolyl, benzofuranyl, benzothieryl, benzothiazolyl, methoxy, ethoxy, phenoxy, acetyl, benzoyl, methoxycarbonyl, phenoxy carbonyl, acetoxyl, benzoyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by methyl, ethyl or aryl,

10 or R_c is acetylamino, benzoylamino, methylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, phenylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by methyl, ethyl or aryl,

15 or R_c is methoxycarbonylamino, phenoxy carbonylamino, methylcarbamoyloxy, phenylcarbamoyloxy, methylsulfonylamino, phenylsulfonylamino, methylaminosulfonyl, phenylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by methyl, ethyl or phenyl, or R_c is fluoro, chloro or oxo,

20 wherein each R_c may be further optionally substituted by one or more R_d;

R_d is methyl, cyclopropyl, phenyl, methoxy, fluoro, chloro or oxo;

20 R₄ and R₅ are each independently hydrogen, C1-4 saturated alkyl, C1-4alkoxyC1-4alkyl, C1-4alkylaminoC1-4alkyl, C1-4alkylthioC1-4alkyl wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, cyclopropyl, cyclopentyl, cyclohexyl, phenyl, naphthyl, benzyl, indanyl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, tetrahydropyranyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl,

25 pyrimidinyl, benzimidazolyl and benzothiazolyl, C1-2alkanoyl, benzoyl, naphthoyl, C1-2 alkoxy carbonyl, benzyloxy carbonyl, phenoxy carbonyl, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-2 alkyl, phenyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl or pyrimidinyl,

30 or R₄ and R₅ are each independently C1-2 alkanoylamino, benzoylamino, C1-2 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, phenylthio wherein

the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-2 alkyl, phenyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, benzimidazolyl or benzothiazolyl,

5 or R₄ and R₅ are each independently C1-2 alkoxy-carbonylamino, phenoxy-carbonylamino, C1-2 alkyl-carbamoyloxy, phenyl-carbamoyloxy, C1-2 alkyl-sulfonylamino, phenyl-sulfonylamino, C1-2 alkyl-aminosulfonyl, phenyl-aminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-2 alkyl, phenyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl or pyrimidinyl,

10 or R₄ and R₅ are each independently fluoro, chloro, bromo, hydroxy, oxo, carboxy or carboxamide,

wherein each R₄ and R₅ may be further optionally independently substituted by one or more R_e;

R_e is C1-3 saturated alkyl, C1-3 alkoxy, C3-6 cycloalkyl, phenyl, naphthyl, indanyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, tetrahydropyranyl, indolyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, C1-2 alkanoyl, aroyl, C1-2 alkanoyloxy, phenoxy, benzyloxy, C1-2 alkoxy-carbonyl, phenoxy-carbonyl, benzoyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-2 alkyl, phenyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl or pyrimidinyl,

25 or R_e is ureido wherein either nitrogen atom may be independently substituted by C1-2 alkyl, phenyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl or pyrimidinyl,

30 or R_e is amino wherein the nitrogen atom may be independently mono or di-substituted by C1-2 alkyl, phenyl, naphthyl, pyrrolidinyl, piperidinyl,

morpholinyl, piperazinyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl or pyrimidinyl,

or R_e is fluoro, chloro, bromo, hydroxy, oxo, carboxy or carboxamide, wherein R_e may be further optionally substituted by one or more R_f;

5 and

R_f is methyl, cyclopentyl, cyclohexyl, phenyl, tolylsulfonyl, methoxy, phenoxy, benzyloxy, fluoro, chloro, hydroxy, oxo, carboxy or carboxamide.

10

6. The compound according to claim 5, wherein:

Each R₁ is independently hydrogen, methyl, ethyl, i-propyl, cyclopropyl, cyclohexyl, , phenyl, benzyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, thiazolyl, imidazolyl, pyridinyl, pyrazinyl, quinolyl, 15 tetrahydroisoquinolyl, or 2H-benzo[e][1,3]oxazine; wherein each R₁ is optionally substituted by one or more R_a; or R₁ is R_a or R_b;

Each R_a is independently methyl, phenyl, thienyl, dihydro-oxazolyl, pyridinyl, 20 methoxy, acetyl, acetoxy, phenoxy, benzyloxy, benzoyl, methoxycarbonyl, benzoyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by methyl or phenyl,

or R_a is acetylamino, methylthio, phenylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be 25 independently substituted by methyl or phenyl,

or R_a is methoxycarbonylamino, piperazinylcarbonylamino, methylcarbamoyloxy, phenylcarbamoyloxy, methylsulfonylamino, phenylsulfonylamino, amino wherein the nitrogen atom may be independently mono or di-substituted by methyl or 30 phenyl,

or R_a is fluoro, chloro, hydroxy, oxo, carboxy, cyano or carboxamide;

wherein R_a may be further optionally substituted by one or more R_b;

R_b is an alkyl group selected from methyl, ethyl, n-propyl or i-propyl, wherein one carbon atom is optionally replaced by O and wherein said alkyl group is optionally independently substituted with an oxo group and/or phenyl or morpholinyl;

or R_b is phenyl, methoxy, phenoxy, fluoro, chloro or oxo;

R₃ is a hydrogen, methyl, ethyl, n-propyl, n-butyl, i-butyl, methoxymethyl, methylthiomethyl, propenyl, butenyl, i-butenyl, cyclohexyl, phenyl, benzyl or naphthylmethyl wherein R₃ is optionally substituted by one or more R_c;

R_c is methyl, ethyl, n-propyl, i-propyl, cyclopropyl, cyclopentyl, cyclohexyl, phenyl, indanyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, bicyclo[4.1.0]heptanyl, bicyclo[3.1.0]hexanyl, bicyclo[1.1.1]pentanyl, cubanyl, 1,2,3,4-tetrahydronaphthyl, pyridinyl, methoxy, phenoxy, acetyl, benzoyl, methoxycarbonyl, phenoxycarbonyl, acetoxy, benzoyloxy, methylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, phenylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, dimethylamino, diethylamino, fluoro, chloro or oxo;

R₄ and R₅ are each independently hydrogen, C1-4 saturated alkyl, C1-2alkoxyC1-2alkyl, C1-2alkylaminoC1-2alkyl, C1-2alkylthioC1-2alkyl wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, , cyclopropyl, cyclopentyl, cyclohexyl, phenyl, benzyl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, tetrahydropyranyl, pyridinyl, and pyrimidinyl, acetyl, benzoyl, methoxycarbonyl, ethoxycarbonyl, benzyloxycarbonyl, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by methyl, ethyl or phenyl,

or R₄ and R₅ are each independently acetylamino, benzoylamino, methylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, phenylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by methyl, ethyl or phenyl,

5 or R₄ and R₅ are each independently methoxycarbonylamino, ethoxycarbonylamino, phenoxycarbonylamino, methylcarbamoyloxy, phenylcarbamoyloxy, methylsulfonylamino, phenylsulfonylamino, methylaminosulfonyl, phenylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by methyl, ethyl or phenyl,

10 or R₄ and R₅ are each independently fluoro, chloro, hydroxy, oxo, carboxy or carboxamide,

wherein each R₄ and R₅ may be further optionally independently substituted by one or more R_e;

15

R_e is methyl, methoxy, ethoxy, cyclopropyl, cyclopentyl, cyclohexyl, phenyl, naphthyl, indanyl, piperidinyl, morpholinyl, indolyl, thienyl, pyridinyl, acetyl, benzoyl, acetyloxy, phenoxy, benzyloxy, methoxycarbonyl, ethoxycarbonyl, carbamoyl wherein the nitrogen atom may be independently mono or di-

20

substituted by methyl, ethyl or phenyl,

or R_e is ureido wherein either nitrogen atom may be independently substituted by methyl, ethyl or phenyl,

or R_e is amino wherein the nitrogen atom may be independently mono or di-substituted by methyl, ethyl or phenyl,

25

or R_e is fluoro, chloro, hydroxy, oxo, carboxy or carboxamide,

wherein R_e may be further optionally substituted by one or more R_f;

and

R_f is methyl, cyclopentyl, cyclohexyl, phenyl, tolylsulfonyl, methoxy, phenoxy, benzyloxy, carboxy, fluoro, chloro or oxo.

30

7. The compound according to claim 6, wherein:

Each R₁ is independently hydrogen, i-propyl, benzyloxy, cyclohexyl, benzyl, phenyl, carboxyphenyl, naphthyl, 4-(acetylamino)-phenyl, 4-(methanesulfonylamino)-phenyl, 4-
5 methoxyphenyl, 3-phenoxyphenyl, 4-chlorophenyl, 3,4-dichlorophenyl, 4-fluorophenyl, 2-fluorophenyl, 2-fluoro-4-chlorophenyl, naphthyl, thienylmethyl, piperidinyl, morpholinyl, pyrrolidinyl, piperazinyl, furanyl, thienyl, thiazolyl, quinolyl, tetrahydroisoquinolyl, 5-chlorothieryl, pyridin-4-yl, pyrazinyl, 2*H*-benzo[e][1,3]oxazine, methylamino, ethylamino, dimethylamino or diethylamino;

10

R₃ is methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, methoxymethyl, methylthiomethyl, vinyl, propenyl, butenyl, i-butenyl, cyclohexyl, phenyl, benzyl or naphthylmethyl wherein R₃ is optionally substituted by one or more R_c;

15

R_c is methyl, cyclopropyl, cyclohexyl, cyclopentyl, phenyl, indanyl, 1,2,3,4-tetrahydronaphthyl, methoxy, methylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, dimethylamino, fluoro or chloro;

20

R₄ and R₅ are each independently hydrogen, methyl, ethyl, n-propyl, n-butyl, t-butyl, i-propyl, i-butyl, methoxymethyl, methylthiomethyl or methylthioethyl wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, cyclopropyl, cyclopentyl, cyclohexyl, phenyl, benzyl, piperidinyl, tetrahydropyranyl, pyrimidinyl, acetyl, benzoyl, ethoxycarbonyl, benzyloxycarbonyl, methylsulfonylamino, phenylsulfonylamino, methylamino, dimethylamino, fluoro, oxo or carboxy,

25

wherein each R₄ and R₅ may each be further optionally independently substituted by one or more R_e;

30

R_e is methyl, cyclopropyl, cyclopentyl, cyclohexyl, phenyl, carboxyphenyl, naphthyl, indanyl, thienyl, methylthienyl, methoxy, phenoxy, benzyloxy, piperidinyl, pyridinyl, indolyl, 1-(tolyl-sulfonyl)-indolyl, carbamoyl wherein the

nitrogen atom may be independently mono or di-substituted by methyl, phenyl or benzyl,
or R_e is hydroxy, fluoro, chloro, oxo, dimethylamino or trifluoromethyl.

5

8. The compound according to claim 7, wherein:

Y is R₁, R₁O- or R₁NH-;

10 Each R₁ is independently hydrogen, phenyl, benzyl, naphthyl, 4-(acetylamino)-phenyl, 4-(methanesulfonylamino)-phenyl, 3-phenoxyphenyl, 4-chlorophenyl, 3,4-dichlorophenyl, 4-fluorophenyl, thienylmethyl, morpholinyl, pyrrolidinyl, piperidinyl, piperazinyl, furanyl, thienyl, thiazolyl, quinolyl, tetrahydroisoquinolyl, 5-chlorothienyl, pyridin-4-yl, 2*H*-benzo[e][1,3]oxazine or pyrazinyl;

15

R₃ is ethyl, n-propyl, n-butyl, i-butyl, 2,2-dimethylpropyl, 3-methylbutyl, 3,3-dimethylbutyl, 2,2,3-trimethylbutyl, 2,2,3,3-tetramethylbutyl, cyclopropylmethyl, cyclohexylmethyl, methoxymethyl, methylthiomethyl, methylsulfonylmethyl, dimethylaminomethyl, propenyl, i-butenyl, cyclohexyl, phenyl, benzyl, 4-methoxybenzyl, 20 4-chlorobenzyl, 3,4-dichlorobenzyl, 3-chlorobenzyl, 2,4-dichlorobenzyl, 4-methylbenzyl, 3-methylbenzyl or naphth-2-ylmethyl;

and

R₄ and R₅ are each independently hydrogen, methyl, ethyl, n-propyl, n-butyl, n-pentyl, 2-pentyl, 3-pentyl, phenylethyl, phenylpropyl, 2,2-dimethylpropyl, t-butyl, i-propyl, i-butyl, 25 cyclopropyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, phenyl, benzyl, naphthylmethyl, indanylmethyl, pyridinylmethyl, indolylmethyl, thienylmethyl, 5-methylthienylmethyl, piperidinyl, piperidinylcarbonyl, pyridinylcarbonyl, tetrahydropyranyl, pyrimidinyl, acetyl, benzoyl, ethoxycarbonyl, benzyloxycarbonyl, t-butoxycarbonyl, methylcarbamoyl, phenylcarbamoyl, 30 benzylcarbamoyl, methylsulfonylamino, phenylsulfonylamino, methylamino, dimethylamino, methylcyclohexyl, methylbenzyl, trifluoromethylbenzyl, methoxybenzyl,

3-carboxyphenylmethoxymethyl, phenoxybenzyl, benzyloxybenzyl, benzyloxymethyl, N-[(4-methylphenyl)-sulfonyl]-indolylmethyl, fluorobenzyl, difluorobenzyl, chlorobenzyl, N,N-dimethylaminoacetyl, trifluoromethylbenzyl, fluoro, oxo or carboxy.

5 9. The compound according to claim 8, wherein:

Each R₁ is independently hydrogen, phenyl, benzyl, naphthyl, tetrahydroisoquinolin-2-yl or morpholin-4-yl,

10 R₃ is ethyl, n-propyl, n-butyl, i-butyl, 2,2-dimethylpropyl, cyclopropylmethyl, cyclohexylmethyl, dimethylaminomethyl, phenyl or benzyl;
and

R₄ is hydrogen;

15 and

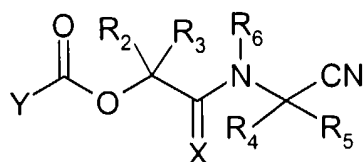
R₅ is methyl, ethyl, n-propyl, n-butyl, n-pentyl, 2-pentyl, 3-pentyl, phenylethyl, phenylpropyl, 2,2-dimethylpropyl, t-butyl, i-propyl, i-butyl, cyclopropyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, phenyl, benzyl, naphthylmethyl, indanylmethyl, pyridinylmethyl, indolylmethyl, thienylmethyl,
20 methylthienylmethyl, methylbenzyl, methoxybenzyl, methoxybenzyl-m-carboxylic acid, phenoxybenzyl, benzyloxybenzyl, benzyloxymethyl, N-[(4-methylphenyl)-sulfonyl]-indolylmethyl, fluorobenzyl, difluorobenzyl, chlorobenzyl, N,N-dimethylaminoacetyl or trifluoromethylbenzyl.

25 10. The compound according to claim 9, wherein:

R₅ phenylethyl, phenylpropyl, 2,2-dimethylpropyl, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, benzyl, naphthylmethyl, indanylmethyl, pyridinylmethyl, indolylmethyl, thienylmethyl, methylthienylmethyl, methylbenzyl,
30 methoxybenzyl, phenoxybenzyl, benzyloxybenzyl, benzyloxymethyl.

11. A compound of formula (I):

5



(I)

wherein:

- 10 Y is C1-6alkoxy, C1-6alkylamino, naphthyl, morpholinyl, tetrahydroisoquinolinyl, phenylamino, benzylamino, naphthylamino, benzyloxy, benzofuranyl, benzothienyl, phenylpiperazinyl, pyridinylthienyl, C1-3alkoxyphenylpiperidinyl- amino, C1-3alkoxycarbonylpiperidinylamino-thiazolyl, benzylpiperazinyl- carbonylamino-phenyl, morpholin-4-yl-C1-3alkoxybenzofuranyl, C1- 15 3alkoxycarbonylamino-phenyl, quinolinylamino, wherein each is optionally substituted by one or more C1-3alkyl or halogen;

R₂ is hydrogen or methyl;

- 20 R₃ is hydrogen;

C1-10 saturated alkyl group optionally substituted by one or more:

halogen;

C3-6cycloalkyl optionally substituted by one or more C1-3alkyl;

phenyl or naphthyl optionally substituted by one or more halogen,

25

C1-3alkyl or C1-3alkoxy;

decahydronaphthyl;

spiro[2.5]octyl optionally substituted by one or more C1-3alkyl;

- indanyl;
 C1-3alkylthio wherein the sulfur atom may oxidized to a sulfoxide or a
 sulfone;
 or biphenyl;
- 5 C2-6alkenyl;
 C3-6cycloalkyl optionally substituted by one or more C1-3alkyl;
- dialkylaminomethyl;
 phenyl
 10 or pyridyl;
- or R₂ and R₃ together with the carbon atom they are attached to form cyclopentyl,
 cyclohexyl, tetrahydropyranyl, pyrrolidinyl optionally substituted with C1-3alkyl,
 C3-6cycloalkyl, C3-6cycloalkyl-C1-3-alkyl or phenyl-C1-3alkyl, or piperidyl
 15 optionally substituted with C1-3alkyl, C3-6cycloalkyl, C3-6cycloalkyl-C1-3-alkyl
 or phenyl-C1-3alkyl;
- R₄ is hydrogen or C1-6 saturated alkyl group;
- 20 R₅ is hydrogen, C1-6 saturated alkyl group, C1-3alkyl-sulfonyl-C1-3alkyl, phenyl-C1-
 3alkyl, trifluoromethylbenzyl, phenylethylindolyl-C1-3-alkyl or benzyloxy-C1-3-alkyl,
 wherein each is optionally substituted by halo, carboxy, or C1-3alkoxy;
- or R₄ and R₅ together with the carbon atom they are attached to form a cyclopropanyl,
 25 cyclobutanyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, tetrahydropyranyl; or
 pyrrolidinyl, piperidinyl or azepanyl, each being optionally substituted with one or more:
 oxo, C1-3alkyl, hydroxyC1-3alkyl, benzyloxyC1-3alkyl, C3-6cycloalkyl, C3-
 6cycloalkyl-C1-3-alkyl, phenyl-C1-3alkyl, tosyl-indolylC1-3alkyl, C1-3alkanoyl,
 phenylC1-3alkanoyl, pyridinylC1-3alkanoyl, morpholinylC1-3alkanoyl, C1-
 30 3alkylcarbamoyl, C1-3alkoxy-C1-3alkylcarbamoyl, C1-3alkoxycarbamoyl, C1-3alkoxy-
 C1-3alkoxycarbamoyl, phenylcarbamoyl, phenylC1-3alkylcarbamoyl,

benzyloxycarbonyl, cyclohexanylethyl, cyclohexylC1-3alkoxycarbonyl,
phenylcarbonyl, phenylC1-3alkoxycarbonyl, piperidinylethyl, piperazinylethyl, or
tetrahydropyranylethyl, wherein each of the foregoing substituents on the
pyrrolidinyl, piperidinyl or azepanyl can be further optionally substituted by one or more
5 C1-3alkyl or halogen;

and

R₆ is hydrogen or methyl.

10

12. The compound according to claim 11, wherein:

15 Y is naphthyl, morpholinyl, tetrahydroisoquinolinyl, benzylamino, naphthylamino,
benzyloxy, 4-phenylpiperazin-1-yl, 5-(pyridin-4-yl)-2-thienyl, 1-(4-
alkoxyphenyl)-piperidin-4-yl amino, 2-[1-(alkoxycarbonyl)-piperidin-4-yl amino]
thiazol-4-yl, 4-[4-(benzyl)-piperazin-1-yl carbonylamino]phenyl or 4-
(alkoxycarbonylamino)phenyl, quinolin-2-yl amino, wherein each is optionally
20 substituted by one or more halogen;

R₂ is hydrogen or methyl;

R₃ is ethyl, n-propyl, n-butyl, i-butyl, 2,2-dimethylpropyl, cyclopropyl,
25 cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl,
cyclohexylmethyl, cyclohexylethyl, dialkylaminomethyl, phenyl, benzyl,
phenylethyl or pyridyl;

or R₂ and R₃ together with the carbon atom they are attached to form cyclopentyl or
30 cyclohexyl;

R₄ is hydrogen, methyl or ethyl;

R₅ is hydrogen, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, methylsulfonylethyl,
benzyl, trifluoromethylbenzyl, phenylethyl, indolylmethyl, benzyloxymethyl, methoxy-
5 benzyloxymethyl or halo-benzyloxymethyl;

or R₄ and R₅ together with the carbon atom they are attached to form a cyclohexanyl;

and

10

R₆ is hydrogen.

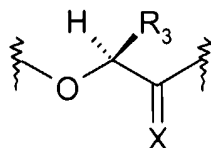
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13. A compound according to claim 1, wherein when R₂ is hydrogen and R₃ is

other than hydrogen, then the stereoconfiguration about the carbon atom to which R₂ and

R₃ are attached is as shown below:

20

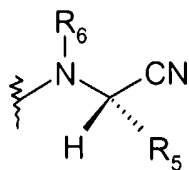


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14. A compound according to claim 1 or 13, wherein when R₄ is hydrogen and R₅ is other

than hydrogen, then the stereoconfiguration about the carbon atom to which R₄ and R₅ are

attached is as shown below:



15. A compound according to claim 1 selected from:
- Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3-
- 5 methyl-butyl ester;
- Benzyl-carbamic acid 1-(4-cyano-1-propyl-piperidin-4-ylcarbamoyl)-3-methyl-butyl ester;
- 10 Benzyl-carbamic acid 1-(1-benzyl-3-cyano-pyrrolidin-3-ylcarbamoyl)-3-methyl-butyl ester;
- Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-3-methyl-butyl ester;
- 15 Morpholine-4-carboxylic acid 1-(4-cyano-1-propyl-piperidin-4-ylcarbamoyl)-3-methyl-butyl ester;
- Morpholine-4-carboxylic acid 1-(1-benzyl-4-cyano-piperidin-4-ylcarbamoyl)-3-methyl-
- 20 butyl ester;
- Morpholine-4-carboxylic acid 1-(1-benzyl-3-cyano-pyrrolidin-3-ylcarbamoyl)-3-methyl-butyl ester;
- 25 Morpholine-4-carboxylic acid 1-(3-cyano-1-cyclohexylmethyl-pyrrolidin-3-ylcarbamoyl)-3-methyl-butyl ester;

Morpholine-4-carboxylic acid 1-(3-cyano-1-cyclohexyl-pyrrolidin-3-ylcarbamoyl)-3-methyl-butyl ester;

5 Morpholine-4-carboxylic acid 1-(3-cyano-1-cyclohexyl-pyrrolidin-3-ylcarbamoyl)-cyclohexyl ester;

Morpholine-4-carboxylic acid 1-(3-cyano-1-cyclohexylmethyl-pyrrolidin-3-ylcarbamoyl)-cyclohexyl ester;

10 Morpholine-4-carboxylic acid 1-(1-benzyl-3-cyano-pyrrolidin-3-ylcarbamoyl)-cyclohexyl ester;

Morpholine-4-carboxylic acid 1-(1-benzyl-4-cyano-piperidin-4-ylcarbamoyl)-cyclohexyl ester;

15 Morpholine-4-carboxylic acid 1-(4-cyano-1-propyl-piperidin-4-ylcarbamoyl)-cyclohexyl ester;

20 Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-cyclohexyl ester;

Benzyl-carbamic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-3-methyl-butyl ester;

25 Benzyl-carbamic acid 1-(1-benzyl-4-cyano-piperidin-4-ylcarbamoyl)-3-methyl-butyl ester;

30 Benzyl-carbamic acid 1-(3-cyano-1-cyclohexylmethyl-pyrrolidin-3-ylcarbamoyl)-3-methyl-butyl ester;

Benzyl-carbamic acid 1-(3-cyano-1-cyclohexyl-pyrrolidin-3-ylcarbamoyle)-3-methyl-butyl ester;

Benzyl-carbamic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyle)-cyclohexyl ester;

5

Benzyl-carbamic acid 1-(4-cyano-1-propyl-piperidin-4-ylcarbamoyle)-cyclohexyl ester;

Benzyl-carbamic acid 1-(1-benzyl-4-cyano-piperidin-4-ylcarbamoyle)-cyclohexyl ester;

10 Benzyl-carbamic acid 1-(1-benzyl-3-cyano-pyrrolidin-3-ylcarbamoyle)-cyclohexyl ester;

Benzyl-carbamic acid 1-(3-cyano-1-cyclohexylmethyl-pyrrolidin-3-ylcarbamoyle)-cyclohexyl ester;

15 Benzyl-carbamic acid 1-(3-cyano-1-cyclohexyl-pyrrolidin-3-ylcarbamoyle)-cyclohexyl ester;

Naphthalen-2-yl-carbamic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyle)-3-methyl-butyl ester;

20

Naphthalen-2-yl-carbamic acid 1-(4-cyano-1-propyl-piperidin-4-ylcarbamoyle)-3-methyl-butyl ester;

Naphthalen-2-yl-carbamic acid 1-(1-benzyl-4-cyano-piperidin-4-ylcarbamoyle)-3-methyl-butyl ester;

25

Naphthalen-2-yl-carbamic acid 1-(1-benzyl-3-cyano-pyrrolidin-3-ylcarbamoyle)-3-methyl-butyl ester;

30 Naphthalen-2-yl-carbamic acid 1-(3-cyano-1-cyclohexylmethyl-pyrrolidin-3-ylcarbamoyle)-3-methyl-butyl ester;

Naphthalen-2-yl-carbamic acid 1-(3-cyano-1-cyclohexyl-pyrrolidin-3-ylcarbamoyl)-3-methyl-butyl ester;

- 5 Naphthalen-2-yl-carbamic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-cyclohexyl ester;

Naphthalen-2-yl-carbamic acid 1-(4-cyano-1-propyl-piperidin-4-ylcarbamoyl)-cyclohexyl ester;

10

Naphthalen-2-yl-carbamic acid 1-(1-benzyl-4-cyano-piperidin-4-ylcarbamoyl)-cyclohexyl ester;

- 15 Naphthalen-2-yl-carbamic acid 1-(1-benzyl-3-cyano-pyrrolidin-3-ylcarbamoyl)-cyclohexyl ester;

Naphthalen-2-yl-carbamic acid 1-(3-cyano-1-cyclohexylmethyl-pyrrolidin-3-ylcarbamoyl)-cyclohexyl ester;

- 20 Naphthalen-2-yl-carbamic acid 1-(3-cyano-1-cyclohexyl-pyrrolidin-3-ylcarbamoyl)-cyclohexyl ester;

Morpholine-4-carboxylic acid 1-[3-cyano-1-(4-fluoro benzyl)-pyrrolidin-3-ylcarbamoyl]-cyclohexyl ester;

- 25 Morpholine-4-carboxylic acid 1-[3-cyano-1-(2,4-difluoro benzyl)-pyrrolidin-3-ylcarbamoyl]-cyclohexyl ester;

Morpholine-4-carboxylic acid 1-[3-cyano-1-(2,4,6-trifluoro-benzyl)-pyrrolidin-3-ylcarbamoyl]-3-methyl-butyl ester;

30

- Benzyl-carbamic acid 1-[3-cyano-1-(2,3,4,5,6-pentafluoro-benzyl)-pyrrolidin-3-ylcarbamoyl]-cyclohexyl ester;
- 5 Morpholine-4-carboxylic acid 1-[4-cyano-1-(2,4-difluoro benzyl)-piperidin-4-ylcarbamoyl]-3-methyl-butyl ester;
- Morpholine-4-carboxylic acid 1-[4-cyano-1-(2,6-difluoro benzyl)-piperidin-4-ylcarbamoyl]-3-methyl-butyl ester;
- 10 Morpholine-4-carboxylic acid 1-[4-cyano-1-(3,5-difluoro benzyl)-piperidin-4-ylcarbamoyl]-3-methyl-butyl ester;
- Benzyl-carbamic acid 1-[4-cyano-1-(2,4,6-trifluoro benzyl)-piperidin-4-ylcarbamoyl]-3-methyl-butyl ester;
- 15 Morpholine-4-carboxylic acid 1-{3-cyano-1-[1-(toluene-4-sulfonyl)-1*H*-indol-3-ylmethyl]-pyrrolidin-3-ylcarbamoyl}-3-methyl-butyl ester;
- Benzyl-carbamic acid 1-{4-cyano-1-[1-(toluene-4-sulfonyl)-1*H*-indol-3-ylmethyl]-piperidin-4-ylcarbamoyl}-3-methyl-butyl ester;
- 20 Benzyl-carbamic acid 1-(cyanomethyl-carbamoyl)-3-methyl-butyl ester;
- Benzyl-carbamic acid 1-(1-cyano-3-methyl-butylcarbamoyl)-3-methyl-butyl ester;
- 25 Benzyl-carbamic acid 1-(1-cyano-cyclopropylcarbamoyl)-3-methyl-butyl ester;
- Benzyl-carbamic acid 1-(cyanomethyl-carbamoyl)-2-cyclopropyl-ethyl ester;
- 30 Benzyl-carbamic acid 1-(1-cyano-3-methyl-butylcarbamoyl)-2-cyclopropyl-ethyl ester;

Benzyl-carbamic acid 1-(1-cyano-cyclopropylcarbamoyl)-2-cyclopropyl-ethyl ester;

Benzyl-carbamic acid 1-(cyanomethyl-carbamoyl)-cyclohexyl ester;

5 Benzyl-carbamic acid 1-(1-cyano-3-methyl-butylcarbamoyl)-cyclohexyl ester;

Benzyl-carbamic acid 1-(1-cyano-cyclopropylcarbamoyl)-cyclohexyl ester;

10 3,4-Dihydro-1H-isoquinoline-2-carboxylic acid 1-{{(2-chloro-benzyloxymethyl)-cyano-methyl]-carbamoyl}-3-methyl-butyl ester;

3,4-Dihydro-1H-isoquinoline-2-carboxylic acid 1-{{cyano-(4-methoxy-benzyloxymethyl)-methyl]-carbamoyl}-3-methyl-butyl ester;

15 3,4-Dihydro-1H-isoquinoline-2-carboxylic acid 1-{{(benzyloxymethyl)-cyano-methyl]-carbamoyl}-3-methyl-butyl ester;

Benzyl-carbamic acid 1-{{(2-chloro-benzyloxymethyl)-cyano-methyl]-carbamoyl}-2-cyclopropyl-ethyl ester;

20

Benzyl-carbamic acid 1-{{cyano-(4-methoxy-benzyloxymethyl)-methyl]-carbamoyl}-2-cyclopropyl-ethyl ester;

25 Benzyl-carbamic acid 1-{{(benzyloxymethyl)-cyano-methyl]-carbamoyl}-2-cyclopropyl-ethyl ester;

Naphthalen-2-yl-carbamic acid 1-{{(2-chloro-benzyloxymethyl)-cyano-methyl]-carbamoyl}-cyclohexyl ester;

30 Naphthalen-2-yl-carbamic acid 1-{{cyano-(4-methoxy-benzyloxymethyl)-methyl]-carbamoyl}-cyclohexyl ester;

- Naphthalen-2-yl-carbamic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-cyclohexyl ester;
- 5 Phenyl-carbamic acid 1-(cyanomethyl-carbamoyl)-2-dimethylamino-ethyl ester;
- (3,4-Dichloro-phenyl)-carbamic acid 1-[(cyano-methyl-methyl)-carbamoyl]-3,3-dimethyl-butyl ester;
- 10 4-Phenyl-piperazine-1-carboxylic acid [(cyano-dimethyl-methyl)-carbamoyl]-phenyl-methyl ester;
- 5-Pyridin-4-yl-thiophene-2-carboxylic acid (1-cyano-3-methanesulfonyl-propylcarbamoyl)-pyridin-3-yl-methyl ester;
- 15 5-Pyridin-4-yl-thiophene-2-carboxylic acid (1-cyano-3-methanesulfonyl-propylcarbamoyl)-pyridin-3-yl-methyl ester;
- 4-(4-{1-[(Benzyl-cyano-methyl)-carbamoyl]-propoxycarbonyl}-thiazol-2-ylamino)-piperidine-1-carboxylic acid ethyl ester;
- 20 4-[(4-Benzyl-piperazine-1-carbonyl)-amino]-benzoic acid 1-{{cyano-(4-methyl-benzyl)-methyl}-carbamoyl}-cyclopentyl ester;
- 25 4-Ethoxycarbonylamino-benzoic acid 4-(4-cyano-tetrahydro-pyran-4-ylcarbamoyl)-tetrahydro-pyran-4-yl ester;
- Quinolin-2-yl-carbamic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-methyl-butyl ester;
- 30

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3-methyl-butyl ester;

5 Benzyl-carbamic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3-methyl-butyl ester;

Naphthalen-2-yl-carbamic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3-methyl-butyl ester;

10 Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-cyclopropyl-ethyl ester;

Naphthalen-2-yl-carbamic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-cyclopropyl-ethyl ester;

15 Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-cyclohexyl ester;

Benzyl-carbamic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-cyclohexyl ester;

20 Naphthalene-2-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3-methyl-butyl ester;

25 Carbonic acid benzyl ester 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3-methyl-butyl ester;

3,4-Dihydro-1H-isoquinoline-2-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-cyclopropyl-ethyl ester;

30 Naphthalene-2-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-cyclopropyl-ethyl ester;

Carbonic acid benzyl ester 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-cyclopropyl-ethyl ester;

- 5 3,4-Dihydro-1H-isoquinoline-2-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-cyclohexyl ester;

Naphthalene-2-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-cyclohexyl ester;

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Carbonic acid benzyl ester 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-cyclohexyl ester;

- 15 Benzyl-carbamic acid 1-[(benzyloxymethyl-cyano-methyl-methyl)-carbamoyl]-3-methyl-butyl ester;

Benzyl-carbamic acid 1-(1-cyano-3-phenyl-propylcarbamoyl)-3-methyl-butyl ester;

- 20 Benzyl-carbamic acid 1-[(benzyloxymethyl-cyano-methyl)-methyl-carbamoyl]-3-methyl-butyl ester;

Benzyl-carbamic acid 1-[(benzyloxymethyl-cyano-methyl-methyl)-carbamoyl]-2-cyclopropyl-ethyl ester;

- 25 Benzyl-carbamic acid 1-(1-cyano-3-phenyl-propylcarbamoyl)-2-cyclopropyl-ethyl ester;

Benzyl-carbamic acid 1-[(benzyloxymethyl-cyano-methyl)-methyl-carbamoyl]-2-cyclopropyl-ethyl ester;

- 30 Benzyl-carbamic acid 1-[(benzyloxymethyl-cyano-methyl-methyl)-carbamoyl]-cyclohexyl ester;

Benzyl-carbamic acid 1-(1-cyano-3-phenyl-propylcarbamoyl)-cyclohexyl ester;

5 Benzyl-carbamic acid 1-[(benzyloxymethyl-cyano-methyl)-methyl-carbamoyl]-
cyclohexyl ester;

3-{2-[(2-Benzylcarbamoyloxy-4-methyl-pentanoyl)-methyl-amino]-2-cyano-
ethoxymethyl}-benzoic acid;

10 Benzo[b]thiophene-2-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3-
methyl-butyl ester;

5-(2-Morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid 1-[(benzyloxymethyl-cyano-
methyl)-carbamoyl]-3-methyl-butyl ester;

15 Benzofuran-2-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3-methyl-
butyl ester;

20 3-Methyl-benzofuran-2-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-
3-methyl-butyl ester;

3,4-Dihydro-1H-isoquinoline-2-carboxylic acid 1-[[3-carboxy-benzyloxymethyl)-cyano-
methyl]-carbamoyl]-3-methyl-butyl ester;

25 3,4-Dihydro-1H-isoquinoline-2-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-
carbamoyl]-3,3-difluoro-propyl ester;

3,4-Dihydro-1H-isoquinoline-2-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-
carbamoyl]-3,3,3-trifluoro-propyl ester;

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Benzyl-carbamic acid 1-(4-cyano-1,2,2,6,6-pentamethyl-piperidin-4-ylcarbamoyl)-3-methyl-butyl ester;

5 Benzyl-carbamic acid 1-(4-cyano-1-methyl-2,6-dioxo-piperidin-4-ylcarbamoyl)-3-methyl-butyl ester;

4-(2-Benzylcarbamoxyloxy-4-methyl-pentanoylamino)-4-cyano-piperidine-1-carboxylic acid ethyl ester;

10 4-(2-Benzylcarbamoxyloxy-4-methyl-pentanoylamino)-4-cyano-piperidine-1-carboxylic acid cyclohexylmethyl ester;

4-(2-Benzylcarbamoxyloxy-4-methyl-pentanoylamino)-4-cyano-piperidine-1-carboxylic acid benzyl ester;

15 Benzyl-carbamic acid 1-(2-benzyl-4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-3-methyl-butyl ester;

20 Benzyl-carbamic acid 1-(2-benzyloxymethyl-4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-3-methyl-butyl ester;

Benzyl-carbamic acid 1-(5-benzyloxymethyl-3-cyano-1-methyl-pyrrolidin-3-ylcarbamoyl)-3-methyl-butyl ester;

25 4-(2-Benzylcarbamoxyloxy-4-methyl-pentanoylamino)-4-cyano-1-methyl-pyrrolidine-2-carboxylic acid methyl ester;

Benzyl-carbamic acid 1-(3-cyano-5-hydroxymethyl-1-methyl-pyrrolidin-3-ylcarbamoyl)-3-methyl-butyl ester;

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Benzyl-carbamic acid 1-(4-cyano-1,2,2-trimethyl-piperidin-4-ylcarbamoyl)-3-methyl-butyl ester;

5 Benzyl-carbamic acid 1-(4-cyano-2-hydroxymethyl-1-methyl-piperidin-4-ylcarbamoyl)-3-methyl-butyl ester;

Benzyl-carbamic acid 1-(4-cyano-1-methyl-2-methylcarbamoyl-piperidin-4-ylcarbamoyl)-3-methyl-butyl ester;

10 Benzyl-carbamic acid 1-(3-cyano-1-methyl-5-methylcarbamoyl-pyrrolidin-3-ylcarbamoyl)-3-methyl-butyl ester;

3-(2-Benzylcarbamoxyloxy-4-methyl-pentanoylamino)-3-cyano-pyrrolidine-1-carboxylic acid ethyl ester;

15 Benzyl-carbamic acid 1-(3-cyano-1-ethylcarbamoyl-pyrrolidin-3-ylcarbamoyl)-3-methyl-butyl ester;

20 Benzyl-carbamic acid 1-(1-benzylcarbamoyl-4-cyano-piperidin-4-ylcarbamoyl)-3-methyl-butyl ester;

Benzyl-carbamic acid 1-(4-cyano-1-cyclohexanecarbonyl-piperidin-4-ylcarbamoyl)-3-methyl-butyl ester;

25 Benzyl-carbamic acid 1-[4-cyano-1-(piperidine-1-carbonyl)-piperidin-4-ylcarbamoyl]-3-methyl-butyl ester;

Benzyl-carbamic acid 1-[4-cyano-1-(4-methyl-piperazine-1-carbonyl)-piperidin-4-ylcarbamoyl]-3-methyl-butyl ester;

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Benzyl-carbamic acid 1-[4-cyano-1-(tetrahydro-pyran-4-carbonyl)-piperidin-4-ylcarbamoyl]-3-methyl-butyl ester;

5 Benzyl-carbamic acid 1-(3-cyano-1-isobutyryl-pyrrolidin-3-ylcarbamoyl)-3-methyl-butyl ester;

Benzyl-carbamic acid 1-[3-cyano-1-(2-pyridin-4-yl-acetyl)-pyrrolidin-3-ylcarbamoyl]-3-methyl-butyl ester;

10 Benzyl-carbamic acid 1-(3-cyano-1-phenylcarbamoyl-pyrrolidin-3-ylcarbamoyl)-3-methyl-butyl ester;

Benzyl-carbamic acid 1-(1-benzylcarbamoyl-3-cyano-pyrrolidin-3-ylcarbamoyl)-3-methyl-butyl ester;

15 3-(2-Benzylcarbamoxyloxy-4-methyl-pentanoylamino)-3-cyano-pyrrolidine-1-carboxylic acid benzyl ester;

Benzyl-carbamic acid 1-(3-cyano-1-ethyl-azepan-3-ylcarbamoyl)-3-methyl-butyl ester;

20 3-(2-Benzylcarbamoxyloxy-4-methyl-pentanoylamino)-3-cyano-azepane-1-carboxylic acid 2-methoxy-ethyl ester;

Benzyl-carbamic acid 1-[3-cyano-1-(2-methoxy-ethylcarbamoyl)-azepan-3-ylcarbamoyl]-3-methyl-butyl ester;

Benzyl-carbamic acid 1-(3-cyano-1-phenylacetyl-azepan-3-ylcarbamoyl)-3-methyl-butyl ester;

30 Benzyl-carbamic acid 1-(1-benzyl-4-cyano-azepan-4-ylcarbamoyl)-3-methyl-butyl ester;

4-(2-Benzylcarbamoyloxy-4-methyl-pentanoylamino)-4-cyano-azepane-1-carboxylic acid isopropyl ester;

5 Benzyl-carbamic acid 1-(1-benzylcarbamoyl-4-cyano-azepan-4-ylcarbamoyl)-3-methyl-butyl ester;

Benzyl-carbamic acid 1-[4-cyano-1-(3-morpholin-4-yl-propionyl)-azepan-4-ylcarbamoyl]-3-methyl-butyl ester;

10 Benzyl-carbamic acid 1-(1-benzyl-4-cyano-7-oxo-azepan-4-ylcarbamoyl)-3-methyl-butyl ester;

Benzyl-carbamic acid 1-(1-benzyl-4-cyano-2-oxo-azepan-4-ylcarbamoyl)-3-methyl-butyl ester;

15 Benzyl-carbamic acid 1-(3-cyano-1-ethyl-2-oxo-azepan-3-ylcarbamoyl)-3-methyl-butyl ester;

20 Benzyl-carbamic acid 1-(3-cyano-1-ethyl-7-oxo-azepan-3-ylcarbamoyl)-3-methyl-butyl ester;

Benzyl-carbamic acid 1-(1-benzyl-3-cyano-5-oxo-pyrrolidin-3-ylcarbamoyl)-3-methyl-butyl ester;

25 Benzyl-carbamic acid 1-(1-benzyl-3-cyano-2-oxo-pyrrolidin-3-ylcarbamoyl)-3-methyl-butyl ester;

Benzyl-carbamic acid 1-(1-benzyl-4-cyano-2-oxo-piperidin-4-ylcarbamoyl)-3-methyl-butyl ester;

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Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-4,4-dimethyl-pentyl ester;

5 Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-4,4-dimethyl-pentyl ester;

Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-4,4-dimethyl-pentyl ester;

10 Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-4-methyl-pentyl ester;

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-4-methyl-pentyl ester;

15 Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-4-methyl-pentyl ester;

20 Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3,3,4,4-tetramethyl-pentyl ester;

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-3,3,4,4-tetramethyl-pentyl ester;

25 Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-3,3,4,4-tetramethyl-pentyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3,3-dimethyl-pentyl ester;

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Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-3,3-dimethyl-pentyl ester;

5 Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-3,3-dimethyl-pentyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3,3,4-trimethyl-pentyl ester;

10 Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-3,3,4-trimethyl-pentyl ester;

Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-3,3,4-trimethyl-pentyl ester;

15 Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3-cyclohexyl-3-methyl-butyl ester;

20 Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-3-cyclohexyl-3-methyl-butyl ester;

Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-3-cyclohexyl-3-methyl-butyl ester;

25 Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3-cyclohexyl-propyl ester;

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-3-cyclohexyl-propyl ester;

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Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-3-cyclohexyl-propyl ester;

5 Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3-phenyl-propyl ester;

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-3-phenyl-propyl ester;

10 Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-3-phenyl-propyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-cyclohexyl-ethyl ester;

15 Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-2-cyclohexyl-ethyl ester;

20 Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-phenyl-ethyl ester;

25 Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-2-phenyl-ethyl ester;

Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-phenyl-ethyl ester;

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Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-(1-methyl-cyclohexyl)-ethyl ester;

5 Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-2-(1-methyl-cyclohexyl)-ethyl ester;

Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-(1-methyl-cyclohexyl)-ethyl ester;

10 Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3,3-dimethyl-butyl ester;

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-3,3-dimethyl-butyl ester;

15 Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-3,3-dimethyl-butyl ester;

20 Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3-methyl-but-3-enyl ester;

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-3-methyl-but-3-enyl ester;

25 Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-3-methyl-but-3-enyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-(3,4-dichloro-phenyl)-ethyl ester;

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Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-2-(3,4-dichloro-phenyl)-ethyl ester;

5 Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-(3,4-dichloro-phenyl)-ethyl ester;

Morpholine-4-carboxylic acid [(benzyloxymethyl-cyano-methyl)-carbamoyl]-cyclohexyl-methyl ester;

10 Morpholine-4-carboxylic acid (3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-cyclohexyl-methyl ester;

Morpholine-4-carboxylic acid (4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-cyclohexyl-methyl ester;

15 Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-naphthalen-2-yl-ethyl ester;

20 Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-2-naphthalen-2-yl-ethyl ester;

Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-naphthalen-2-yl-ethyl ester;

25 Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-(decahydro-naphthalen-2-yl)-ethyl ester;

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-2-(decahydro-naphthalen-2-yl)-ethyl ester;

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Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-(decahydro-naphthalen-2-yl)-ethyl ester;

5 Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-(4,4-dimethyl-cyclohexyl)-ethyl ester;

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-2-(4,4-dimethyl-cyclohexyl)-ethyl ester;

10 Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-(4,4-dimethyl-cyclohexyl)-ethyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-(4,8-dimethyl-spiro[2.5]oct-6-yl)-ethyl ester;

15 Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-2-(4,8-dimethyl-spiro[2.5]oct-6-yl)-ethyl ester;

20 Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-(4,8-dimethyl-spiro[2.5]oct-6-yl)-ethyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-(2,2-dimethyl-cyclohexyl)-ethyl ester;

25 Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-2-(2,2-dimethyl-cyclohexyl)-ethyl ester;

Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-(2,2-dimethyl-cyclohexyl)-ethyl ester;

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Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-(3,3,5,5-tetramethyl-cyclohexyl)-ethyl ester;

5 Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-2-(3,3,5,5-tetramethyl-cyclohexyl)-ethyl ester;

Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-(3,3,5,5-tetramethyl-cyclohexyl)-ethyl ester;

10 Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-indan-1-yl-ethyl ester;

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-2-indan-1-yl-ethyl ester;

15 Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-indan-1-yl-ethyl ester;

20 Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-indan-2-yl-ethyl ester;

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-2-indan-2-yl-ethyl ester;

25 Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-indan-2-yl-ethyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3-methanesulfonyl-propyl ester;

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Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-3-methanesulfonyl-propyl ester;

5 Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-3-methanesulfonyl-propyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-naphthalen-1-yl-ethyl ester;

10 Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-2-naphthalen-1-yl-ethyl ester;

Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-naphthalen-1-yl-ethyl ester;

15 Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-biphenyl-4-yl-ethyl ester;

20 Morpholine-4-carboxylic acid 2-biphenyl-4-yl-1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-ethyl ester;

Morpholine-4-carboxylic acid 2-biphenyl-4-yl-1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-ethyl ester;

25 Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-(4-methoxy-phenyl)-ethyl ester;

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-2-(4-methoxy-phenyl)-ethyl ester;

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Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-(4-methoxy-phenyl)-ethyl ester;

5 Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3-methylsulfanyl-propyl ester;

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-3-methylsulfanyl-propyl ester;

10 Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-3-methylsulfanyl-propyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-methyl-butyl ester;

15 Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-2-methyl-butyl ester;

20 Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-methyl-butyl ester;

3,4-Dihydro-1H-isoquinoline-2-carboxylic acid [(benzyloxymethyl-cyano-methyl)-carbamoyl]-(2,2-dimethyl-cyclopropyl)-methyl ester;

25 3,4-Dihydro-1H-isoquinoline-2-carboxylic acid [(benzyloxymethyl-cyano-methyl)-carbamoyl]-cyclopropyl-methyl ester;

3,4-Dihydro-1H-isoquinoline-2-carboxylic acid [(benzyloxymethyl-cyano-methyl)-carbamoyl]-methyl ester;

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3,4-Dihydro-1H-isoquinoline-2-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-
carbamoyl]-ethyl ester;

3,4-Dihydro-1H-isoquinoline-2-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-
5 carbamoyl]-propyl ester;

3,4-Dihydro-1H-isoquinoline-2-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-
carbamoyl]-butyl ester;

10 Carbonic acid (S)-1-(((R)-benzyloxymethyl-cyano-methyl)-carbamoyl]-3-methyl-butyl
ester tert-butyl ester; and

tert-Butyl-carbamic acid (S)-1-(((R)-benzyloxymethyl-cyano-methyl)-carbamoyl]-3-
methyl-butyl ester;

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and the pharmaceutically acceptable derivatives thereof.

16. A compound according to claim 1, selected from:

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(3,4-Dichloro-phenyl)-carbamic acid 1-[(cyano-methyl-methyl)-carbamoyl]-3,3-dimethyl-
butyl ester;

3-(2-Benzylcarbamoyloxy-4-methyl-pentanoylamino)-3-cyano-azepane-1-carboxylic acid
2-methoxy-ethyl ester;

3-(2-Benzylcarbamoyloxy-4-methyl-pentanoylamino)-3-cyano-pyrrolidine-1-carboxylic
acid ethyl ester;

3-(2-Benzylcarbamoyloxy-4-methyl-pentanoylamino)-3-cyano-pyrrolidine-1-carboxylic
acid benzyl ester;

3,4-Dihydro-1H-isoquinoline-2-carboxylic acid [(benzyloxymethyl-cyano-methyl)-
carbamoyl]-(2,2-dimethyl-cyclopropyl)-methyl ester;

3,4-Dihydro-1H-isoquinoline-2-carboxylic acid [(benzyloxymethyl-cyano-methyl)-
carbamoyl]-cyclopropyl-methyl ester;

3,4-Dihydro-1H-isoquinoline-2-carboxylic acid [(benzyloxymethyl-cyano-methyl)-
carbamoyl]-methyl ester;

3,4-Dihydro-1H-isoquinoline-2-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-
carbamoyl]-3-methyl-butyl ester;

3,4-Dihydro-1H-isoquinoline-2-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-
carbamoyl]-2-cyclopropyl-ethyl ester;

3,4-Dihydro-1H-isoquinoline-2-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-
carbamoyl]-cyclohexyl ester;

3,4-Dihydro-1H-isoquinoline-2-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-
carbamoyl]-3,3-difluoro-propyl ester;

3,4-Dihydro-1H-isoquinoline-2-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-
carbamoyl]-3,3,3-trifluoro-propyl ester;

3,4-Dihydro-1H-isoquinoline-2-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-
carbamoyl]-ethyl ester;

3,4-Dihydro-1H-isoquinoline-2-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-
carbamoyl]-propyl ester;

3,4-Dihydro-1H-isoquinoline-2-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-butyl ester;

3,4-Dihydro-1H-isoquinoline-2-carboxylic acid 1-{{(2-chloro-benzyloxymethyl)-cyano-methyl]-carbamoyl}-3-methyl-butyl ester;

3,4-Dihydro-1H-isoquinoline-2-carboxylic acid 1-{{(3-carboxy-benzyloxymethyl)-cyano-methyl]-carbamoyl}-3-methyl-butyl ester;

3,4-Dihydro-1H-isoquinoline-2-carboxylic acid 1-{{cyano-(4-methoxy-benzyloxymethyl)-methyl]-carbamoyl}-3-methyl-butyl ester;

3-{2-[(2-Benzylcarbamoyloxy-4-methyl-pentanoyl)-methyl-amino]-2-cyano-ethoxymethyl}-benzoic acid;

3-Methyl-benzofuran-2-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3-methyl-butyl ester;

4-(2-Benzylcarbamoyloxy-4-methyl-pentanoylamino)-4-cyano-1-methyl-pyrrolidine-2-carboxylic acid methyl ester;

4-(2-Benzylcarbamoyloxy-4-methyl-pentanoylamino)-4-cyano-azepane-1-carboxylic acid isopropyl ester;

4-(2-Benzylcarbamoyloxy-4-methyl-pentanoylamino)-4-cyano-piperidine-1-carboxylic acid ethyl ester;

4-(2-Benzylcarbamoyloxy-4-methyl-pentanoylamino)-4-cyano-piperidine-1-carboxylic acid cyclohexylmethyl ester;

4-(2-Benzylcarbamoyloxy-4-methyl-pentanoylamino)-4-cyano-piperidine-1-carboxylic

acid benzyl ester;

4-(4-{1-[(Benzyl-cyano-methyl)-carbamoyl]-propoxycarbonyl}-thiazol-2-ylamino)-piperidine-1-carboxylic acid ethyl ester;

4-[(4-Benzyl-piperazine-1-carbonyl)-amino]-benzoic acid 1-{{cyano-(4-methyl-benzyl)-methyl}-carbamoyl}-cyclopentyl ester;

4-Ethoxycarbonylamino-benzoic acid 4-(4-cyano-tetrahydro-pyran-4-ylcarbamoyl)-tetrahydro-pyran-4-yl ester;

4-Phenyl-piperazine-1-carboxylic acid [(cyano-dimethyl-methyl)-carbamoyl]-phenyl-methyl ester;

5-(2-Morpholin-4-yl-ethoxy)-benzofuran-2-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3-methyl-butyl ester;

5-Pyridin-4-yl-thiophene-2-carboxylic acid (1-cyano-3-methanesulfonyl-propylcarbamoyl)-pyridin-3-yl-methyl ester;

5-Pyridin-4-yl-thiophene-2-carboxylic acid (1-cyano-3-methanesulfonyl-propylcarbamoyl)-pyridin-3-yl-methyl ester;

Benzo[b]thiophene-2-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3-methyl-butyl ester;

Benzofuran-2-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3-methyl-butyl ester;

Benzyl-carbamic acid 1-(1-benzyl-3-cyano-2-oxo-pyrrolidin-3-ylcarbamoyl)-3-methyl-butyl ester;

Benzyl-carbamic acid 1-(1-benzyl-3-cyano-5-oxo-pyrrolidin-3-ylcarbamoyle)-3-methyl-butyl ester;

Benzyl-carbamic acid 1-(1-benzyl-4-cyano-2-oxo-azepan-4-ylcarbamoyle)-3-methyl-butyl ester;

Benzyl-carbamic acid 1-(1-benzyl-4-cyano-2-oxo-piperidin-4-ylcarbamoyle)-3-methyl-butyl ester;

Benzyl-carbamic acid 1-(1-benzyl-4-cyano-7-oxo-azepan-4-ylcarbamoyle)-3-methyl-butyl ester;

Benzyl-carbamic acid 1-(1-benzyl-4-cyano-azepan-4-ylcarbamoyle)-3-methyl-butyl ester;

Benzyl-carbamic acid 1-(1-benzylcarbamoyle-3-cyano-pyrrolidin-3-ylcarbamoyle)-3-methyl-butyl ester;

Benzyl-carbamic acid 1-(1-benzylcarbamoyle-4-cyano-azepan-4-ylcarbamoyle)-3-methyl-butyl ester;

Benzyl-carbamic acid 1-(1-benzylcarbamoyle-4-cyano-piperidin-4-ylcarbamoyle)-3-methyl-butyl ester;

Benzyl-carbamic acid 1-(1-cyano-3-methyl-butylcarbamoyle)-2-cyclopropyl-ethyl ester;

Benzyl-carbamic acid 1-(1-cyano-3-methyl-butylcarbamoyle)-3-methyl-butyl ester;

Benzyl-carbamic acid 1-(1-cyano-3-methyl-butylcarbamoyle)-cyclohexyl ester;

Benzyl-carbamic acid 1-(1-cyano-3-phenyl-propylcarbamoyle)-2-cyclopropyl-ethyl ester;

Benzyl-carbamic acid 1-(1-cyano-3-phenyl-propylcarbamoyl)-3-methyl-butyl ester;

Benzyl-carbamic acid 1-(1-cyano-3-phenyl-propylcarbamoyl)-cyclohexyl ester;

Benzyl-carbamic acid 1-(1-cyano-cyclopropylcarbamoyl)-2-cyclopropyl-ethyl ester;

Benzyl-carbamic acid 1-(1-cyano-cyclopropylcarbamoyl)-3-methyl-butyl ester;

Benzyl-carbamic acid 1-(1-cyano-cyclopropylcarbamoyl)-cyclohexyl ester;

Benzyl-carbamic acid 1-(2-benzyl-4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-3-methyl-butyl ester;

Benzyl-carbamic acid 1-(2-benzyloxymethyl-4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-3-methyl-butyl ester;

Benzyl-carbamic acid 1-(3-cyano-1-ethyl-2-oxo-azepan-3-ylcarbamoyl)-3-methyl-butyl ester;

Benzyl-carbamic acid 1-(3-cyano-1-ethyl-7-oxo-azepan-3-ylcarbamoyl)-3-methyl-butyl ester;

Benzyl-carbamic acid 1-(3-cyano-1-ethyl-azepan-3-ylcarbamoyl)-3-methyl-butyl ester;

Benzyl-carbamic acid 1-(3-cyano-1-ethylcarbamoyl-pyrrolidin-3-ylcarbamoyl)-3-methyl-butyl ester;

Benzyl-carbamic acid 1-(3-cyano-1-isobutyryl-pyrrolidin-3-ylcarbamoyl)-3-methyl-butyl ester;

Benzyl-carbamic acid 1-(3-cyano-1-methyl-5-methylcarbamoyl-pyrrolidin-3-ylcarbamoyl)-3-methyl-butyl ester;

Benzyl-carbamic acid 1-(3-cyano-1-phenylacetyl-azepan-3-ylcarbamoyl)-3-methyl-butyl ester;

Benzyl-carbamic acid 1-(3-cyano-1-phenylcarbamoyl-pyrrolidin-3-ylcarbamoyl)-3-methyl-butyl ester;

Benzyl-carbamic acid 1-(3-cyano-5-hydroxymethyl-1-methyl-pyrrolidin-3-ylcarbamoyl)-3-methyl-butyl ester;

Benzyl-carbamic acid 1-(4-cyano-1,2,2,6,6-pentamethyl-piperidin-4-ylcarbamoyl)-3-methyl-butyl ester;

Benzyl-carbamic acid 1-(4-cyano-1,2,2-trimethyl-piperidin-4-ylcarbamoyl)-3-methyl-butyl ester;

Benzyl-carbamic acid 1-(4-cyano-1-cyclohexanecarbonyl-piperidin-4-ylcarbamoyl)-3-methyl-butyl ester;

Benzyl-carbamic acid 1-(4-cyano-1-methyl-2,6-dioxo-piperidin-4-ylcarbamoyl)-3-methyl-butyl ester;

Benzyl-carbamic acid 1-(4-cyano-1-methyl-2-methylcarbamoyl-piperidin-4-ylcarbamoyl)-3-methyl-butyl ester;

Benzyl-carbamic acid 1-(4-cyano-2-hydroxymethyl-1-methyl-piperidin-4-ylcarbamoyl)-3-methyl-butyl ester;

Benzyl-carbamic acid 1-(5-benzyloxymethyl-3-cyano-1-methyl-pyrrolidin-3-ylcarbamoyl)-

3-methyl-butyl ester;

Benzyl-carbamic acid 1-(cyanomethyl-carbamoyl)-2-cyclopropyl-ethyl ester;

Benzyl-carbamic acid 1-(cyanomethyl-carbamoyl)-3-methyl-butyl ester;

Benzyl-carbamic acid 1-(cyanomethyl-carbamoyl)-cyclohexyl ester;

Benzyl-carbamic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-cyclopropyl-ethyl ester;

Benzyl-carbamic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3-methyl-butyl ester;

Benzyl-carbamic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-cyclohexyl ester;

Benzyl-carbamic acid 1-[(benzyloxymethyl-cyano-methyl)-methyl-carbamoyl]-3-methyl-butyl ester;

Benzyl-carbamic acid 1-[(benzyloxymethyl-cyano-methyl)-methyl-carbamoyl]-2-cyclopropyl-ethyl ester;

Benzyl-carbamic acid 1-[(benzyloxymethyl-cyano-methyl)-methyl-carbamoyl]-cyclohexyl ester;

Benzyl-carbamic acid 1-[(benzyloxymethyl-cyano-methyl-methyl)-carbamoyl]-3-methyl-butyl ester;

Benzyl-carbamic acid 1-[(benzyloxymethyl-cyano-methyl-methyl)-carbamoyl]-2-cyclopropyl-ethyl ester;

Benzyl-carbamic acid 1-[(benzyloxymethyl-cyano-methyl-methyl)-carbamoyl]-cyclohexyl ester;

Benzyl-carbamic acid 1-[3-cyano-1-(2-methoxy-ethylcarbamoyl)-azepan-3-ylcarbamoyl]-3-methyl-butyl ester;

Benzyl-carbamic acid 1-[3-cyano-1-(2-pyridin-4-yl-acetyl)-pyrrolidin-3-ylcarbamoyl]-3-methyl-butyl ester;

Benzyl-carbamic acid 1-[4-cyano-1-(3-morpholin-4-yl-propionyl)-azepan-4-ylcarbamoyl]-3-methyl-butyl ester;

Benzyl-carbamic acid 1-[4-cyano-1-(4-methyl-piperazine-1-carbonyl)-piperidin-4-ylcarbamoyl]-3-methyl-butyl ester;

Benzyl-carbamic acid 1-[4-cyano-1-(piperidine-1-carbonyl)-piperidin-4-ylcarbamoyl]-3-methyl-butyl ester;

Benzyl-carbamic acid 1-[4-cyano-1-(tetrahydro-pyran-4-carbonyl)-piperidin-4-ylcarbamoyl]-3-methyl-butyl ester;

Benzyl-carbamic acid 1-[[2-chloro-benzyloxymethyl)-cyano-methyl]-carbamoyl]-2-cyclopropyl-ethyl ester;

Benzyl-carbamic acid 1-[[cyano-(4-methoxy-benzyloxymethyl)-methyl]-carbamoyl]-2-cyclopropyl-ethyl ester;

Carbonic acid (S)-1-(((R)-benzyloxymethyl-cyano-methyl)-carbamoyl]-3-methyl-butyl ester tert-butyl ester;

Carbonic acid benzyl ester 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3-methyl-

butyl ester;

Carbonic acid benzyl ester 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-cyclopropyl-ethyl ester;

Carbonic acid benzyl ester 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-cyclohexyl ester;

Naphthalen-2-yl-carbamic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-cyclohexyl ester;

Naphthalen-2-yl-carbamic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3-methyl-butyl ester;

Naphthalen-2-yl-carbamic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-cyclopropyl-ethyl ester;

Naphthalen-2-yl-carbamic acid 1-[[2-chloro-benzyloxymethyl]-cyano-methyl]-carbamoyl}-cyclohexyl ester;

Naphthalen-2-yl-carbamic acid 1-[[cyano-(4-methoxy-benzyloxymethyl)-methyl]-carbamoyl}-cyclohexyl ester;

Naphthalene-2-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3-methyl-butyl ester;

Naphthalene-2-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-cyclopropyl-ethyl ester;

Naphthalene-2-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-cyclohexyl ester;

Phenyl-carbamic acid 1-(cyanomethyl-carbamoyl)-2-dimethylamino-ethyl ester;

Quinolin-2-yl-carbamic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-methyl-butyl ester; and

tert-Butyl-carbamic acid (S)-1-[(R)-benzyloxymethyl-cyano-methyl)-carbamoyl]-3-methyl-butyl ester;

or a pharmaceutically acceptable derivative thereof.

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17. A compound according to claim 1 selected from:

Morpholine-4-carboxylic acid (3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-cyclohexyl-methyl ester;

Morpholine-4-carboxylic acid (4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-cyclohexyl-methyl ester;

Morpholine-4-carboxylic acid [(benzyloxymethyl-cyano-methyl)-carbamoyl]-cyclohexyl-methyl ester;

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-4,4-dimethyl-pentyl ester;

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-4-methyl-pentyl ester;

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-3,3,4,4-

tetramethyl-pentyl ester;

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-3,3-dimethyl-pentyl ester;

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-3,3,4-trimethyl-pentyl ester;

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-3-cyclohexyl-3-methyl-butyl ester;

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-3-cyclohexyl-propyl ester;

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-3-phenyl-propyl ester;

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-2-cyclohexyl-ethyl ester;

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-2-phenyl-ethyl ester;

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-2-(1-methyl-cyclohexyl)-ethyl ester;

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-3,3-dimethyl-butyl ester;

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-3-methyl-but-3-enyl ester;

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-2-(3,4-dichloro-phenyl)-ethyl ester;

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-2-naphthalen-2-yl-ethyl ester;

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-2-(decahydro-naphthalen-2-yl)-ethyl ester;

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-2-(4,4-dimethyl-cyclohexyl)-ethyl ester;

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-2-(4,8-dimethyl-spiro[2.5]oct-6-yl)-ethyl ester;

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-2-(2,2-dimethyl-cyclohexyl)-ethyl ester;

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-2-(3,3,5,5-tetramethyl-cyclohexyl)-ethyl ester;

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-2-indan-1-yl-ethyl ester;

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-2-indan-2-yl-ethyl ester;

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-3-methanesulfonyl-propyl ester;

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-2-naphthalen-1-yl-ethyl ester;

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-2-(4-methoxyphenyl)-ethyl ester;

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-3-methylsulfanyl-propyl ester;

Morpholine-4-carboxylic acid 1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-2-methyl-butyl ester;

Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-4,4-dimethyl-pentyl ester;

Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-4-methyl-pentyl ester;

Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-3,3,4,4-tetramethyl-pentyl ester;

Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-3,3-dimethyl-pentyl ester;

Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-3,3,4-trimethyl-pentyl ester;

Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-3-cyclohexyl-3-methyl-butyl ester;

Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-3-cyclohexyl-

propyl ester;

Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-3-phenyl-propyl ester;

Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexylethyl ester;

Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-phenylethyl ester;

Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-(1-methylcyclohexyl)-ethyl ester;

Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-3,3-dimethylbutyl ester;

Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-3-methylbut-3-enyl ester;

Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-(3,4-dichlorophenyl)-ethyl ester;

Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-naphthalen-2-yl-ethyl ester;

Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-(decahydronaphthalen-2-yl)-ethyl ester;

Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-(4,4-dimethylcyclohexyl)-ethyl ester;

Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyle)-2-(4,8-dimethyl-spiro[2.5]oct-6-yl)-ethyl ester;

Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyle)-2-(2,2-dimethyl-cyclohexyl)-ethyl ester;

Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyle)-2-(3,3,5,5-tetramethyl-cyclohexyl)-ethyl ester;

Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyle)-2-indan-1-yl-ethyl ester;

Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyle)-2-indan-2-yl-ethyl ester;

Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyle)-3-methanesulfonyl-propyl ester;

Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyle)-2-naphthalen-1-yl-ethyl ester;

Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyle)-2-(4-methoxy-phenyl)-ethyl ester;

Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyle)-3-methylsulfanyl-propyl ester;

Morpholine-4-carboxylic acid 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyle)-2-methyl-butyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3-methyl-butyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-cyclopropyl-ethyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-cyclohexyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-4,4-dimethyl-pentyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-4-methyl-pentyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3,3,4,4-tetramethyl-pentyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3,3-dimethyl-pentyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3,3,4-trimethyl-pentyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3-cyclohexyl-3-methyl-butyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3-cyclohexyl-propyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3-phenyl-

propyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-cyclohexyl-ethyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-phenyl-ethyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-(1-methyl-cyclohexyl)-ethyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3,3-dimethyl-butyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3-methyl-but-3-enyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-(3,4-dichloro-phenyl)-ethyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-naphthalen-2-yl-ethyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-(decahydro-naphthalen-2-yl)-ethyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-(4,4-dimethyl-cyclohexyl)-ethyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-(4,8-dimethyl-spiro[2.5]oct-6-yl)-ethyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-(2,2-dimethyl-cyclohexyl)-ethyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-(3,3,5,5-tetramethyl-cyclohexyl)-ethyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-indan-1-yl-ethyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-indan-2-yl-ethyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3-methanesulfonyl-propyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-naphthalen-1-yl-ethyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-biphenyl-4-yl-ethyl ester

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-(4-methoxy-phenyl)-ethyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-3-methylsulfanyl-propyl ester;

Morpholine-4-carboxylic acid 1-[(benzyloxymethyl-cyano-methyl)-carbamoyl]-2-methyl-butyl ester;

Morpholine-4-carboxylic acid 2-biphenyl-4-yl-1-(3-cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-ethyl ester; and

Morpholine-4-carboxylic acid 2-biphenyl-4-yl-1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-ethyl ester;

or the pharmaceutically acceptable derivatives thereof.

18. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to claim 1, 11 or 15.
- 5
19. A method of treating a cysteine protease mediated disease comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound according to claim 1, 11 or 15, or a pharmaceutically acceptable derivative thereof.
- 10
20. A method according to claim 19, wherein the cysteine protease is cathepsin S.
21. A method according to claim 19, wherein the cysteine protease is cathepsin K.
- 15
22. A method according to claim 19, wherein the disease is selected from chronic inflammatory disorders, emphysema, malaria, Chagas' disease, a disease characterized by bone resorption, bone loss or excessive cartilage or bone matrix degradation, autoimmune diseases, Alzheimer's disease, atherosclerosis, endometriosis, asthma and airway inflammatory diseases.
- 20
23. A method according to claim 22, wherein said disease characterized by bone resorption, bone loss or excessive cartilage or bone matrix degradation is selected from osteoporosis, Paget's disease, Gaucher disease, gingivitis, periodontitis, osteoarthritis and rheumatoid arthritis.
- 25

24. The method according to claim 22 wherein the autoimmune disease is rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, ulcerative colitis, multiple sclerosis, Guillain-Barre syndrome, psoriasis, Grave's disease, myasthenia gravis, scleroderma, glomerulonephritis, atopic dermatitis or insulin-dependent diabetes mellitus.

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25. A method according to claim 19, wherein the disease is characterized by excessive elastin degradation.

26. A method according to claim 25, wherein the disease is selected from lymphangiomyomatosis, vascular inflammation, and cardiovascular disease.

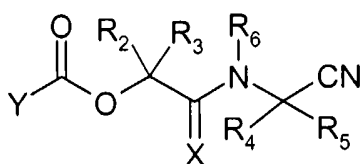
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27. A method according to claim 19, wherein the disease is characterized by increases in bone resorption and demineralization of bone.

28. A method according to claim 27, wherein the disease is selected from cancer and bone metastases of breast or prostate tumors.

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29. A method of making a compound of formula (I):



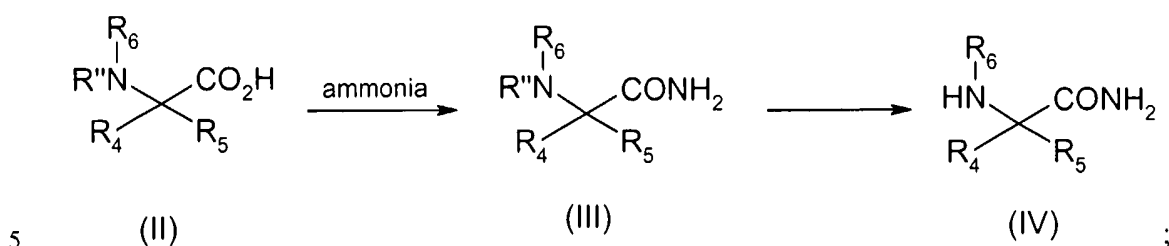
(I)

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wherein X is oxygen, and R₂, R₃, R₄, R₅, R₆ and Y are as defined in claim 1, said method comprising steps (a), (b1) and (c), or comprising steps (a), (b2) and (c):

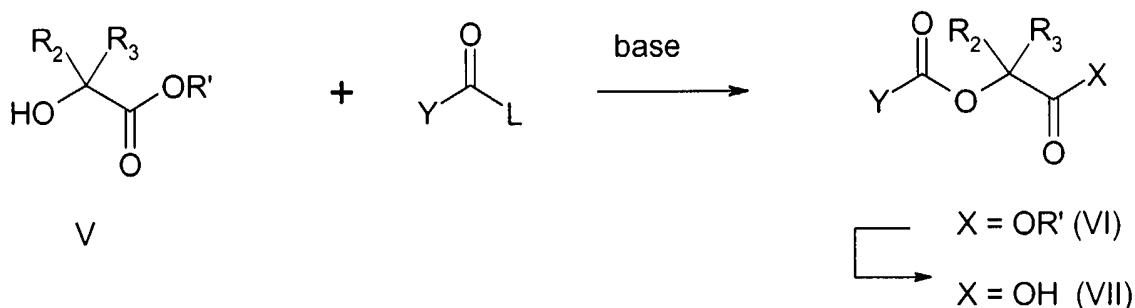
25 a) reacting a protected amino acid compound of formula (II), wherein R'' is a protecting group, with ammonia under coupling conditions to provide an amide

compound of formula (III), followed by deprotection to provide the amino acid amide compound of formula (IV):



b1) reacting a hydroxy ester (V), wherein R' is a protecting group, with an activated acid compound YC(O)L wherein Y is R₁, R₁O-, R₁S(O)_m- or (R₁)₃C-, wherein R₁ is as defined in claim 1 and L is a leaving group, in the presence of a suitable base to provide the compound of formula (VI), followed by hydrolysis to provide a carboxylic acid of formula (VII):

10

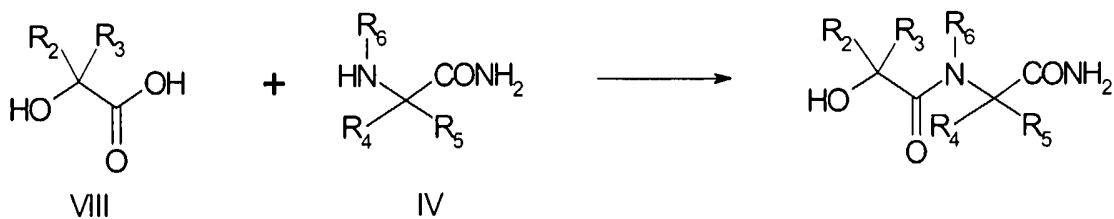


15 or

b2) reacting the hydroxy ester (V) above with a chloroformate to provide a mixed anhydride, followed by reacting the mixed anhydride with an amine compound (R₁)₂NH to provide a compound of formula (VI) wherein Y is (R₁)₂N-, followed by hydrolysis of the compound of formula (VI) to provide a carboxylic acid of formula (VII):

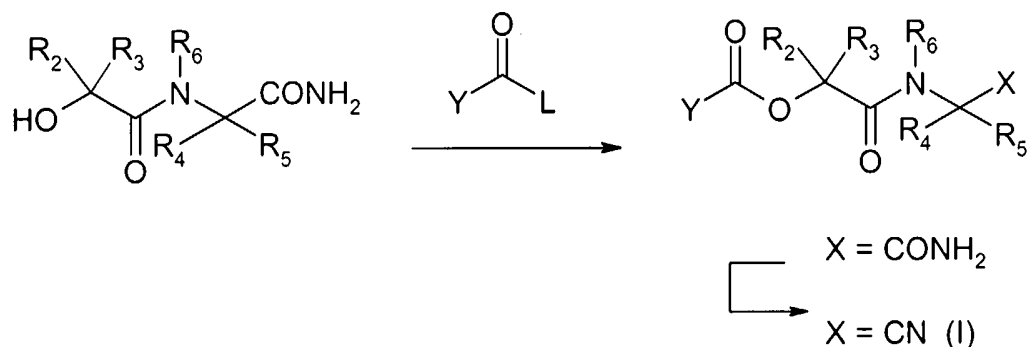
20

a) reacting a hydroxy acid (VIII) with an amino acid amide (IV) under suitable coupling conditions:



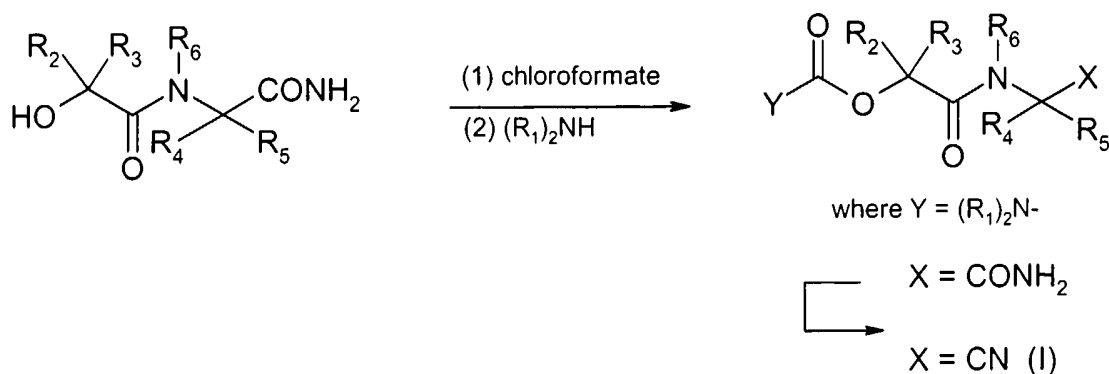
5 b1) reacting the product of step (a) with an activated acid compound $\text{YC}(\text{O})\text{L}$ wherein Y is R_1 , $\text{R}_1\text{O}-$, $\text{R}_1\text{S}(\text{O})_m-$ or $(\text{R}_1)_3\text{C}-$, wherein R_1 is as defined in claim 1 and L is a leaving group, in the presence of a suitable base, followed by dehydrating the resulting amide compound to provide a nitrile of formula (I):

10

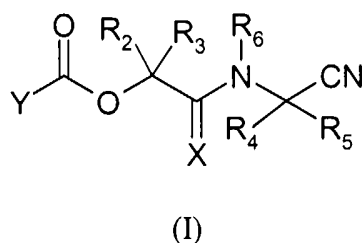


or

15 b2) reacting the product of step (a) with a chloroformate to provide a mixed anhydride, followed by reacting the mixed anhydride with an amine compound $(\text{R}_1)_2\text{NH}$, followed by dehydrating the resulting amide compound to provide a nitrile of formula (I):



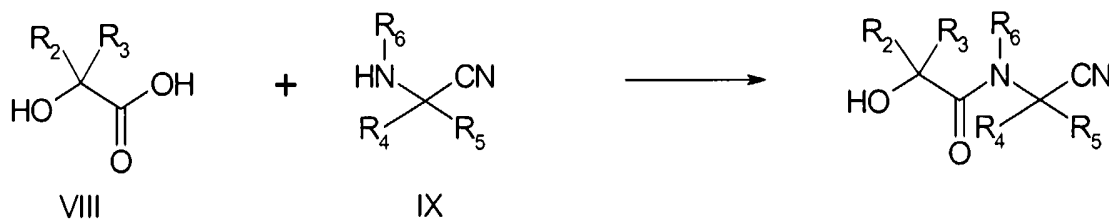
31. A method of making a compound of formula (I):



5

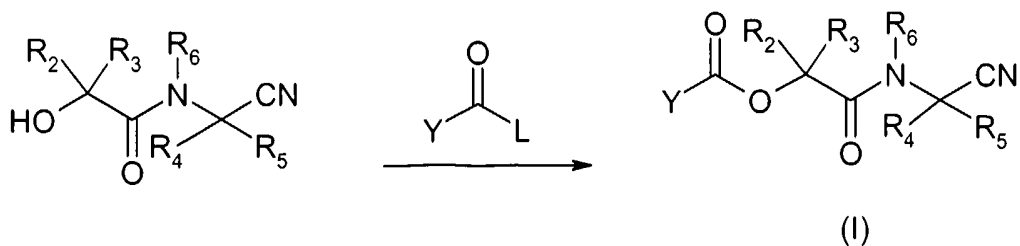
wherein X is oxygen and R_2 , R_3 , R_4 , R_5 , R_6 and Y are as defined in claim 1, said method comprising steps (a) and (b1) or steps (a) and (b2):

a) reacting a hydroxy acid (VIII) with an amino nitrile (IX) under coupling conditions:



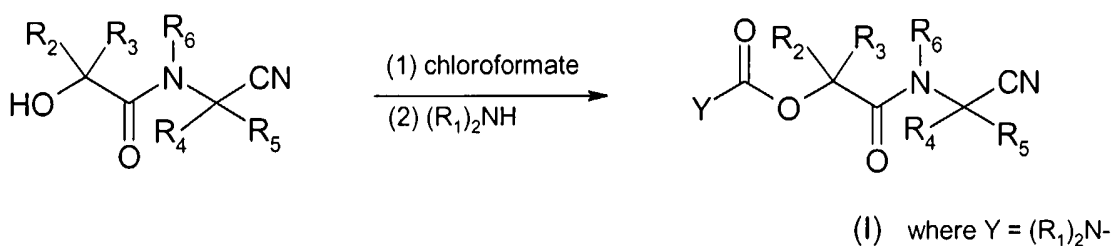
10

b1) reacting the product of step (a) with an activated acid compound $YC(O)L$ wherein Y is R_1 , R_1O- , $R_1S(O)_m-$ or $(R_1)_3C-$, wherein R_1 is as defined in claim 1 and L is a leaving group, in the presence of a suitable base, to provide a nitrile of formula (I):



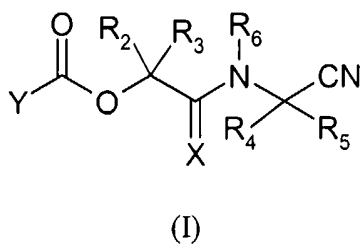
or

- b2) reacting the product of step (a) with a chloroformate to provide a mixed anhydride,
 5 followed by reacting the mixed anhydride with an amine compound $(R_1)_2NH$,
 to provide a nitrile of formula (I):



10

32. A method of making a compound of formula (I):



15

- wherein X is oxygen, and R_2 , R_3 , R_4 , R_5 , R_6 and Y are as defined in claim 1,
 said method comprising steps (a1) and (b), or comprising steps (a2) and (b):

