(54) Title: NICOTINYL ASPARTYL KETONES AS INHIBITORS OF CASPASE-3

(57) Abstract: Caspase-3 inhibiting compounds of formula (I): as well as pharmaceutical compositions and methods of treatment are disclosed. The compounds are useful for treating caspase-3 mediated diseases and conditions, among which are cardiac or cerebral ischemia or reperfusion injury, type I diabetes, immune deficiency syndrome, including AIDS, cerebral and spinal cord trauma injury, organ damage during transplantation, alopecia, aging, Parkinson's disease, Alzheimer's disease, Down's syndrome, spinal muscular atrophy, multiple sclerosis and neurodegenerative disorders.
TITLE OF THE INVENTION
NICOTINYL ASPARTYL KETONES AS INHIBITORS OF CASPASE-3

BACKGROUND OF THE INVENTION

Apoptotic cell suicide is a fundamentally important biological process that is required to maintain the integrity and homeostasis of multicellular organisms. Inappropriate apoptosis, however, underlies the etiology of many of the most intractable of human diseases. In only the last few years, many of the molecules that participate in a conserved biochemical pathway that mediates the highly ordered process of apoptotic cell suicide have been identified. At the heart of this pathway are a family of cysteine proteases, the 'caspases', that are related to mammalian interleukin-18 converting enzyme (ICE/caspase-1) and to CED-3, the product of a gene that is necessary for apoptotic suicide in the nematode C. elegans (Nicholson et al., 1997, Trends Biochem Sci 22:299-306). The role of these proteases in cell suicide is to disable critical homeostatic and repair processes as well as to cleave key structural components, resulting in the systematic and orderly disassembly of the dying cell.

The central importance of caspases in these processes has been demonstrated with both macromolecular and peptide-based inhibitors (which prevent apoptosis from occurring in vitro and in vivo) as well as by genetic approaches. Inhibition of apoptosis via attenuation of caspase activity should therefore be useful in the treatment of human diseases where inappropriate apoptosis is prominent or contributes to disease pathogenesis. Caspase inhibitors would thus be useful for the treatment of human diseases including, but not limited to, acute disorders such as cardiac and cerebral ischemia/reperfusion injury (e.g. stroke), spinal cord injury and organ damage during transplantation, as well as chronic disorders such as neurodegenerative diseases (e.g. Alzheimer's, polyglutamine-repeat disorders, Down's, spinal muscular atrophy, multiple sclerosis), immunodeficiency (e.g. HIV), diabetes, alopecia and aging.

Ten caspases have so far been identified in human cells. Each is synthesized as a catalytically dormant proenzyme containing an amino-terminal prodomain followed by the large and small subunits of the heterodimeric active enzyme. The subunits are excised from the proenzyme by cleavage at Asp-X junctions (Nicholson et al., 1997, Trends Biochem Sci 22:299-306). The strict requirement by caspases for Asp in the P1 position of substrates is consistent with a
mechanism whereby proenzyme maturation can be either autocatalytic or performed by other caspases. The three dimensional crystal structures of mature caspase-1 and -3 show that the large subunit contains the principle components of the catalytic machinery, including the active site Cys residue which is harbored within the conserved pentapeptide motif, QACxG,1 and residues that stabilize the oxyanion of the tetrahedral transition state (Wilson et al., 1994, Nature 370:270-75; Walker et al., 1994, Cell 78:342-52; Rotonda et al., 1996, Nat Struct Biol 3:619-25). Both subunits contribute residues which stabilize the P1 Asp of substrates while the small subunit appears to contain most of the determinants that dictate substrate specificity and, in particular, those which form the specificity-determining S4 subsite. One distinctive feature of these proteases is the absolute requirement for an aspartic acid residue in the substrate P1 position. The carboxylate side chain of the substrate P1 Asp is tethered by four residues in caspase-1 (Arg179, Gln238 from p20 and Arg341, Ser347 from p10) that are absolutely conserved in all caspase family members. Catalysis involves a typical cysteine protease mechanism involving a catalytic dyad, composed of His237 and Cys285 (contained within an absolutely conserved QACxG pentapeptide) and an ‘oxyanion hole’ involving Gly238 and Cys285. Inhibitors bind, however, in an unexpected non-transition state configuration (which raises important considerations for inhibitor design) with the oxyanion of the thiohemiacetal being stabilized by the active site His237.

Members of the caspase family can be divided into three functional subgroups based on their substrate specificities which have been defined by a positional-scanning combinatorial substrate approach. The principle effectors of apoptosis (group II caspases, which include caspases-2, -3 and -7 as well as C. elegans CED-3) have specificity for [P4]ExD[P1], a motif found at the cleavage site of most proteins known to be cleaved during apoptosis. On the other hand, the specificity of group III caspases (caspases-6, -8, -9 and -10, as well as CTL-derived granzyme B) is [P4](I,V,L)ExD[P1] which corresponds to the activation site at the junction between the large and small subunits of other caspase proenzymes including group II (effector) family members. This and other evidence indicates that group III caspases function as upstream activators of group II caspases in a proteolytic cascade that amplifies the death signal. The role of group I caspases (caspases-1, -4 and -5) appears to be to mediate cytokine maturation and their role in apoptosis, if any, has not been substantiated.
A tetrapeptide corresponding to the substrate P4-P1 residues is sufficient for specific recognition by caspases and as a consequence has formed the basis for inhibitor design. In addition to the requirement for a P1 Asp, the P4 residue in particular appears to be most important for substrate recognition and specificity. Caspase-1, for example, prefers a hydrophobic residue such as Tyr in P4 (which corresponds to its YVHD cleavage site within proIL-1β) whereas caspase-3 (and other group II enzymes) has a preference for an anionic Asp residue (which corresponds to the DXXD cleavage sites within most polypeptides that are cleaved by these enzymes during apoptosis). Peptide aldehydes, nitriles and ketones are potent reversible inhibitors of these proteases while compounds that form thiomethylketone adducts with the active site cysteine (e.g. peptide (acyloxy)methylketones) are potent irreversible inhibitors. For example, the tetrapeptide aldehyde Ac-YVAD-CHO (which was designed to mimic the YVHD caspase-1 recognition sequence within proIL-1β) is a potent inhibitor of caspase-1 (Ki < 1 nM) but a poor inhibitor of caspase-3 (Ki = 12 µM) (Thornberry et al., 1992, Nature 356:768-74). In contrast, the Ac-DEVD-CHO tetrapeptide aldehyde (which was designed to mimic the caspase-3 recognition site) is a very potent inhibitor of caspase-3 (Ki < 1 nM) although it is also a weaker but reasonable inhibitor of caspase-1, presumably owing to promiscuity in the S4 subsite of this enzyme (Nicholson et al., 1995, Nature 376:37-43).

Several features plague these peptide-derived inhibitors as a platform for drug design. In addition to their metabolic instability and membrane impermeability, the slow-binding time-dependent inhibition of activity (e.g. kon caspase-1:Ac-YVAD-CHO = 3.8 x 105 M-1s-1; kon caspase-3:Ac-DEVD-CHO = 1.3 x 105 M-1s-1) precludes them from the rapid inhibition that may be necessary to abolish enzymatic activity in vivo. The present patent application describes the resolution of this issue with the discovery of several novel gamma-ketoacids that make highly suitable caspase inhibitors.
SUMMARY OF THE INVENTION

The present invention relates to compounds represented by formula I:

![Chemical structure diagram]

as well as pharmaceutically acceptable salts, hydrates and esters thereof, wherein:

- $R_1$ represents H, NH$_2$, NHC$_1$-6alkyl, NHC(O)C$_1$-6alkyl, NHC(O)OC$_1$-6alkyl, or NHC(O)Aryl, said alkyl and the alkyl and aryl portions of which are optionally substituted with 1-3 members selected from the group consisting of: CO$_2$H, CO$_2$C$_1$-6alkyl, aryl, NH$_2$, NHC$_1$-3alkyl, NH-Aryl, N(C$_1$-3alkyl)$_2$ and Hetcy;

- $R_2$ is selected from the group consisting of:
  - (a) H, OH, halo, NH$_2$, CN, C$_1$-6alkyl, C$_2$-6alkenyl, C$_2$-6alkynyl, CO$_2$H, Aryl and Hetcy;
  - (b) OC$_1$-6alkyl and OC$_3$-6alkenyl;
  - (c) $\text{S(O)}_y$C$_1$-6alkyl, $\text{S(O)}_y$C$_3$-6alkenyl, $\text{S(O)}_y$Aryl and $\text{S(O)}_y$Hetcy,

- wherein $y$ is 0, 1 or 2;

- (d) NHC$_1$-6alkyl, NH-Aryl and NH-Hetcy;

- (e) C(O)C$_1$-6alkyl, C(O)C$_3$-6alkenyl and C(O)Hetcy;

- (f) C(O)NH$_2$, C(O)NHC$_1$-6alkyl, C(O)N(C$_1$-6alkyl)$_2$, C(O)NH-Aryl and C(O)N(C$_1$-6alkyl)-Aryl;

- (g) NHC(O)C$_1$-6alkyl, NHC(O)C$_3$-6alkenyl, N(C$_1$-6alkyl)C(O)C$_1$-6alkyl, N(C$_1$-6alkyl)C(O)C$_3$-6alkenyl and N(C$_1$-6alkyl)C(O)Aryl;

- (h) S(O)$_2$NH$_2$, S(O)$_2$NHC$_1$-6alkyl, SO$_2$NH-Hetcy, S(O)$_2$NHC$_3$-6alkenyl, S(O)$_2$N(C$_1$-6alkyl)$_2$, S(O)$_2$N(C$_1$-6alkyl)C$_3$-6alkenyl, SO$_2$NH-Aryl, SO$_2$NH-Hetcy, SO$_2$N(C$_1$-6alkyl)Aryl and SO$_2$N(C$_1$-6alkyl)Hetcy;

- (i) NHSO$_2$C$_1$-6alkyl, NHC$_1$-6alkenyl, N(C$_1$-6alkyl)SO$_2$C$_1$-6alkyl and N(C$_1$-6alkyl)SO$_2$C$_3$-6alkenyl,

said C$_1$-6alkyl, C$_2$-6alkenyl, C$_3$-6alkenyl and C$_2$-6alkynyl groups and portions in (a) through (i) above being optionally substituted with 1-6 members
selected from the group consisting of: halo, OH, NH₂, CN, CO₂H, Hetcy, Aryl, CO₂C₁₋₆alkyl, OC₁₋₆alkyl, O-Aryl, CO₂C₃₋₄alkenyl, C(O)NH₂, C(O)NHC₁₋₃alkyl, C(O)N(C₁₋₃alkyl)₂, C(O)NH-Aryl, C(O)N(C₁₋₃alkyl)-Aryl, C(O)C₁₋₃alkyl, C(O)C₃₋₄alkenyl, -S(O)₂C₁₋₃alkyl, -S(O)₂C₃₋₄alkenyl, S(O)y-(C₁₋₃alkyl-aryl), wherein y is as previously defined; OC₁₋₃alkyl-aryl, NH(C₁₋₃alkyl-aryl), N(C₁₋₃alkyl)C(O)C₁₋₃alkyl, N(C₁₋₃alkyl)C(O)C₃₋₄alkenyl, N(C₁₋₃alkyl)C(O)Aryl, N(C₁₋₃alkyl)Hetcy, S(O)₂NH₂, S(O)₂NHC₁₋₃alkyl, S(O)₂NH-Aryl, S(O)₂NHHetcy, S(O)₂N(C₁₋₃alkyl)₂, S(O)₂N(C₁₋₃alkyl)C₃₋₄alkenyl, S(O)₂N(C₁₋₃alkyl)Aryl, S(O)₂N(C₁₋₃alkyl)Hetcy, NHSO₃H, NHSO₂C₁₋₃alkyl, NHSO₂C₃₋₄alkenyl, NHSO₂Aryl, NHSO₂Hetcy, N(C₁₋₃alkyl)SO₃H, N(C₁₋₃alkyl)SO₂C₁₋₃alkyl, N(C₁₋₃alkyl)SO₂C₃₋₄alkenyl, N(C₁₋₃alkyl)SO₂Aryl and N(C₁₋₃alkyl)SO₂Hetcy;

R³ represents H, halo or C₁₋₃alkyl, and

R⁴ is selected from the group consisting of: H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl and Hetcy, said C₁₋₆alkyl, C₂₋₆alkenyl and C₂₋₆alkynyl groups being optionally substituted with 1-6 members selected from the group consisting of: halo, OH, NH₂, NHC₁₋₁₀alkyl, N(C₁₋₁₀alkyl)₂, CN, CO₂H, Hetcy, Aryl, CO₂C₁₋₆alkyl, OC₁₋₆alkyl, O-Aryl, CO₂C₁₋₃alkyl, CO₂C₃₋₄alkenyl, C(O)NH₂, C(O)NH-C₁₋₃alkyl, C(O)N(C₁₋₃alkyl)₂, C(O)NH-Aryl, C(O)N(C₁₋₃alkyl)-Aryl, C(O)C₁₋₃alkyl, C(O)C₃₋₄alkenyl, -S(O)₂C₁₋₃alkyl, -S(O)₂C₃₋₄alkenyl, S(O)y-(C₁₋₃alkyl-aryl), wherein y is as previously defined; OC₁₋₃alkyl-aryl, NH(C₁₋₃alkyl-aryl), N(C₁₋₃alkyl)C(O)C₁₋₃alkyl, N(C₁₋₃alkyl)C(O)C₃₋₄alkenyl, N(C₁₋₃alkyl)C(O)Aryl, N(C₁₋₃alkyl)Hetcy, S(O)₂NH₂, S(O)₂NHC₁₋₃alkyl, S(O)₂NH-Aryl, S(O)₂NHHetcy, S(O)₂N(C₁₋₃alkyl)₂, S(O)₂N(C₁₋₃alkyl)C₃₋₄alkenyl, S(O)₂N(C₁₋₃alkyl)Aryl, S(O)₂N(C₁₋₃alkyl)Hetcy, NHSO₃H, NHSO₂C₁₋₃alkyl, NHSO₂C₃₋₄alkenyl, NHSO₂Aryl, NHSO₂Hetcy, N(C₁₋₃alkyl)SO₃H, N(C₁₋₃alkyl)SO₂C₁₋₃alkyl, N(C₁₋₃alkyl)SO₂C₃₋₄alkenyl, N(C₁₋₃alkyl)SO₂Aryl and N(C₁₋₃alkyl)SO₂Hetcy;

Aryl represents a 6-14 membered aromatic ring system and

Hetcy represents a 5-10 membered ring system, aromatic or non-aromatic, containing at least one heteroatom and optionally containing up to 2 additional heteroatoms, said heteroatoms being selected from O, S(O)y with y as defined above and N,
said Aryl and Hetcy groups and portions thereof being optionally substituted with 1-6 members selected from the group consisting of: -(CH₂)₀.₄-CO₂H, -(CH₂)₀.₃CO₂C₁-₃alkyl, halo, CN, NH₂, phenyl, pyrrolidinyl, NHCH₃, C₁-₆alkyl, SO₂NH₂ and SO₂CH₃.

The invention also encompasses a pharmaceutical composition comprising a compound of formula I in combination with a pharmaceutically acceptable carrier.

The invention also encompasses a method of treating cardiac and cerebral ischemia/reperfusion injury (e.g. stroke), type I diabetes, immune deficiency syndrome (including AIDS), cerebral and spinal cord trauma injury, organ damage during transplantation, alopecia, aging, Parkinson’s disease, Alzheimer’s disease, Down’s syndrome, spinal muscular atrophy, multiple sclerosis and neurodegenerative disorders, comprising administering to a mammalian patient in need of such treatment an effective amount of a compound of formula I.

DETAILED DESCRIPTION OF THE INVENTION

The invention is described using the following definitions unless otherwise specified.

For purposes of this specification alkyl means linear, branched or cyclic structures and combinations thereof, containing one to twenty carbon atoms unless otherwise specified. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, s- and t-butyl, pentyl, hexyl, heptyl, octyl, nonyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, eicosyl, 3,7-dieethyl-2,2-dimethyl- 4-propynonyl, cyclopropyl, cyclopentyl, cycloheptyl, adamantyl, cyclododecylmethyl, 2-ethyl-1-bicyclo[4.4.0]decyl and the like.

Alkylcarbonyl signifies groups having the formula -C(O)-alkyl, wherein alkyl is defined as above.

Alkylsulfonyl signifies groups having the formula -S(O)₂-alkyl, wherein alkyl is defined as above.

Fluoroalkyl means linear, branched or cyclic alkyl groups and combinations thereof, of one to ten carbon atoms, in which one or more hydrogen but no more than six is replaced by fluorine. Examples are -CF₃, -CH₂CH₂F, and -CH₂CF₃ and the like. Haloalkyl means linear, branched or cyclic alkyl groups having up to six halo groups attached.
Alkoxy means alkoxy groups of one to ten carbon atoms of a straight, branched or cyclic configuration. Examples of alkoxy groups include methoxy, ethoxy, propoxy, isopropoxy and the like.

Alkoxy carbonyl signifies groups having the formula -C(O)-alkoxy, wherein alkoxy is defined as above.

Alkylthio means alkylthio groups of one to ten carbon atoms of a straight, branched or cyclic configuration. Examples of alkylthio groups include methylthio, propylthio, isopropylthio, etc. By way of illustration, the propylthio group signifies -SCH₂CH₂CH₃.

Aryl represents a 6-14 membered aromatic ring system, optionally substituted with 1-6 members selected from the group consisting of: -(CH₂)₀₋₆-CO₂H, -(CH₂)₀₋₆CO₂C₁₋₆alkyl, OH, halo, CN, NH₂, phenyl, naphthyl, pyrrolyl, pyridyl, piperidyl, pyrrolidinyl, furanyl, thienyl, NHCH₃, C₁₋₆alkyl, NHSO₃H, SO₂NH₂, and SO₂CH₃. Aryl is, for example, phenyl or naphthyl. When aryl is present in a substituent on alkyl, alkenyl, alkynyl or Hetcy, it is optionally substituted as described above.

The groups -(CH₂)₀₋₆-CO₂H and -(CH₂)₀₋₆CO₂C₁₋₆alkyl refer to carboxylic acids and esters, alkanolic acids and alkyl esters thereof. Thus, these include CO₂H and CO₂C₁₋₆alkyl.

Hetcy as used herein refers to a 5-14 membered ring system that is aromatic, non-aromatic or partially aromatic, and that contains at least one heteroatom. Up to 3 additional heteroatoms selected from O, S(O)₂ and N, with y representing 0, 1 or 2 are included. Hetcy is optionally substituted with 1-6 members selected from the group consisting of: -(CH₂)₀₋₆-CO₂H, -(CH₂)₀₋₆CO₂C₁₋₆alkyl, OH, halo, CN, NH₂, phenyl, naphthyl, pyrrolyl, pyridyl, piperidyl, pyrrolidinyl, furanyl, thienyl, NHCH₃, C₁₋₆alkyl, NHSO₃H, SO₂NH₂, and SO₂CH₃.

Heteroaryl is an aromatic subset of Hetcy, and thus includes, e.g., pyridyl, furyl, thienyl, thiazolyl, isothiazolyl, imidazolyl, benzimidazolyl, pyrazinyl, pyrimidyl, quinolyl, isoquinolyl, benzofuryl, benzothienyl, pyrazolyl, indolyl, purinyl, isoazolyl, oxazolyl and coumarinyl.

Halo includes F, Cl, Br and I.

For purposes of this specification, the following abbreviations have the indicated meanings:

Alloc = allyloxy carbonyl

APCI = atmospheric pressure chemical ionization
BOC = t-butyloxycarbonyl
CBZ = carbobenzoxy
DCC = 1,3-dicyclohexylcarbodiimide
DIBAL = diisobutyl aluminum hydride
5 DIEA = N,N-diisopropylethylamine
DMAP = 4-(dimethylamino)pyridine
EDCI = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
EDTA = ethylenediaminetetraacetic acid, tetraysodium salt

10 hydrate
ESI = electrospray ionization
FAB = fast atom bombardment
FMOC = 9-fluorenylmethoxycarbonyl
HMPA = hexamethylphosphoramide

15 HATU = O-(7-Azabenzotriazol-1-yl)N,N,N',N'-tetramethyluronium hexafluorophosphate
HOBt = 1-hydroxybenzotriazole
HRMS = high resolution mass spectrometry
ICl = iodine monochloride

20 IBCF = isobutyl chloroformate
KHMDM = potassium hexamethyldisilazane
LDA = lithium diisopropylamide
MCPBA = metachloroperbenzoic acid
Ms = methanesulfonyl = mesyl

25 MsO = methanesulfonate = mesylate
NBS = N-bromosuccinimide
NMM = 4-methylmorpholine
PCC = pyridinium chlorochromate
PDC = pyridinium dichromate

30 Ph = phenyl
PPTS = pyridinium p-toluene sulfonate
pTSA = p-toluene sulfonic acid
r.t. = room temperature
rac. = racemic

35 TfO = trifluoromethanesulfonate = triflate
TLC = thin layer chromatography

Alkyl group abbreviations:
Me = methyl
Et = ethyl
n-Pr = normal propyl
i-Pr = isopropyl
n-Bu = normal butyl
i-Bu = isobutyl
s-Bu = secondary butyl
t-Bu = tertiary butyl

An aspect of the invention that is of interest relates to compounds of formula I:

![Chemical Structure](image)

as well as pharmaceutically acceptable salts, hydrates and esters thereof, wherein:

R\(^1\) represents H, NH\(_2\), NHC\(_1\)-alkyl, NHC(O)C\(_1\)-alkyl, NHC(O)OC\(_1\)-alkyl, or NHC(O)Aryl, said alkyl and the alkyl and aryl portions of which are optionally substituted with 1-3 members selected from the group consisting of: CO\(_2\)H, CO\(_2\)C\(_1\)-alkyl, aryl, NH\(_2\), NHC\(_1\)-alkyl, NH-Aryl, N(C\(_1\)-alkyl)\(_2\) and Hetcy;

R\(^2\) is selected from the group consisting of:

(a) H, OH, halo, NH\(_2\), CN, C\(_1\)-alkyl, C\(_2\)-alkenyl, C\(_2\)-alkynyl, CO\(_2\)H, Aryl and Hetcy;
(b) OC\(_1\)-alkyl and OC\(_3\)-alkenyl;
(c) -S(O)\(_y\)C\(_1\)-alkyl, -S(O)\(_y\)C\(_3\)-alkenyl, -S(O)\(_y\)Aryl and S(O)\(_y\)Hetcy,
wherein y is 0, 1 or 2;
(d) NHC\(_1\)-alkyl, NH-Aryl and NH-Hetcy;
(e) C(O)C₁₋₆alkyl, C(O)C₃₋₆alkenyl and C(O)Hetcy;
(f) C(O)NH₂, C(O)NHCH₁₋₆alkyl, C(O)N(C₁₋₆alkyl)₂, C(O)NH-Aryl
and C(O)N(C₁₋₆alkyl)-Aryl;
(g) NHC(O)C₁₋₆alkyl, NHC(O)C₃₋₆alkenyl, N(C₁₋₆alkyl)C(O)C₁₋₆alkyl,
N(C₁₋₆alkyl)C(O)C₃₋₆alkenyl and N(C₁₋₆alkyl)C(O)Aryl;
(h) S(O)₂NH₂, S(O)₂NHC₁₋₆alkyl, SO₂NHHetcy, S(O)₂NHC₃₋₆alkenyl, S(O)₂N(C₁₋₆alkyl)₂, S(O)₂N(C₁₋₆alkyl)C₃₋₆alkenyl, SO₂NH-Aryl,
SO₂NH-Hetcy, SO₂N(C₁₋₆alkyl)Aryl and SO₂N(C₁₋₆alkyl)Hetcy;
(i) NHSO₂C₁₋₆alkyl, NHSO₂C₃₋₆alkenyl, N(C₁₋₆alkyl)SO₂C₁₋₆alkyl
and N(C₁₋₆alkyl)SO₂C₃₋₆alkenyl;

said C₁₋₆alkyl, C₂₋₆alkenyl, C₃₋₆alkenyl and C₂₋₆alkynyl groups
and portions in (a) through (i) above being optionally substituted with 1-6 members
selected from the group consisting of: halo, OH, NH₂, CN, CO₂H, Hetcy, Aryl,
CO₂C₁₋₆alkyl, OC₁₋₆alkyl, O-Aryl, CO₂C₃₋₆alkenyl, C(O)NH₂, C(O)NHC₁₋₆alkyl,
20 C(O)N(C₁₋₆alkyl)₂, C(O)NH-Aryl, C(O)N(C₁₋₆alkyl)-Aryl, C(O)C₁₋₆alkyl,
C(O)C₃₋₆alkenyl -S(O)₂-C₁₋₆alkyl, -S(O)₂C₃₋₆alkenyl, S(O)₂-(C₁₋₆alkyl-aryl), wherein y
is as previously defined; OC₁₋₆alkyl-aryl, NH(C₁₋₆alkyl-aryl), N(C₁₋₆alkyl)C(O)C₁₋₆alkyl,
N(C₁₋₆alkyl)C(O)C₃₋₆alkenyl, N(C₁₋₆alkyl)C(O)Aryl, N(C₁₋₆alkyl)C(O)Hetcy,
S(O)₂NH₂, S(O)₂NHC₁₋₆alkyl, S(O)₂NHC₃₋₆alkenyl,
S(O)₂N(C₁₋₆alkyl)₂, S(O)₂N(C₁₋₆alkyl)C₃₋₆alkenyl, S(O)₂N(C₁₋₆alkyl)Aryl, S(O)₂N(C₁₋₆alkyl)Hetcy,
NH₂SO₂H, NH₂SO₂C₁₋₆alkyl, NH₂SO₂C₃₋₆alkenyl, NH₂SO₂Aryl, NH₂SO₂Hetcy,
N(C₁₋₆alkyl)SO₂H, N(C₁₋₆alkyl)SO₂Aryl and N(C₁₋₆alkyl)SO₂Hetcy;

R³ represents H, halo or C₁₋₃alkyl, and

R⁴ is selected from the group consisting of: H, C₁₋₆alkyl, C₂₋₆alkenyl,
C₂₋₆alkynyl and Hetcy, said C₁₋₆alkyl, C₂₋₆alkenyl and C₂₋₆alkynyl groups being
optionally substituted with 1-6 members selected from the group consisting of: halo,
OH, NH₂, NHC₁₋₆alkyl, N(C₁₋₆alkyl)₂, CN, CO₂H, Hetcy, Aryl, CO₂C₁₋₆alkyl,
OC₁₋₆alkyl, O-Aryl, CO₂C₁₋₆alkyl, CO₂C₃₋₆alkenyl, C(O)NH₂, C(O)NHC₁₋₆alkyl,
C(O)N(C₁₋₆alkyl)₂, C(O)NH-Aryl, C(O)N(C₁₋₆alkyl)-Aryl, C(O)C₁₋₆alkyl, C(O)C₃₋₆alkenyl,
-S(O)₂-C₁₋₆alkyl, -S(O)₂C₃₋₆alkenyl, S(O)₂-(C₁₋₆alkyl-aryl), wherein y
is as previously defined; OC₁₋₆alkyl-aryl, NH(C₁₋₆alkyl-aryl), N(C₁₋₆alkyl)C(O)C₁₋₆alkyl,
N(C₁₋₆alkyl)C(O)C₃₋₆alkenyl, N(C₁₋₆alkyl)C(O)Aryl, N(C₁₋₆alkyl)C(O)Hetcy,
S(O)₂NH₂, S(O)₂NHC₁₋₆alkyl, S(O)₂NHC₃₋₆alkenyl,
S(O)₂N(C₁₋₆alkyl)₂, S(O)₂N(C₁₋₆alkyl)C₃₋₆alkenyl, S(O)₂N(C₁₋₆alkyl)Aryl, S(O)₂N(C₁₋₆alkyl)Hetcy,
NH₂SO₂H, NH₂SO₂C₁₋₆alkyl, NH₂SO₂C₃₋₆alkenyl, NH₂SO₂Aryl, NH₂SO₂Hetcy,
N(C₁₋₆alkyl)SO₂H, N(C₁₋₆alkyl)SO₂Aryl and N(C₁₋₆alkyl)SO₂Hetcy;
3alkyl)C(O)Hetcy, S(O)2NH2, S(O)2NHC1-3alkyl, S(O)2NHC3-4alkenyl, 
S(O)2NHArly, S(O)2NHetcy, S(O)2N(C1-3alkyl)2, S(O)2N(C1-3alkyl)CO3- 
4alkenyl, S(O)2N(C1-3alkyl)Arly, S(O)2N(C1-3alkyl)Hetcy, NSO3H, NSO2C1- 
3alkyl, NSO2C3-4alkenyl, NSO2Arly, NSO2Hetcy, N(C1-3alkyl)SO3H, N(C1- 
3alkyl)SO2C1-3alkyl, N(C1-3alkyl)SO2C3-4alkenyl, N(C1-3alkyl)SO2Arly and 
N(C1-3alkyl)SO2Hetcy;

Aryl represents a 6-14 membered aromatic ring system and 
Hetcy represents a 5-10 membered ring system, aromatic or non- 
aromatic, containing at least one heteroatom and optionally containing up to 2 
additional heteroatoms, said heteroatoms being selected from O, S(O)y with y as 
defined above and N,
said Aryl and Hetcy groups and portions thereof being optionally 
substituted with 1-6 members selected from the group consisting of: -(CH2)0-4- 
CO2H, -(CH2)0-3CO2C1-3alkyl, halo, CN, NH2, phenyl, pyrrolidiny1, NHCH3, C1- 
6alkyl, SO2NH2 and SO2CH3.

A particular aspect of the invention that is of interest relates to a subset 
of compounds of formula I wherein:

R1 represents H, NH2, NHC1-6alkyl, NHC(O)C1-6alkyl, 
NHC(O)OC1-6alkyl or NHC(O)Arly, said alkyl and the alkyl and aryl portions of 
which are optionally substituted with 1-2 members selected from the group consisting 
of: CO2H, CO2C1-6alkyl, aryl, NH2, NHC1-3alkyl, NH-Aryl and N(C1-3alkyl)2. 
Within this subset, all other variables are as originally defined.

Another particular aspect of the invention that is of interest relates to a 
subset of compounds of formula I wherein:

R2 is selected from the group consisting of:
(a) H, OH, halo, NH2, CN, C1-6alkyl, C2-6alkenyl, C2-6alkynyl, 
CO2H, Aryl and Hetcy;
(b) OC1-6alkyl and OC3-6alkenyl;
(c) -S(O)yC1-6alkyl, -S(O)yC3-6alkenyl, -S(O)yAryl and S(O)yHetcy,

wherein y is 0 or 2;
(d) NHC1-6alkyl;
(e) C(O)C1-6alkyl, C(O)C2-6alkenyl and C(O)Hetcy;
(f) C(O)NH2, C(O)NHC1-6alkyl, C(O)N(C1-6alkyl)2, C(O)NH-Aryl 
and C(O)N(C1-6alkyl)-Aryl;
(g) NHC(O)C₆₋₆alkyl, NHC(O)C₃₋₆alkenyl, N(C₁₋₆alkyl)C(O)C₁₋₆alkyl, N(C₁₋₆alkyl)C(O)C₃₋₆alkenyl and N(C₁₋₆alkyl)C(O)Aryl;
(h) S(O)₂NH₂, S(O)₂NHHC₁₋₆alkyl, S(O)₂NH₃₋₆alkenyl, S(O)₂NHHetcy, S(O)₂N(C₁₋₆alkyl)₂ and S(O)₂N(C₁₋₆alkyl)C₃₋₆alkenyl, and
(i) NH₂SO₂C₁₋₆alkyl, NH₂SO₂C₃₋₆alkenyl, N(C₁₋₆alkyl)SO₂C₁₋₆alkyl and N(C₁₋₆alkyl)SO₂C₃₋₆alkenyl;
said C₁₋₆alkyl, C₂₋₆alkenyl, C₃₋₆alkenyl and C₂₋₆alkynyl groups and
the alkyl, alkenyl and alkynyl portions in (a) through (i) above being optionally
substituted with 1-6 members selected from the group consisting of: halo, OH, NH₂, CN, CO₂H, Hetcy, Aryl, CO₂C₁₋₆alkyl, OC₁₋₆alkyl, CO₂C₁₋₃alkyl, CO₂C₃₋₄alkenyl, C(O)NH₂, C(O)NHHC₁₋₃alkyl, C(O)N(C₁₋₃alkyl)₂, C(O)NH-Aryl, C(O)N(C₁₋₃alkyl)-Aryl, C(O)C₁₋₃alkyl, C(O)C₃₋₄alkenyl, -SO₂yC₁₋₃alkyl, -
S(O)₂yC₃₋₄alkenyl, S(O)y-(C₁₋₃alkyl-aryl), wherein y is as previously defined; OC₁₋₃alkyl-aryl, NH(C₁₋₃alkyl-aryl), NH(C₁₋₃alkyl)C(O)C₁₋₃alkyl, N(C₁₋₃alkyl)C(O)C₃₋₄alkenyl, N(C₁₋₃alkyl)C(O)Aryl, N(C₁₋₃alkyl)C(O)Hetcy, S(O)₂NH₂, S(O)₂NH₃₋₆alkyl, S(O)₂NH₂C₁₋₃alkyl, S(O)₂NH₃₋₆alkenyl, S(O)₂NHC₁₋₃alkyl, S(O)₂NHC₃₋₄alkenyl, S(O)₂NHHetcy, S(O)₂N(C₁₋₃alkyl)₂, S(O)₂N(C₁₋₃alkyl)Aryl, S(O)₂N(C₁₋₃alkyl)Hetcy, NH₂SO₂C₁₋₃alkyl, NH₂SO₂C₃₋₄alkenyl, NH₂SO₂Aryl, NH₂SO₂Hetcy, N(C₁₋₃alkyl)SO₂H, N(C₁₋₃alkyl)SO₂C₁₋₃alkyl, N(C₁₋₃alkyl)SO₂C₃₋₄alkenyl,
N(C₁₋₃alkyl)SO₂Aryl and N(C₁₋₃alkyl)SO₂Hetcy;
Aryl represents a 6-14 membered aromatic ring system and
Hetcy represents a 5-14 membered ring system, aromatic, non-aromatic
or partially aromatic, containing at least one heteroatom and optionally containing up
to 3 additional heteroatoms, said heteroatoms being selected from O, S(O)y with y as
defined above and N,
said Aryl and Hetcy groups and portions thereof being optionally
substituted with 1-6 members selected from the group consisting of: -(CH₂)₀₋₄-
CO₂H, -(CH₂)₀₋₄CO₂C₁₋₃alkyl, halo, CN, NH₂, phenyl, pyrrolidinyl, NHCH₃, C₁₋₆alkyl, SO₂NH₂ and SO₂CH₃. Within this subset, all other variables are as originally
defined.

Another subset of compounds of the present invention that is of interest
relates to compounds of formula I wherein:
R³ represents H or C₁₋₃alkyl. Within this subset, all other variables
are as originally defined.
Another subset of compounds of the present invention that is of interest relates to compounds of formula I wherein:

R^4 is selected from the group consisting of: H, C\textsubscript{1-6}alkyl, C\textsubscript{2-6}alkenyl, C\textsubscript{2-6}alkynyl and Hetcy,

said C\textsubscript{1-6}alkyl, C\textsubscript{2-6}alkenyl and C\textsubscript{2-6}alkynyl groups being optionally substituted with 1-6 members selected from the group consisting of: halo, OH, NH\textsubscript{2}, CN, CO\textsubscript{2}H, Hetcy, N(C\textsubscript{1-10} alkyl)\textsubscript{2}, Aryl, CO\textsubscript{2}C\textsubscript{1-6}alkyl, OC\textsubscript{1-6}alkyl, Oaryl, CO\textsubscript{2}C\textsubscript{1-3}alkyl, CO\textsubscript{2}C\textsubscript{3-4}alkenyl, C(O)NH\textsubscript{2}, C(O)NHC\textsubscript{1-3}alkyl, C(O)N(C\textsubscript{1-3}alkyl)\textsubscript{2}, C(O)NH-Aryl, C(O)N(C\textsubscript{1-3}alkyl)-Aryl, C(O)C\textsubscript{1-3}alkyl, C(O)C\textsubscript{3-4}alkenyl, -SO\textsubscript{2}O\textsubscript{y}C\textsubscript{1-3}alkyl, -SO\textsubscript{2}yC\textsubscript{3-4}alkenyl, S(O)\textsubscript{y}-(C\textsubscript{1-3}alkyl-aryl), wherein y is as previously defined; OC\textsubscript{1-3}alkyl-aryl, NH(C\textsubscript{1-3}alkyl-aryl), N(C\textsubscript{1-3}alkyl)C(O)C\textsubscript{1-3}alkyl, N(C\textsubscript{1-3}alkyl)C(O)C\textsubscript{3-4}alkenyl, N(C\textsubscript{1-3}alkyl)C(O)Aryl, N(C\textsubscript{1-3}alkyl)C(O)Hetcy, S(O)\textsubscript{2}NH\textsubscript{2}, S(O)\textsubscript{2}NHC\textsubscript{1-3}alkyl, S(O)\textsubscript{2}NHC\textsubscript{3-4}alkenyl, S(O)\textsubscript{2}NHAr\textsubscript{y}, S(O)\textsubscript{2}NHetcy, S(O)\textsubscript{2}N(C\textsubscript{1-3}alkyl)\textsubscript{2}, S(O)\textsubscript{2}N(C\textsubscript{1-3}alkyl)C\textsubscript{3-4}alkenyl, S(O)\textsubscript{2}N(C\textsubscript{1-3}alkyl)Aryl, S(O)\textsubscript{2}N(C\textsubscript{1-3}alkyl)Hetcy, NH\textsubscript{SO\textsubscript{3}}H, NH\textsubscript{SO\textsubscript{2}C\textsubscript{1-3}alkyl}, NH\textsubscript{SO\textsubscript{2}C\textsubscript{3-4}alkenyl}, NH\textsubscript{SO\textsubscript{2}Aryl}, NH\textsubscript{SO\textsubscript{2}Hetcy}, N(C\textsubscript{1-3}alkyl)SO\textsubscript{3}H, N(C\textsubscript{1-3}alkyl)SO\textsubscript{2}C\textsubscript{1-3}alkyl, N(C\textsubscript{1-3}alkyl)SO\textsubscript{2}C\textsubscript{3-4}alkenyl, N(C\textsubscript{1-3}alkyl)SO\textsubscript{2}Aryl and N(C\textsubscript{1-3}alkyl)SO\textsubscript{2}Hetcy;

Aryl represents a 6-14 membered aromatic ring system and

Hetcy represents a 5-10 membered ring system, aromatic or non-aromatic, containing at least one heteroatom and optionally containing up to 2 additional heteroatoms, said heteroatoms being selected from O, S(O)\textsubscript{y} with y as defined above and N,

said Aryl and Hetcy groups and portions thereof being optionally substituted with 1-3 members selected from the group consisting of: -(CH\textsubscript{2})\textsubscript{0-4}CO\textsubscript{2}H, -(CH\textsubscript{2})\textsubscript{0-3}CO\textsubscript{2}C\textsubscript{1-3}alkyl, halo, CN, NH\textsubscript{2}, phenyl, pyrrolidinyl, NHCH\textsubscript{3}, C\textsubscript{1-6}alkyl, SO\textsubscript{2}NH\textsubscript{2} and SO\textsubscript{2}CH\textsubscript{3}. Within this subset, all other variables are as originally defined.

A further subset of compounds within the present invention that is of particular interest relates to compounds of formula I wherein:

R\textsuperscript{1} is selected from the group consisting of: H, NH\textsubscript{2}, NHC\textsubscript{1-6}alkyl, NHC(O)C\textsubscript{1-6}alkyl, NH\textsubscript{C}(O)OC\textsubscript{1-6}alkyl and NH\textsubscript{C}(O)Aryl, said alkyl and the alkyl and aryl portions of which are optionally substituted with 1-2 members selected from the group consisting of: CO\textsubscript{2}H and CO\textsubscript{2}C\textsubscript{1-6}alkyl. Within this subset, all other variables are as originally defined.
Another subset of compounds of the present invention that is of particular interest relates to a subset of compounds of formula I wherein:

R² is selected from the group consisting of:

(a) H, OH, halo, NH₂, C₁₋₆-alkyl, C₂₋₆-alkynyl, CO₂H, Aryl and

(b) -S(O)ᵢC₁₋₆-alkyl and S(O)ᵢHetcy, wherein i is 0 or 2;

(c) C(O)Hetcy;

(d) C(O)NHC₁₋₆-alkyl and C(O)N(C₁₋₆-alkyl)₂;

(e) NHC(O)C₁₋₆-alkyl;

(f) S(O)₂NHC₁₋₆-alkyl, S(O)₂NHHetcy and S(O)₂N(C₁₋₆-alkyl)₂,

and

(g) NHSO₂C₁₋₆-alkyl,

said C₁₋₆-alkyl and C₂₋₆-alkynyl groups and portions in (a) through (g) above being optionally substituted with 1-2 members selected from the group consisting of: CN, CO₂H, Aryl, O-Aryl, CO₂C₁₋₆-alkyl and OC₁₋₆-alkyl;

Aryl represents a 6-10 membered aromatic ring system and Hetcy represents a 5-10 membered ring system, aromatic or non-aromatic, containing at least one heteroatom and optionally containing up to 3 additional heteroatoms, said heteroatoms being selected from O, S and N,

said Aryl and Hetcy groups and portions thereof being optionally substituted with 1-6 members selected from the group consisting of: -(CH₂)₀₋₆-CO₂H and -(CH₂)₀₋₆-CO₂C₁₋₆-alkyl. Within this subset, all other variables are as originally defined.

Another subset of compounds of the present invention that is of particular interest relates to compounds of formula I wherein R³ represents H. Within this subset, all other variables are as originally defined.

Another subset of compounds of the present invention that is of particular interest relates to compounds of formula I wherein:

R⁴ is selected from the group consisting of: H and C₁₋₄-alkyl,

optionally substituted with a member selected from the group consisting of: Hetcy, N(C₁₋₁₀-alkyl)₂, Aryl, O-Aryl, OC₁₋₆-alkyl, S(O)ᵢC₁₋₆-alkyl, S(O)ᵢ-(C₁₋₆-alkyl-aryl), wherein i is 0 or 2, OC₁₋₆-alkyl-aryl and NH(C₁₋₆-alkyl-aryl), wherein Aryl represents phenyl optionally substituted with 1-3 halo groups. Within this subset, all other variables are as originally defined.
Another subset of compounds of the present invention that is of particular interest relates to compounds of formula I wherein:

R^1 is selected from the group consisting of: H, NH\(_2\), NH\(_2\)C\(_1\)-alkyl, NH\(_2\)(O)C\(_1\)-alkyl, NH\(_2\)(O)OC\(_1\)-alkyl and NH\(_2\)(O)Aryl, said alkyl and the alkyl

and aryl portions of which are optionally substituted with 1-2 members selected from the group consisting of: CO\(_2\)H and CO\(_2\)C\(_1\)-alkyl;

R^2 is selected from the group consisting of:

- (a) H, OH, halo, NH\(_2\), C\(_1\)-alkyl, C\(_2\)-alkynyl, CO\(_2\)H, Aryl and Hetcy;

- (b) -S(\(O\))\(_y\)C\(_1\)-alkyl and S(\(O\))\(_y\)Hetcy, wherein \(y\) is 0 or 2;

- (c) C(\(O\))Hetcy;

- (d) C(\(O\))NH\(_2\)C\(_1\)-alkyl and C(\(O\))N(C\(_1\)-alkyl)\(_2\);

- (e) NH\(_2\)(O)C\(_1\)-alkyl;

- (f) S(\(O\))\(_2\)NH\(_2\)C\(_1\)-alkyl, S(\(O\))\(_2\)NHHetcy and S(\(O\))\(_2\)N(C\(_1\)-alkyl)\(_2\),

and

- (g) NH\(_2\)SO\(_2\)C\(_1\)-alkyl, said C\(_1\)-alkyl and C\(_2\)-alkynyl groups and portions in (a) through (g) above being optionally substituted with 1-2 members selected from the group consisting of: CN, CO\(_2\)H, Aryl, O-Aryl, CO\(_2\)C\(_1\)-alkyl, OC\(_1\)-alkyl;

Aryl represents a 6-10 membered aromatic ring system and

Hetcy represents a 5-10 membered ring system, aromatic or non-aromatic, containing at least one heteroatom and optionally containing up to 3 additional heteroatoms, said heteroatoms being selected from O, S and N,

said Aryl and Hetcy groups and portions thereof being optionally substituted with 1-6 members selected from the group consisting of: -(CH\(_2\))\(_{0-6}\)-CO\(_2\)H and -(CH\(_2\))\(_{0-6}\)CO\(_2\)C\(_1\)-alkyl;

R\(^3\) represents H, and

R\(^4\) is selected from the group consisting of: H and C\(_1\)-alkyl optionally substituted with a member selected from the group consisting of: Hetcy, Aryl, O-Aryl, OC\(_1\)-alkyl, S(\(O\))\(_y\)C\(_1\)-alkyl, N(C\(_1\)-alkyl)\(_2\), S(\(O\))\(_y\)-(C\(_1\)-alkyl-aryl), wherein \(y\) is 0 or 2, OC\(_1\)-alkyl-aryl and NH(C\(_1\)-alkyl-aryl), wherein Aryl represents phenyl optionally substituted with 1-3 halo groups.
Representative examples of compounds of formula I are found in Table I below.

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The compounds described herein, and in particular, in Table I, are intended to include salts, enantiomers, esters and hydrates, in pure form and as a mixture thereof.

While chiral structures are shown below, by substituting into the synthesis schemes an enantiomer other than the one shown, or by substituting into the schemes a mixture of enantiomers, a different isomer or a racemic mixture can be achieved. Thus, all such isomers and mixtures are included in the present invention.

In another embodiment, the invention encompasses a method of treating a caspase-3 mediated disease in a mammalian patient in need of such treatment, comprising administering to said patient a compound of formula I in an amount effective to treat said caspase-3 mediated disease.
In another embodiment, the invention encompasses a method of treating cardiac and cerebral ischemia/reperfusion injury (e.g. stroke), type I diabetes, immune deficiency syndrome (including AIDS), cerebral and spinal cord trauma injury, organ damage during transplantation, alopecia, aging, Parkinson's disease, Alzheimer's disease, Down’s syndrome, spinal muscular atrophy, multiple sclerosis and neurodegenerative disorders, comprising administering to a mammalian patient in need of such treatment an effective amount of a compound of formula I.

In another embodiment, the invention encompasses a method of treating acute disorders, including cardiac and cerebral ischemia/reperfusion injury (e.g. stroke), spinal cord injury and organ damage during transplantation, in a mammalian patient in need of such treatment, comprising administering to said patient a compound of formula I in an amount effective to treat said acute disorder.

In another embodiment, the invention encompasses a method of treating chronic disorders, including neurodegenerative diseases (e.g. Alzheimer’s, polyglutamine-repeat disorders, Down’s, spinal muscular atrophy, multiple sclerosis), immunodeficiency (e.g. HIV), diabetes, alopecia and aging, in a mammalian patient in need of such treatment, comprising administering to said patient a compound of formula I in an amount effective to treat said chronic disorder.

In another embodiment, the invention encompasses a method of treating a caspase-3 mediated disease in a mammalian patient in need of such treatment, comprising administering to said patient a compound of formula I in an amount effective to treat said caspase-3 mediated disease.

In particular, these compounds are preferably useful to treat, prevent or ameliorate in mammals and especially in humans, diseases including but not limited to:

cardiac and cerebral ischemia/reperfusion injury (e.g. stroke)
type I diabetes
immune deficiency syndrome (including AIDS)
cerebral and spinal cord trauma injury
organ damage during transplantation
alopecia
aging
Parkinson's disease
Alzheimer's disease
Down’s syndrome
spinal muscular atrophy
multiple sclerosis
neurodegenerative disorders.

The compound is administered to a mammalian patient in need of such
treatment or prevention an amount of a compound as described herein that is effective
to treat or prevent the disease or condition.

The compounds described typically contain asymmetric centers and
may thus give rise to diastereomers and optical isomers. The present invention
includes all such possible diastereomers as well as their racemic and resolved,
enantiomerically pure forms and pharmaceutically acceptable salts thereof.

Some of the compounds described herein contain olefinic double
bonds, and unless specified otherwise, are meant to include both E and Z geometric
isomers.

The pharmaceutical compositions of the present invention comprise a
compound of formula I as an active ingredient or a pharmaceutically acceptable salt
thereof in combination with a pharmaceutically acceptable carrier, and optionally
other therapeutic ingredients. The term "pharmaceutically acceptable salts" refers to
salts prepared from pharmaceutically acceptable bases including inorganic bases and
organic bases. Representative salts derived from inorganic bases include aluminum,
ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts,
manganous, ammonium, potassium, sodium, zinc and the like. Particularly preferred
are the calcium, magnesium, potassium, and sodium salts. Representative salts
derived from pharmaceutically acceptable organic bases include salts of primary,
secondary and tertiary amines, substituted amines including naturally occurring
substituted amines, cyclic amines, and basic ion exchange resins, such as arginine,
betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-
diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-
ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydabamine,
isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine,
polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine,
tripropylamine, tromethamine and the like.

When the compound of the present invention is basic, salts may be
prepared from pharmaceutically acceptable non-toxic acids, including inorganic and
organic acids. Examples of such acids include acetic, benzenesulfonic, benzoic,
camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic,
hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric and tartaric acids.

In the discussion of methods of treatment which follows, reference to the compounds of formula I are meant to also include the pharmaceutically acceptable salts.

The ability of the compounds of formula I to inhibit caspase-3 make them useful research tools in the field of apoptosis.

The magnitude of therapeutic dose of a compound of formula I will, of course, vary with the nature of the severity of the condition to be treated and with the particular compound of formula I and its route of administration and vary upon the clinician's judgement. It will also vary according to the age, weight and response of the individual patient. An effective dosage amount of the active component can thus be determined by the clinician after a consideration of all the criteria and using his/her best judgement on the patient's behalf. A representative dose will range from 0.001 mpk/d to about 100 mpk/d.

An ophthalmic preparation for ocular administration comprising 0.001-1% by weight solutions or suspensions of the compounds of formula I in an acceptable ophthalmic formulation may be used.

Any suitable route of administration may be employed for providing an effective dosage of a compound of the present invention. For example, oral, parenteral and topical may be employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, creams, ointments, aerosols, and the like.

The compositions include compositions suitable for oral, parenteral and ocular (ophthalmic). They may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

In practical use, the compounds of formula I can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration. In preparing the compositions for oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, alcohols, oils, flavoring agents, preservatives, coloring agents and the like in the case of oral liquid preparations, such
as, for example, suspensions, elixirs and solutions; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the case or oral solid preparations such as, for example, powders, capsules and tablets, with the solid oral preparations being preferred over the liquid preparations. Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques.

Pharmaceutical compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient, as a powder or granules or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion or a water-in-oil emulsion. Such compositions may be prepared by any of the methods of pharmacy but all methods include the step of bringing into active ingredient with the carrier which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation. For example, a tablet may be prepared by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. For example, each dosage unit may contain from about 0.01 mg to about 1.0 g of the active ingredient.

Method of Synthesis

Compounds of the present invention are conveniently prepared using the procedures described generally below and more explicitly described in the Example section thereafter.

Aspartyl aldehyde 1 is prepared as illustrated in Scheme 1. Reaction of N-fluorenlymethoxycarbonyl-L-aspartic acid β-tert-butyl ester (Fmoc-L-Asp (OtBu)-OH) (2) (Novabiochem) with iso-butyl chloroformate (IBCF) followed by
treating the reaction mixture with sodium borohydride gives alcohol 3. This is oxidized under Swern conditions to give 1.

Scheme 1: Preparation of Aldehyde 1

\[
\begin{align*}
\text{FmocNH} & \quad \text{OH} \\
\text{CO}_2\text{-t-Bu} & \quad \text{1) IBCF, DIEA} \\
\text{THF, -78}^\circ\text{C} - 0^\circ\text{C} & \quad \text{FmocNH} \\
\text{CO}_2\text{-t-Bu} & \quad \text{2) NaBH}_4, \text{THF/MeOH} \\
\text{2} & \quad \text{Swern} \\
\text{H} & \quad \text{1}
\end{align*}
\]

This aldehyde may be loaded onto resin by the two-step procedure shown in Scheme 2. Treatment of compound 4 (Webb et al, J. Am. Chem. Soc. 114, 3156 (1992)) with a commercial amino-Merrifield resin in the presence of EDCI and HOBT in dichloromethane followed by removal of the Boc group with trifluoroacetic acid (TFA) in dichloromethane afforded Resin A. Cleavage of the Fmoc group using piperidine in DMF provided Resin B. An appropriately substituted 3-pyridylcarboxylic acid was then coupled with Resin B to provide Resin C using a peptide coupling reagent such as EDCI/HOBt or HATU/iPr₂NEt. The desired compound was then cleaved from the resin with 9:1 TFA:H₂O with concomitant cleavage of the t-butyl ester protecting group.
Scheme 2: Preparation of aldehyde caspase inhibitors

\[ \text{H}_2\text{N} \xrightarrow{1} \text{FmocNH} \xrightarrow{\text{EDCI, HOBT}} \]

\[ \text{CO}_2\text{tBu} \]

\[ \text{CO}_2\text{H} \]

\[ \text{NR} \xrightarrow{\text{DMF}} \text{Resin B} \]

\[ \text{R}_1 \xrightarrow{\text{Resin A}} \text{R}_2 \xrightarrow{\text{R}_3} \]

\[ \text{HATU/DIEA} \]

\[ \text{R}_1 \xrightarrow{9:1 \text{TFA/H}_2\text{O}} \text{R}_2 \xrightarrow{\text{R}_3} \]

\[ \text{t-Bu-O}_2\text{C} \]

\[ \text{Resin C} \]
The semicarbazide Resin D is prepared according to Scheme 3. Treatment of compound 6 (Webb et al., J. Am. Chem. Soc. 114, 3156 (1992)) with a commercial amino-Merrifield resin in the presence of EDCI and HOBT in dichloromethane followed by removal of the Boc group with trifluoroacetic acid (TFA) in dichloromethane afforded Resin D.

Scheme 3: Preparation of semicarbazide Resin D

Aspartyl ketone derivatives could be prepared as shown in Scheme 4. An organometallic reagent such as an alkyl Grignard (RMgBr) can be added to aldehyde 7 (prepared in direct analogy to aldehyde 1), and the resulting alcohol oxidized to the ketone with an oxidizing agent such as Dess-Martin periodinane. Ketone 9 can be loaded onto Resin D with catalytic HOAc in THF to provide Resin E. Cleavage of the Alloc group may be accomplished with Pd(PPh3)4 in the presence of pyrrolidine or tributyltin hydride, generating Resin F. This may be coupled with pyridine carboxylic acid derivatives as shown in Scheme 2 to generate compounds of the present invention.
Scheme 4: Preparation of Ketone Derivatives

Alternatively, ketone derivatives containing a heteroatom in the □-position could be prepared from bromomethylketone 11. As shown in Scheme 5, reaction of N-fluorenylmethyloxycarbonyl-L-aspartic acid □-tert-butyl ester (Fmoc-L-Asp (OtBu)-OH) (1) (Novabiochem) with iso-butyl chloroformate (IBCF) followed by treating the reaction mixture with an excess of diazomethane yields the diazomethylketone intermediate 10. This intermediate is subjected in situ to a 1:1 mixture of AcOH and 45% aqueous hydrobromic acid (HBr) to give compound 11 as a white powder.
Scheme 5: Preparation of Bromomethylketone 11

The general procedure for the solid phase synthesis of nicotinic acid derivatives I incorporating a sulfide P1' sulfur side chain is illustrated in Scheme 6. Bromomethyl ketone 11 is mixed with Resin D in THF in the presence of AcOH overnight to furnish Resin G. Nucleophilic displacement with an appropriate thiol in the presence of suitable bases give Resin H as shown. The Fmoc group on Resin H is cleaved with 20% (v) piperidine in DMF and the resultant Resin I reacted with a substituted nicotinic acid using O-(7-Azabenzotriazol-1-yl)N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) as the activating agent and diisopropylethylamine (DIEA) as the base, affording Resin J. The final product I is released from solid support by treating Resin J with trifluoroacetic acid (TFA) in water (9/1, v/v).
Nicotinic acid derivatives bearing a carboxamide substituent in the 5-position were prepared as shown in Scheme 7. Nucleophilic displacement of the bromine in Resin G with 4-fluorobenzylmercaptan in the presence of suitable bases followed by Fmoc cleavage with 20% (v) piperidine in DMF gave Resin K. This resin was reacted with pyridinedicarboxylic acid using O-(7-Azabenzotriazol-1-yl)N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) as the activating agent and diisopropylethylamine (DIEA) as the base, affording Resin L. This resin may be coupled with primary or secondary amines, or anilines using HATU and DIEA to give the resin-bound amides (Resin M). The final product I is released from solid support by treating Resin M with trifluoroacetic acid (TFA) in water (9/1, v/v).
Nicotinic acid derivatives containing a sulfone in the 5-position were prepared as shown in Scheme 8. Thus 5-bromonicotinic acid underwent Fischer esterification followed by sodium thiomethoxide displacement of the bromine to give thioether 14. Oxidation of the sulfide to the sulfoxide 15 could be accomplished with an oxidant such as MMPP. Pummerer rearrangement was achieved by warming with TFAA, then concentrating and treating the residue with triethylamine in MeOH to give the thiol 16. This thiol may be alkylated with alkyl halides in DMF in the presence of an amine base. The resulting sulfide 17 can be oxidized to the sulfone with an oxidant such as MMPP, and the ester can be hydrolized under basic conditions to give nicotinic acid derivative 18. This acid may be coupled to Resin K as previously described, and the resin cleaved with TFA/H₂O to provide the sulfone derivatives which are examples of the present invention.
Nicotinic acid derivatives containing a sulfonamide in the 5-position were prepared as shown in Scheme 9. The ester moiety of thiol 16 (or its corresponding disulfide) may be hydrolized under basic conditions to give acid 20 (or its corresponding disulfide). Oxidation to the sulfonyl chloride 21 may be accomplished with chlorine gas in HOAc. Primary or secondary amines may be reacted with 21 to give sulfonamides 22. These acids may be coupled to Resin K as previously described, and the resin cleaved with TFA/H$_2$O to provide the sulfonamide derivatives which are examples of the present invention.
Scheme 9: Preparation of Sulfonamide Derivatives

Caspase inhibitors containing aryloxyalkylketones and acyloxyalkyl ketones may be prepared as shown in Scheme 10. Resin G in DMF may be treated with a phenol or substituted phenol in the presence of a base such as cesium carbonate to give Resin M. Alternatively, Resin G in DMF may be treated with a carboxylic acid, preferably an aromatic acid, in the presence of a base such as potassium fluoride to give Resin M. Coupling of an appropriately substituted nicotinic acid under standard conditions then provides Resin N, which may be cleaved with TFA/H₂O to provide compounds of the present invention.
Scheme 10: Preparation of oxymethylketones

Caspase inhibitors containing aryloxymethylketones and acyloxymethyl ketones may be prepared as shown in Scheme 11. Resin O is prepared from Alloc-L-Asp (OtBu)-OH as described in Schemes 5 and 6. Treatment of Resin O with a primary amine in DMF followed by Boc protection generates Resin P. The Alloc group may then be removed using a palladium catalyst and a hydride source. The resulting amine may be coupled with an appropriately substituted nicotinic acid under standard conditions to provide Resin Q. This may be cleaved with TFA/H₂O to provide compounds of the present invention.
Scheme 11: Preparation of aminomethylketones

Resin O

1) RNH₂, DMF
2) Boc₂O

Resin P

R = aryl or acyl

1) Pd(PPh₃)₄
PhSiH₃

2) HATU/DIEA

9:1 TFA/H₂O

Resin Q

The invention is further illustrated using the following non-limiting examples.
EXAMPLE 1
(3S)-3-[(5-BROMO-3-PYRIDYL)CARBONYL]AMINO-4-OXO-BUTANOIC ACID

Step 1:

5 t-Butyl (3S)-3-[(9H-9-fluorenylethoxy)carbonyl]amino-4-hydroxy-butanoate (3)

To a solution of N-Fmoc-L-aspartic acid β-tert-butyl ester (10.01 g, 24.3 mmol) in 100 mL of tetrahydrofuran (THF) at 0 °C was added N-methylmorpholine (NMM, 2.9 mL, 26.7 mmol) followed by isobutyl chloroformate (IBCF, 3.3 mL, 25.6 mmol). After stirring for 45 minutes at 0 °C, this mixture was cooled to -78 °C for 15 minutes. To the mixture was then added sodium borohydride (1.93 g, 51 mmol) followed by 20 mL MeOH. The mixture was stirred at -78 °C for 2h, the quenched with saturated aqueous ammonium chloride. The mixture was extracted three times with ethyl acetate (250 mL). The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated. The crude product was purified by flash chromatography. Eluting with hexanes/ethyl acetate (1:1 to 1:9) afforded the desired product as a white powder (9.14 g).

1H NMR (400 MHz, acetone-d6): δ 7.85 (d, 2H), 7.69 (d, 2H), 7.41 (t, 2H), 7.32 (t, 2H), 7.02 (bd, 1H, NH), 4.70 (dd, 1H), 4.51-4.41 (m, 2H), 4.38-4.30 (m, 2H), 4.25 (t, 1H), 2.85 (dd, 1H), 2.70 (dd, 1H), 1.41 (s, 9H).

Step 2 t-Butyl (3S)-3-[(9H-9-fluorenylethoxy)carbonyl]amino-4-oxo-butanoate (1)
To a -78°C solution of oxalyl chloride (3.7 mL, 41.9 mmol) in 275 mL CH₂Cl₂ was added DMSO (5.5 mL, 76.8 mmol) dropwise. The resulting solution was stirred 20 min, then a solution of the alcohol from Step 1 (13.88 g, 34.9 mmol) in 75 mL CH₂Cl₂ was added via cannula. The mixture was stirred for 1h, then diisopropylethylamine (18 mL, 105 mmol) was added. The mixture was stirred 1h at -78 °C, and -15 °C for 20 min, then poured into 1M HCl, and extracted with CH₂Cl₂. The organic phase was washed with NaHCO₃ solution, brine and dried over MgSO₄. Evaporation provided 13.97 g of the title compound.

Step 3: Semicarbazone

To a solution of crude aldehyde 2 (13.97 g, 35 mmol) in 100 mL EtOH was added NaOAc (3.11 g, 38 mmol), followed by the Webb semicarbazide, TFA salt (11.36 g, 34.5 mmol) as a solution in 220 mL EtOH and 110 mL H₂O. The mixture was stirred 15 h at RT, giving a ppt. The reaction mixture was partitioned between 1M NaOH and EtOAc and extracted 3x with EtOAc. The combined organic layers were washed with brine and dried over Na₂SO₄. Purification by flash chromatography (10% MeOH in CH₂Cl₂ to 10% MeOH, 10% THF in CH₂Cl₂) provided 17.56 g of the title compound.

Step 4 Resin A

To a solution of HOBt (3.26 g, 24.1 mmol) in 250 mL CH₂Cl₂ was added a solution of semicarbazone (11.91 g, 20.1 mmol) in 100 mL CH₂Cl₂. Amino-Merrifield resin (19.14 g, 13.4 mmol) was then added, and the suspension was cooled to 0 °C. EDCI (4.62 g, 24.12 mmol) was added in three portions, and the mixture was stirred 23 h at RT. The resin was then filtered and washed with aq. NH₄Cl (6x), water
(2x), aq. NaHCO₃ (3x), water (3x), 50% aq THF (3x), THF (3x), EtOAc (1x) and CH₂Cl₂ (1x), then dried in vacuo to give 29.49 g of the title compound.

Step 5 Resin B

152 mg of resin was suspended in 2 mL DMF. Piperidine (0.4 mL) was added, and the mixture was rotated for 25 min. The resin was filtered and washed with DMF (3 x), THF (3x) and CH₂Cl₂ (3x).

Step 6 (3S)-3-[(5-Bromo-3-pyridyl)carbamoyl]amino-4-oxo-butanoic acid

The resin from Step 5 was suspended in 1.6 mL DMF and EDCI (87 mg, 0.45 mmol), HOBT (70 mg, 0.45 mmol) and 5-bromonicotinic acid (77 mg, 0.38 mmol) were added. The mixture was rotated at RT for 3h, then filtered and washed with DMF, THF, CH₂Cl₂ and EtOAc (3x each). The resin was then treated with 9:1 TFA:H₂O (2.5 mL) and rotated for 35 min. The resin was filtered and washed with 9:1 TFA:H₂O (2 x 2.5 mL), and the filtrates were concentrated. The residue was dissolved in 1:1 HOAc:H₂O and lyophilized to provide 19.3 mg of the title compound.

**¹H NMR (D₂O, 400 MHz) δ 8.65 (m, 2H), 8.23 (br s, 1H), 5.00 (d, 1H), 4.27 (m, 1H), 2.51 (dd, 1H), 2.32 (dd, 1H).**

**EXAMPLE 2**

(3S)-3-[(5-HYDROXY-3-PYRIDYL)CARBONYL]AMINO-4-OXO-BUTANOIC ACID

**¹H NMR (D₂O, 400 MHz) δ 8.44 (m, 1H), 8.25 (m, 1H), 8.08 (m, 1H), 4.95 (d, 1H), 4.30 (m, 1H), 2.65 (dd, 1H), 2.48 (dd, 1H).**

**EXAMPLE 3**

(3S)-3-[(5-AMINO-3-PYRIDYL)CARBONYL]AMINO-4-OXO-BUTANOIC ACID

**¹H NMR (D₂O, 400 MHz) δ 8.22 (s, 1H), 7.98 (m, 1H), 7.95 (m, 1H), 4.95 (d, 1H), 4.28 (m, 1H), 2.65 (dd, 1H), 2.48 (dd, 1H).**
EXAMPLE 4

(3S)-3-[(6-(9H-9-(FLUORENYLMETHOXY)CARBONYLAMINO)-3-PYRIDYL)CARBONYL]AMINO-4-OXO-BUTANOIC ACID

$^1$H NMR (d$_6$-DMSO, 400 MHz) $\delta$ 8.86 (m, 1H), 8.77 (m, 1H), 8.17 (m, 1H), 7.89 (m, 2H), 7.80 (m, 2H), 7.42 (m, 2H), 7.33 (m, 2H), 4.97 (d, 1H), 4.4-4.2 (m, 4H), 3.0 (m, 1H), 2.7 (m, 1H).

EXAMPLE 5

(3S)-3-[(3-PYRIDYL)CARBONYL]AMINO-4-OXO-BUTANOIC ACID

$^1$H NMR (D$_2$O, 400 MHz) $\delta$ 8.70 (br s, 1H), 8.50 (m, 1H), 8.02 (m, 1H), 7.40 (m, 1H), 4.96 (d, 1H), 4.27 (m, 1H), 2.50 (dd, 1H), 2.31 (dd, 1H).

EXAMPLE 6

(3S)-3-[(6-AMINO-3-PYRIDYL)CARBONYL]AMINO-4-OXO-BUTANOIC ACID

$^1$H NMR (D$_2$O, 400 MHz) $\delta$ 8.15 (m, 1H), 8.00 (m, 1H), 6.88 (d, 1H), 4.98 (d, 1H), 4.30 (m, 1H), 2.68 (dd, 1H), 2.49 (dd, 1H).

EXAMPLE 7

(3S)-3-[(6-((3-CARBOXYPROPANOYL)AMINO)-3-PYRIDYL)CARBONYL]AMINO-4-OXO-BUTANOIC ACID

Resin B was reacted with 6-aminonicotinic acid as described in Example 1, Step 6. The resulting resin-bound aniline (104.8 mg) was suspended in 2 mL of pyridine with 77 mg of succinic anhydride and heated to 94°C for 4 h. The resin was washed with DMF (3 x), THF (3x) and CH$_2$Cl$_2$ (3x). The resulting resin was treated with TFA as described in Example 1, Step 6 to provide the title compound as a mixture of cyclic acetals.

$^1$H NMR (D$_2$O, 400 MHz) $\delta$ 8.7-8.1 (m, 2H), 7.35 (m, 1H), 4.95 (m, 0.6H), 4.80 (m, 0.4H), 4.28 (m,0.6H), 4.02 (m, 0.4H), 2.7-2.3 (m, 6H).
EXAMPLE 8

2-(((5-(((1S)-2-CARBOXY-1-FORMYLETHYL)AMINO)CARBONYL)-2-PYRIDYL)AMINO)CARBONYL)BENZOIC ACID

$^1$H NMR (D$_2$O/d$_6$-acetone, 400 MHz) $\delta$ 8.55 (m, 1H), 8.15 (m, 1H), 7.95 (m, 1H), 7.83 (d, 1H), 7.56 (m, 1H), 7.50 (m, 1H), 7.44 (m, 1H), 5.00 (d, 1H), 4.32 (m, 1H), 2.68 (dd, 1H), 2.50 (dd, 1H).

EXAMPLE 9

(3S)-3-(((6-((4-CARBOXYBUTANOYL)AMINO)-3-PYRIDYL)CARBONYL)AMINO)-4-OXO-BUTANOIC ACID

$^1$H NMR (D$_2$O, 400 MHz) $\delta$ 8.50 (m, 1H), 8.26 (m, 1H), 7.45 (d, 1H), 4.95 (d, 1H), 4.28 (m, 1H), 2.65 (m, 2H), 2.43 (m, 2H), 2.27 (m, 2H), 1.75 (m, 2H).

EXAMPLE 10

4-(((5-(((1S)-2-CARBOXY-1-FORMYLETHYL)AMINO)CARBONYL)-3-PYRIDYL)BENZOIC ACID

Resin B was reacted with 5-bromonicotinic acid as described in Example 1, Step 6. The resulting resin (0.5 mmol/g, 153 mg) was suspended in DME (2 mL). Aq. sodium carbonate (2M, 0.19 mL), 4-carboxyphenylboronic acid (64 mg, 0.38 mmol) and Pd(Ph$_3$P)$_4$ (9 mg, 0.008 mmol) were added, and the mixture was heated at 90 °C for 16h, then cooled. The resin was filtered and washed with aq NH$_4$Cl (3 x), H$_2$O (3x), THF (3x) and CH$_2$Cl$_2$ (3x). The resulting resin was treated with TFA as described in Example 1, Step 6 to provide the title compound.

$^1$H NMR (D$_2$O, 400 MHz) $\delta$ 8.82 (s, 1H), 8.79 (s, 1H), 8.30 (m, 1H), 7.82 (d, 2H), 7.64 (d, 2H), 4.98 (d, 1H), 4.27 (m, 1H), 2.49 (m, 2H), 2.32 (m, 2H).

EXAMPLE 11

(3S)-5-(BENZYSULFANYL)-3-[(5-BROMO-3-PYRIDYL)CARBONYL]AMINO-4-OXOPENTANOIC ACID

Step 1: t-Butyl (3S)-5-bromo-3-[(9H-9-fluorenlymethoxy)carbonyl]amino-4-oxopentanoate (11)

To a solution of N-Fmoc-L-aspartic acid β-tert-butyl ester (21.0 g, 51.0 mmol) in 300 mL of tetrahydrofuran (THF) at 78 °C was added N-methylmorpholine 

-45-
(NMM, 7.9 mL, 71.4 mmol) followed by isobutyl chloroformate (IBCF, 8.6 mL, 66.3 mmol). After stirring for 30 minutes at -78 °C, this mixture was warmed to -15 °C for 15 minutes. To the mixture was then added twice, in a 10 minutes interval, a solution of diazomethane in ether (1 M, 40 mL) with stirring. The mixture was allowed to warm to 0 °C and to it was added another 60 mL of the diazomethane solution. The solution was then warmed to room temperature and stirred for 10 minutes, recooled back to 0 °C and treated with a solution of HBr (48% aqueous)/AcOH (1/1, v/v, 100 mL) for 5 minutes, diluted with ethyl acetate and water. The organic phase was separated, washed with water and brine, dried over magnesium sulfate, filtered and concentrated. The crude product was purified by flash chromatography. Eluting with hexanes/ethyl acetate (3:1) afforded the desired product as a white powder (20 g, 81% yield).

\[ ^1H \text{NMR (400 MHz, acetone-d}_6\]:} \delta 7.85 (d, 2H), 7.69 (d, 2H), 7.41 (t, 2H), 7.32 (t, 2H), 7.02 (bd, 1H, NH), 4.70 (dd, 1H), 4.51-4.41 (m, 2H), 4.38-4.30 (2xd, 2H), 4.25 (t, 1H), 2.85 (dd, 1H), 2.70 (dd, 1H), 1.41 (s, 9H).

Step 2: Preparation of Resin D

A suspension of amino-Merrifield resin (Novabiochem, 30 grams, 31.2 mmol), acid 6 (14.7 g, 46.8 mmol), EDCI (10.77 g, 56.12 mmol) and HOBT (8.6 g, 56.16 mmol) in DMF (240 mL) was shaken on an orbital shaker at 190 rpm overnight. The mixture was filtered and the residual resin washed sequentially with DMF, methanol, dichloromethane and methanol and dried under vacuum. The resin then was suspended in a solution of TFA/dichloromethane (1:2, 300 mL) and shaken for 2h on an orbital shaker. The suspension was filtered, washed with dichloromethane (5x) and methanol (5x) and then dried under vacuum overnight to yield Resin D (40.5 g, 0.81 mmol/g).

Step 3:
Loading of ketone 11 to Resin D

A suspension of ketone 11 (4.5 g, 9.22 mmol) and Resin D (8.85 g, 7.13 mmol) in THF (70 mL) in the presence of AcOH (0.2 mL, 3.4 mmol) was shaken on an orbital shaker at 200 rpm overnight. The suspension was filtered and residual resin was washed sequentially with THF, dichloromethane, ethyl acetate and diethyl ether. Drying under high vacuum afforded Resin G (11.7 g).
Step 4:
Preparation of Resin I

To a suspension of Resin G (1.6 g) in DMF (6 mL) in a fritted reservoir was added a solution of benzylmercaptan (5.5 mL, 1 M in DMF) and N,N-diisopropylethylamine (DIEA) and the mixture was rotated on a disc (Glas-Col™) for 3 h and filtered. The resin was washed with DMF and then subjected to a solution of 20% piperidine in DMF for 20 minutes and then washed sequentially with DMF, methanol, dichloromethane and methanol and dried under high vacuum to afford Resin I.

Step 5:
(3S)-5-(Benzylsulfanyl)-3-[(5-bromo-3-pyridyl)carbonyl]amino-4-oxopentanoic acid

Resin I (100 mg, 0.05 mmol) was suspended in 3 mL DMF and HATU (96 mg, 0.25 mmol) and 5-bromonicotinic acid (51 mg, 0.25 mmol) were added. DIEA (0.04 mL, 0.25 mmol) was then added and the mixture was rotated at RT for 3 h, then filtered and washed with DMF, MeOH, THF, and CH₂Cl₂ (3x each). The resin was then treated with 9:1 TFA:Η₂O (2.5 mL) and rotated for 35 min. The resin was filtered and washed with CH₃CN and the filtrates were concentrated to provide 16 mg of the title compound.

¹H NMR (400 MHz, acetone-d₆): δ 9.10 (br s, 1H, NH), 8.55 (br s, 1H), 8.45 (s, 2H), 7.35-7.20 (m, 5H), 5.25 (q, 1H), 3.75 (s, 2H), 3.50 (dd, 2H), 3.05 (dd, 1H), 2.88 (dd, 1H). MS: m/z 437.2, 439.2 (M+1).
EXAMPLE 12
(3S)-5-(PHENYLSULFANYL)-3-[(5-BROMO-3-PYRIDYL)CARBONYL]AMINO-4-OXOPENTANOIC ACID

5 Step 1:
Resin G (100 mg), DMF (3 ml) and thiophenol (26 μl) were mixed together in a fritted syringe. It was shaken for 30 sec., then (iPr)2NET (44 μl) was added. It was rotated for 2h. The resin was washed with DMF (4x), MeOH (4x), THF (4x) and CH2Cl2 (4x). It was dried under a N2 flow for 10 min.

10 Step 2:
The resin thus obtained and 3.0 ml of a 20% piperidine/DMF v/v solution were mixed together in a fritted syringe and it was rotated for 25 min. The resin was washed with DMF (4x), THF (4x) and CH2Cl2 (4x). It was dried under N2 flow for 10 min.

15 Step 3:
5-Bromonicotinic acid (51 mg) was coupled to the resin as described previously and the coupled resin was treated with TFA/H2O to afford the title compound (18 mg).

1H NMR (400 MHz, acetone-d6): δ 9.05 (br s, 1H, NH) 8.55 (br s, 1H), 8.40 (s, 2H), 7.35 (d, 2H), 7.25 (t, 2H), 7.16 (t, 1H), 5.20 (q, 1H), 4.20 (s, 1H), 3.05 (dd, 1H), 2.92 (dd, 1H). MS: m/z 423.0, 425.0 (M+1).

EXAMPLE 13
(3S)-5-(((3-(4-(FLUOROBENZYL)SULFANYL)-1-CARBOXYMETHYL)-2-OXOPROPYL)AMINOCARBONYL)NICOTINIC ACID

Step 1
A mixture of Resin K (1.52 g, 0.76 mmol), 3,5-pyridinedicarboxylic acid (1.44g, 8.6 mmol) and HATU (1.10 g, 2.9 mmol) was suspended in 10 mL DMF and shaken. Diethylisopropylamine (1.2 mL, 6.9 mmol) was then added and the mixture rotated for 2.5 h. The resin was washed with DMF (3x), MeOH (3x), THF (3x) and CH2Cl2 (3x) and dried to give Resin L.
Step 2

60 mg of Resin L was treated with 9:1 TFA:H₂O and rotated for 15 min. The resin was filtered and washed with acetonitrile, and the filtrates were concentrated to give 9 mg of the title compound.

1H NMR (400 MHz, acetone-d6): δ 9.28 (br s, 2H), 8.79 (m, 1H), 8.67 (d, 1H), 7.37 (m, 2H), 7.03 (m, 2H), 5.26 (dd, 1H), 3.73 (s, 2H), 3.58 (d, 1H), 3.45 (d, 1H) 3.10 (dd, 1H), 2.90 (dd, 1H).

EXAMPLE 14

(3S)-5-(4-FLUOROBENZYL SULFANYL)-3-[(5-
(DIETHYLAMINO)CARBONYL)-3-PYRIDYL]CARBONYL]AMINO-4-
OXOPENTANOIC ACID

A mixture of Resin L (74 mg) and HATU (60 mg) was suspended in DMF (2 mL). Excess diethylamine (~0.5 mL) was added and the mixture was rotated for 1.5h. The resin was washed with DMF (3x), MeOH (3x), THF (3x) and CH₂Cl₂ (3x). The resin was then treated with 9:1 TFA:H₂O and rotated for 15 min. The resin was filtered and washed with acetonitrile, and the filtrates were concentrated to give 13 mg of the title compound.

MS (APCI, neg. ion) m/z 474 (M-1, 100), 419 (45), 334 (15), 288 (43).

EXAMPLE 15

(3S)-5-(4-FLUOROBENZYL SULFANYL)-3-[(5-((BENZYLAMINO)CARBONYL)-3-PYRIDYL]CARBONYL]AMINO-4-OXOPENTANOIC ACID

MS (APCI, neg. ion) m/z 508 (M-1, 100), 419 (45), 334 (15), 288 (43).

EXAMPLE 16

(3S)-5-(4-FLUOROBENZYL SULFANYL)-3-[(5-((N-PHENYL-N-METHYLAMINO)CARBONYL)-3-PYRIDYL]CARBAMOYL]4-
OXOPENTANOIC ACID

MS (APCI, neg. ion) m/z 508 (M-1, 70), 419 (100), 279 (30).
EXAMPLE 17
(3S)-3-[[6-((3-(CARBOXYMETHYL)PROPANOYL)AMINO)-3-PYRIDYL]CARBONYL]AMINO-4-OXO-BUTANOIC ACID
1H NMR (400 MHz, acetone-d6): δ 10.35 (br s, 1H), 8.88 (s, 1H), 8.40-8.23 (m, 3H), 4.55 (t, 1H), 3.62 (s, 3H), 3.10 (dd, 1H), 2.91-2.83 (m, 2H), 2.75-2.65 (m, 2H), 2.60 (dd, 1H). MS: m/z 352.4 (M+1).

EXAMPLE 18
(3S)-5-[(2’CHLORO-6’-FLUOROBENZYL)SULFANYL]-3-[(5-BROMO-3-PYRIDYL)CARBONYL]AMINO-4-OXOPENTANOIC ACID
1H NMR (400 MHz, acetone-d6): δ 9.05 (br s, 1H), 8.85 (br s, 1H), 8.55 (br s, 1H, NH), 8.40 (br s, 1H), 7.35-7.25 (m, 2H), 7.12-7.06 (m, 1H), 5.18 (q, 1H), 3.90 (s, 2H), 3.75 (s, 2H), 3.05 (dd, 1H), 2.90 (dd, 1H). MS: m/z 489.6 (M+1).

EXAMPLE 19
(3S)-5-[(2’CHLORO-6’-FLUOROBENZYL-OXY]-3-[(5-BROMO-3-PYRIDYL)CARBONYL]AMINO-4-OXOPENTANOIC ACID
1H NMR (400 MHz, acetone-d6): δ 9.13 (br s, 1H), 8.97 (br s, 1H), 8.55 (br s, 1H), 8.45 (br s, 1H), 7.48-7.37 (m, 1H), 7.31 (t, 1H), 7.15 (q, 1H), 5.10 (q, 1H), 4.82-4.72 (m, 2H) 4.58-4.45 (m, 2H), 2.98-2.80 (m, 2H). MS: m/z 473.2, 475.1, 477.0 (M+1).

EXAMPLE 20
(3S)-5-[[4-FLUOROBENZYL]SULFANYL]-3-[(5-ISOPROPOMETHYL)-3-PYRIDYL]CARBONYL]AMINO-4-OXOPENTANOIC ACID
Step 1 3-Bromo-5-hydroxymethylpyridine
To a suspension of 5-bromonicotinic acid (8.5 g, 42 mmol) in 120 mL EtOH was added conc. sulfuric acid (2 mL). The mixture was heated to reflux for 15 h, then cooled and concentrated. The residue was partitioned between ether and saturated NaHCO₃. The organic phase was washed with brine, dried over MgSO₄ and evaporated to give 9.4 g of a colorless oil. This material was dissolved in 150 mL of EtOH and treated with NaBH₄ (10.3 g, 272 mmol). The mixture was stirred for 2 days at room temperature, then was quenched with 30 mL water and was concentrated. The residue was diluted with water and was extracted 4x with CH₂Cl₂. The combined organic phases were washed with brine, filtered through cotton and
evaporated to give 7 g of an oil. Purification by flash chromatography (ether) gave 3.2 g of the title compound.

Step 2 3-Bromo-5-(isopropoxymethyl)pyridine

To a 0 °C solution of 3-bromo-5-hydroxymethylpyridine (211 mg, 1.22 mmol) in CH₂Cl₂ (10 mL) was added Et₃N (0.4 mL) and MsCl (0.13 mL, 1.7 mmol). The solution was stirred for 45 min, then isopropanol (1 mL) was added, and the solution was stirred overnight. Concentration followed by flash chromatography (50% ether/hexanes) provided 130 mg of 3-bromo-5-chloromethylpyridine. This material was dissolved in isopropanol and treated with sodium hydride and tetramethylammonium iodide. The reaction mixture was warmed to 50 °C overnight, then concentrated and partitioned between EtOAc and water. The organic phase was washed with brine and dried over MgSO₄ to give 130 mg of the title compound.

Step 3 5-(Isopropoxymethyl)nicotinic acid

A mixture of 3-bromo-5-(isopropoxymethyl)pyridine (130 mg, 0.56 mmol), PdCl₂(Ph₃P)₂ (9 mg, 0.013 mmol), PPh₃ (26 mg, 0.10 mmol) and Bu₃N (125 mg, 0.67 mmol) were combined in a 2 mL vial with a stir bar. Degassed water (0.03 mL, 1.6 mmol) was added and the vial was placed in a stainless steel bomb. The bomb was charged with CO (200 psi), and heated to 120 °C for 20 h (ref: J. Org. Chem. 46, 4614, 1981). The bomb was cooled and depressurized, and the reaction mixture was partitioned between ethyl acetate and aq. ammonium chloride. The organic phase was washed with brine and dried over MgSO₄ to give 75 mg of the title compound contaminated with Ph₃P.

Step 4 3S)-5-((4-Fluorobenzyl)sulfanyl)-3-[(5-(isopropoxymethyl)-3-pyridyl)carbonyl]amino-4-oxopentanoic acid

Unpurified 5-(isopropoxymethyl)nicotinic acid (75 mg) was added to Resin K as described previously, then cleaved with TFA:H₂O to provide 38 mg of the title compound.

¹H NMR (400 MHz, acetone-d₆): δ 9.17 (br s, 1H), 8.94 (br s, 1H), 8.6 (m, 2H), 7.37 (m, 2H), 7.05 (m, 2H), 5.26 (q, 1H), 4.78 (s, 2H), 3.80 (m, 1H), 3.72 (s, 2H), 3.52 (dd, 2H), 3.07 (dd, 1H), 2.92 (dd, 1H).
EXAMPLE 21

(3S)-5-(4-FLUOROBENZYL SULFANYL)-3-[(5-((DIISOPROPYLAMINO)CARBONYL)-3-PYRIDYL)CARBONYL]AMINO-4-OXOPENTANOIC ACID

MS (APCI, neg. ion) m/z 502 (M-1, 100), 362 (20), 316 (16).

EXAMPLE 22

(3S)-5-(4-FLUOROBENZYL SULFANYL)-3-[(5-PHENYL-3-PYRIDYL)CARBONYL]AMINO-4-OXOPENTANOIC ACID

$^{1}$H NMR (400 MHz, acetone-d$_6$): $\delta$ 9.10 (m, 2H), 8.67-8.56 (m, 2H), 7.78 (d, 2H), 7.58-7.48 (m, 3H), 7.42-7.35 (m, 2H), 7.05 (t, 2H), 5.30 (m, 1H), 3.75 (s, 2H), 3.53 (dd, 2H), 3.10 (dd, 1H), 2.90 (dd, 1H). MS: m/z 453.3 (M+1).

EXAMPLE 23

(3S)-5-(4-FLUOROBENZYL SULFANYL)-4-OXO-3-[(5-(PHENYL-1-ETHENYL)-3-PYRIDYL)CARBONYL]AMINO)PENTANOIC ACID

$^{1}$H NMR (400 MHz, acetone-d$_6$): $\delta$ 9.08 (br s, 1H), 8.92 (br s, 1H), 8.58 (d, 1H), 8.40 (s, 1H), 7.65-7.60 (m, 2H), 7.50-7.43 (m, 3H), 7.40-7.33 (m, 2H), 7.02 (t, 2H), 5.28 (q, 1H), 3.72 (s, 2H), 3.52 (dd, 2H), 3.10 (dd, 1H), 2.90 (dd, 1H).

MS: m/z 477.2 (M+1).

EXAMPLE 24

((3S)-5-(4-FLUOROBENZYL SULFANYL)-3-[(6-METHYL-3-PYRIDYL)CARBONYL]AMINO-4-OXOPENTANOIC ACID

$^{1}$H NMR (400 MHz, acetone-d$_6$): $\delta$ 9.25 (br s, 1H), 8.88-8.75 (m, 2H), 7.98 (d, 1H), 7.40-7.32 (m, 2H), 7.05 (t, 2H), 5.28 (q, 1H), 3.71 (s, 2H), 3.50 (dd, 2H), 3.08 (dd, 1H), 2.90 (dd, 1H), 2.82 (s, 3H). MS: m/z 391.3 (M+1).

EXAMPLE 25

(3S)-5-(4-FLUOROBENZYL SULFANYL)-4-OXO-3-[(5-(PIPERIDINOCARBONYL)-3-PYRIDYL)CARBONYL]AMINOPENTANOIC ACID

$^{1}$H NMR (300 MHz, acetone-d$_6$): $\delta$ 8.7 (m, 2H), 8.6 (d, 1H), 8.25 (m, 1H), 7.40-7.32 (m, 2H), 7.1-7.0 (m, 2H), 5.25 (m, 1H), 3.71 (s, 2H), 3.50 (dd, 2H), 3.35 (m, 2H), 3.1 (m, 3H), 2.90 (dd, 1H), 1.9-1.5 (m, 6H).
EXAMPLE 26

(3S)-5-(4-FLUOROBENZYSULFANYL)-3-[(5-
((((METHYL CARBOXY)PROPYL)AMINOCARBONYL)-3-
PYRIDYL)CARBONYL]AMINO-4-OXOPENTANOIC ACID

$^1$H NMR (400 MHz, acetone-d6): $\delta$ 9.27 (br s, 1H), 9.20 (br s, 1H),
8.69 (br s, 1H), 8.64 (m, 1H), 7.40-7.32 (m, 2H), 7.05 (t, 2H), 5.28 (m, 1H), 3.72 (s,
2H), 3.59 (s, 3H), 3.50 (dd, 2H), 3.47 (m, 2H), 3.08 (dd, 1H), 2.90 (dd, 1H), 2.43 (t,
2H), 1.90 (m, 2H). MS m/z 520.3 (M+1).

EXAMPLE 27

(3S)-5-(4-FLUOROBENZYSULFANYL)-3-[(5-((ETHYL-(4-
PYRIDYL)METHYL)AMINO)CARBONYL)-3-PYRIDYL)CARBONYL]AMINO-4-
OXOPENTANOIC ACID

MS (APCI, neg. ion) m/z 537 (M-1, 100), 397 (40), 351 (45).

EXAMPLE 28

(3S)-5-(4-FLUOROBENZYSULFANYL)-3-[(5-((BUTYL-(2-
CYANOETHYL)AMINO)CARBONYL)-3-PYRIDYL)CARBONYL]AMINO-4-
OXOPENTANOIC ACID

MS (APCI, neg. ion) m/z 527 (M-1, 100), 474 (30), 387 (20), 288 (35).

EXAMPLE 29

(3S)-5-(4-FLUOROBENZYSULFANYL)-3-[(5-
((((METHYL CARBOXY)BUTYL)AMINOCARBONYL)-3-
PYRIDYL)CARBONYL]AMINO-4-OXOPENTANOIC ACID

$^1$H NMR (400MHz, acetone-d6): $\delta$ 9.15 (br s, 1H), 8.65 (s, 1H), 8.58
(m, 1H), 8.15 (br s, 1H, NH), 7.40-7.33 (m, 2H), 7.05 (t, 2H), 5.28 (q, 1H), 3.75 (s,
2H), 3.58 (s, 3H), 3.50 (dd ABX, 2H), 3.50-3.43 (m, 2H), 3.05 (dd, 1H), 2.92 (dd,
1H), 2.35 (t, 2H), 1.67 (m, 4H). MS m/z 534.3 (M+1).
EXAMPLE 30
(3S)-5-(4-FLUOROBENZYSULFANYL)-3-{(5-((METHYL CARBOXY) ETHYLAMINOCARBONYL)-3-PYRIDYL) CARBONYL}AMINO-4-OXOPENTANOIC ACID

$^{1}$H NMR (400 MHz, acetone-d6): $\delta$ 9.28 (br s, 1H, NH), 9.18 (br s, 1H), 8.68 (s, 1H), 8.62 (m, 1H), 8.27 (br s, 1H, NH), 7.39-7.34 (m, 2H), 7.05 (t, 2H), 5.25 (q, 1H), 4.09 (q, 2H), 3.73 (s, 2H), 3.68 (q, 2H), 3.50 (dd, ABX, 2H), 3.07 (dd, 1H), 2.90 (dd, 1H), 2.65 (t, 2H), 1.18 (t, 3H). MS: m/z 520.4 (M+1).

EXAMPLE 31
(3S)-5-(4-FLUOROBENZYSULFANYL)-3-{((6-(3-CARBOXYPROPA NOYL)AMINO)-3-PYRIDYL)CARBONYL}AMINO-4-OXOPENTANOIC ACID

$^{1}$H NMR (400 MHz, acetone-d6): $\delta$ 9.05 (s, 1H), 8.50 (m, 1H, NH), 8.38 (d, 1H), 7.45 (d, 1H), 7.39-7.35 (m, 2H), 7.05 (t, 2H), 5.25 (m, 1H), 3.72 (s, 2H), 3.50 (dd, ABX, 2H), 3.08 (dd, 1H), 2.90 (s, 4H), 2.85 (dd, 1H). □ MS: m/z 492.3 (M+1).

EXAMPLE 32
(3S)-5-(4-FLUOROBENZYSULFANYL)-3-{(5-((METHYL CARBOXY)PENTYL)AMINOCARBONYL)-3-PYRIDYL)CARBONYL}AMINO-4-OXOPENTANOIC ACID

$^{1}$H NMR (300 MHz, acetone-d6): $\delta$ 9.21 (s, 1H), 8.78 (s, 1H), 8.68 (d, 1H), 8.24 (br s, 1H, NH), 7.42-7.35 (m, 2H), 7.05 (t, 2H), 5.28 (q, 1H), 3.72 (s, 2H), 3.60 (s, 3H), 3.50 (dd ABX, 2H), 3.45 (t, 2H), 3.08 (dd, 1H), 2.91 (dd, 1H), 2.30 (t, 2H), 1.69-1.58 (m, 4H), 1.49-1.38 (m, 2H). MS: m/z 548.3 (M+1).
EXAMPLE 33
(3S)-5-(4-FLUOROBENZYL SULFANYL)-3-[(5-(PROPYLTHIO)-3-PYRIDYL)CARBONYL]AMINO-4-OXOPENTANOIC ACID

Step 1
5 Methyl 5-bromonicotinate

To a solution of 5-bromonicotinic acid (10 g, 49.5 mmol) in MeOH (200 mL) was added 2 mL conc H₂SO₄. The mixture was heated to reflux overnight, then cooled and concentrated. The residue was diluted with aq NaHCO₃ and extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over MgSO₄ and concentrated to give 8.75 g of the title compound.

Step 2
Methyl 5-(thiomethyl)nicotinate

To a solution of methyl 5-bromonicotinate (5.0 g, 23.1 mmol) in DMF (100 mL) was added NaSMe (1.78 g, 25.5 mmol). The mixture was heated to 80 °C and stirred overnight. The mixture was cooled, diluted with aq NaHCO₃ and extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over MgSO₄ and concentrated to give 2.0 g of the title compound.

Step 3
Methyl 5(sulfinylmethyl)nicotinate

To a solution of methyl 5-(thiomethyl)nicotinate (2.93 g, 16.0 mmol) in 1:1 CH₂Cl₂/MeOH (160 mL) was added MMPP (80%, 4.94 g, 8.0 mmol) portionwise. The mixture was diluted with water, then concentrated. Aq. NaHCO₃ was added, and the mixture was extracted three times with CH₂Cl₂. The organic extracts were washed with brine, filtered through cotton and evaporated to give the title compound which was used in the next step without purification.

Step 4
Methyl 5-mercaptonicotinate

To a solution of unpurified sulfoxide in CH₂Cl₂ (110 mL) was added TFAA (50 mL). The solution was heated to reflux for 4h then cooled and concentrated. The residue was dissolved in 1:1 MeOH/Et₃N (60 mL) and evaporated. This was repeated two more times, then the residue was dissolved in CH₂Cl₂ and
washed with aq NH₄Cl, and brine, filtered through cotton and concentrated to give the title compound as a mixture with the corresponding disulfide.

Step 5
5-Mercaptonicotinic acid
To a solution of methyl 5-mercaptopnicotinate (1.0 g, 5.9 mmol) in MeOH (30 mL) and water (20 mL) was added LiOH•H₂O (744 mg, 17.7 mmol). The mixture was stirred at room temperature for 3h, then concentrated. The residue was dissolved in water, acidified to pH 3 with 1M HCl, and extracted three times with ethyl acetate. The combined organic layers were dried over MgSO₄ and concentrated to give the title compound as a mixture with the corresponding disulfide.

Step 6
5-(Propylthio)nicotinic acid
To a solution of 5-mercaptopnicotinic acid (90 mg, 0.58 mmol) in DMF was added DIEA (0.35 mL, 2.1 mmol) followed by 1-bromopropane (0.09 mL, 0.93 mmol). The mixture was stirred at room temperature for 24h, then partitioned between NaHCO₃ and EtOAc. The organic phase was evaporated to give 33 mg of propyl 5-(propylthio)nicotinate. The aqueous phase was acidified to pH 3 and extracted three times with EtOAc. The organic layers were washed with brine, dried over MgSO₄ and concentrated to give 35 mg of the title compound.

Step 7
(3S)-5-(4-Fluorobenzylsulfanyl)-3-[(5-(propylthio)-3-pyridyl)carbamoyl]amino-4-oxopentanoic acid
Resin I (88 mg) was treated with of 5-(propylthio)nicotinic acid (35 mg) as described in Example 12 to provide 20 mg of the title compound.
MS m/z 451 (M+1).
EXAMPLE 34
(3S)-5-(4-FLUOROBENZYSULFANYL)-4-OXO-3-([(5-(PROPYSULFONYL)-3-
PYRIDYL)CARBONYL]AMINO)PENTANOIC ACID

Step 1
Propyl 5-(propylsulfonyl)nicotinate
To a solution of propyl 5-(propylthio)nicotinate (33 mg, 0.14 mmol) in
1:1 CH₂Cl₂:MeOH (1.2 mL) was added MMPP (80%, 110 mg, 0.22 mmol), and the
mixture was stirred overnight, then partitioned between EtOAc and NaHCO₃. The
organic phase was washed with brine, dried over MgSO₄ and evaporated to give 21
mg of the title compound.

Step 2
5-(Propylsulfonyl)nicotinic acid
To a solution of propyl 5-(propylsulfonyl)nicotinate (21 mg, 0.08
mmol) in 1:1 MeOH:H₂O (1 mL) was added LiOH·H₂O (34 mg, 0.8 mmol). The
mixture was stirred for 1h, then acidified to pH 3 with 1M HCl. The mixture was
extracted three times with ethyl acetate, washed with brine and dried over MgSO₄ to
give 13 mg of the title compound.

Step 3
(3S)-5-(4-Fluorobenzylsulfanyl)-3-([(5-(propylsulfonyl)-3-pyridyl)carbamoyl]amino-4-
oxopentanoic acid
Resin I (60 mg) was treated with 5-(propylsulfonyl)nicotinic acid (13
mg) as described in Example 12 to provide 15 mg of the title compound.
MS m/z 483 (M+1).
EXAMPLE 35
(3S)-5-(4-FLUOROBENZYL SULFANYL)-3-[(5-((DIETHYLAMINO)SULFONYL)-3-PYRIDYL)CARBONYL]AMINO-4-OXOPENTANOIC ACID
MS m/z 512 (M+1).

EXAMPLE 36
(3S)-5-(4-FLUOROBENZYL SULFANYL)-3-[(5-((ISOPROPYL SULFONYL)AMINO)-3-PYRIDYL)CARBONYL]AMINO-4-OXOPENTANOIC ACID
MS m/z 498 (M+1).

EXAMPLE 37
(3S)-5-(4-FLUOROBENZYL SULFANYL)-3-[(5-((Cyclopropylamino)SULFONYL)-3-PYRIDYL)CARBONYL]AMINO-4-OXOPENTANOIC ACID
MS m/z 496 (M+1).

EXAMPLE 38
(3S)-5-(4-FLUOROBENZYL SULFANYL)-3-[(5-((PYRROLIDINO)SULFONYL)-3-PYRIDYL)CARBONYL]AMINO-4-OXOPENTANOIC ACID

Step 1
5-(Chlorosulfonyl)nicotinic acid

To a solution of 5-mercaptanotinic acid (130 mg) in AcOH (10 mL) was added a slow stream of chlorine gas for 5 min. The solution was then evaporated using toluene as an azeotrope to give 161 mg of the title compound.

Step 2
5-(Pyrrolidino)sulfonyl)nicotinic acid

To a suspension of 5-(chlorosulfonyl)nicotinic acid (50 mg, 0.22 mmol) in CH₂Cl₂ (1.5 mL) was added pyrrolidine (10 drops), giving a solution. After 2.5h, the reaction was partitioned between CH₂Cl₂ and dilute NaHCO₃. The aqueous phase was acidified to pH3 and extracted three times with CH₂Cl₂. The combined organic phases were filtered through cotton and evaporated to give 42 mg of the title compound.
Step 3
(3S)-5-(4-Fluorobenzylsulfanyl)-3-[(5-((pyrrolidino)sulfonyl)-3-pyridyl)carbonyl]amino-4-oxopentanoic acid

Resin I (80 mg) was treated with 5-((pyrrolidino)sulfonyl)nicotinic acid (42 mg) as described in Example 12 to provide 20 mg of the title compound. MS m/z 510 (M+1).

EXAMPLE 39
(3S)-5-(4-FLUOROBENZYL SULFANYL)-3-[(5-((N-CYCLOPROPYL-N-METHYL)AMINO)SULFONYL)-3-PYRIDYL]CARBONYL]AMINO-4-OXOPENTANOIC ACID

MS m/z 510 (M+1).

EXAMPLE 40
(3S)-5-PHENOXY-3-[(5-((CYCLOPROPYLAMINO)SULFONYL)-3-PYRIDYL]CARBONYL]AMINO-4-OXOPENTANOIC ACID

To a suspension of Resin G (200 mg, 0.086 mmol) in DMF (6 mL) was added phenol (41 mg, 0.43 mmol) and cesium carbonate (140 mg, 0.43 mmol). The suspension was rotated for 2.5 h, then washed with DMF (3x), water (3x), DMF (3x), THF (3x), MeOH (3x), and CH₂Cl₂ (3x). The resulting resin was suspended in 20% piperidine/DMF, rotated for 10 min, then washed with DMF (3x), THF (3x), MeOH (3x), and CH₂Cl₂ (3x) to give Resin M.

Resin M (200 mg, 0.086 mmol), 5-((cyclopropylamino)sulfonyl)nicotinic acid (46 mg, 0.189 mmol), and HATU (72 mg, 0.189 mmol) were suspended in DMF (4 mL) then treated with DIEA (0.033 mL, 0.2 mmol). The suspension was rotated 2.5 h, then washed with DMF (3x), THF (3x), MeOH (3x), and CH₂Cl₂ (3x). The resulting resin was rotated with 9:1 TFA:H₂O for 10 min, then filtered and washed with acetonitrile. The filtrate was concentrated to give the title compound.

¹H NMR (500 MHz, acetone-d6): 9.32 (m, 1H), 9.03 (m, 1H), 8.74 (m, 1H, NH), 8.62 (m, 1H), 8.45 (m, 1H, NH), 7.32-7.22 (m, 2H), 7.01-6.88 (m, 3H), 5.21-5.06 (m, 2H), 4.30 (q, 1H), 3.16-2.89 3.16 (m, 2H), 2.31 (m, 1H), 0.59 (m, 2H), 0.52 (m, 2H). MS m/z 448.3 (M+1).
EXAMPLE 41

(3S)-3-[[5-((CYCLOPROPYLAMINO)-SULFONYL)-3-
PYRIDYL]CARBONYL]AMINO-5-[[1-NAPHTHYL]CARBONYL]OXY]-4-
OXOPENTANOIC ACID

To a suspension of Resin G (200 mg, 0.086 mmol) in DMF (6 mL) was
added 1-naphthoic acid (74 mg, 0.43 mmol) and potassium fluoride (25 mg, 0.43
mmol). The suspension was rotated for 2.5 h, then washed with DMF (3x), water
(3x), DMF (3x), THF (3x), MeOH (3x), and CH₂Cl₂ (3x). The resulting resin was
converted to the title compound in the same manner as described in Example 52.

¹H NMR (500 MHz, acetone-d₆): 9.38 (m, 1H), 9.15 (m, 1H), 8.95-
8.8 (m, 2H, 2 NH), 8.29 (m, 1H), 8.17 (m, 1H), 7.99 (m, 1H), 7.65-7.51 (m, 3H),
7.15 (m, 1H), 5.49-5.35 (q, 2H), 5.30-5.22 (q, 1H), 3.20-2.97 (m, 2H), 2.32 (m, 1H),
0.58 (m, 2H), 0.51 (m, 2H). MS m/z 526.5 (M+1).

EXAMPLE 42

(3S)-5-[(2,6-DIFLUOROBENZYLAMINO)-3-[[5-
((CYCLOPROPYLAMINO)-SULFONYL)-3-PYRIDYL]CARBONYL]AMINO-4-
OXOPENTANOIC ACID

To a suspension of Resin O (500 mg, 0.225 mmol) in DMF (15 mL)
was added 2,6-difluorobenzylamine (0.11 mL, 1.12 mmol). The suspension was
rotated for 1.5 h, then washed with DMF (3x), THF (3x), MeOH (3x), and CH₂Cl₂
(3x). The resin was resuspended in CH₂Cl₂ and treated with di-t-butyldicarbonate
(0.15 mL, 0.67 mmol) and DIEA (0.12 mL, 0.67 mmol). The mixture was rotated for
2 h, then washed with DMF (3x), THF (3x), MeOH (3x), and CH₂Cl₂ (3x). The
resulting Resin P was suspended in CH₂Cl₂ (15 mL) and treated with Pd(PPh₃)₄ (25
mg, 0.023 mmol) and phenylsilane (0.66 mL, 5.4 mmol). The mixture was rotated for
30 min, then washed with DMF (3x), THF (3x), MeOH (3x), and CH₂Cl₂ (3x). The
resulting resin was converted to the title compound in the same manner as described
in Example 52.

MS m/z 497.3 (M+1).
Assays for Determining Biological Activity

(a) Measurement of caspase activity by cleavage of a fluorogenic substrate
(b) A fluorogenic derivative of the tetrapeptide recognized by caspase-3 and corresponding to the P₁ to P₄ amino acids of the PARP cleavage site, Ac-DEVD-AMC (AMC, amino-4-methylcoumarin) was prepared as follows: i) synthesis of N-Ac-Asp(Obn)-Glu(Obn)-Val-CO₂H, ii) coupling with Asp(Obn)-7-amino-4-methylcoumarin, iii) removal of benzyl groups.

![Chemical Structure](image)

Standard reaction mixtures (300 µL final volume), contained Ac-DEVD-AMC and purified or crude caspase-3 enzyme in 50 mM Hepes/KOH (pH 7.0), 10% (v/v) glycerol, 0.1% (w/v) CHAPS, 2 mM EDTA, 5 mM dithiothreitol, and were incubated at 25°C. Reactions were monitored continuously in a spectrofluorometer at an excitation wavelength of 380 nm and an emission wavelength of 460 nm.

(c) Cell Death Detection ELISA (Whole Cell Assay)

Photometric immunoassay for the qualitative and quantitative in vitro determination of cytoplasmic histone-associated-DNA-fragments (mono- and oligonucleosomes) after induced cell death. This assay was performed using the commercially available kit from Boehringer Mannheim, cat. No. 1 920 685.

(d) In Vivo Myocardial Ischemia and Reperfusion Injury in Rats

Male Sprague-Dawley rats (300-400g) were fasted overnight, and then anesthetized with intraperitoneal administration of sodium pentobarbital (65 mg/kg). To monitor heart rate and aortic pressure the left carotid artery was isolated and a cannula placed in the vessel. The aortic cannula was interfaced with a pressure transducer which was connected to a physiologic recorder. The left jugular vein was isolated and cannulated for administration of a caspase inhibitor compound or vehicle.
(2 % dimethylsulfoxide in 0.9% NaCl). A left thoracotomy was performed in the region overlying the heart and the pericardium opened, exposing the heart. The origin of the left coronary artery was visualized and a 4.0 suture passed under the artery approximately 2 - 3 mm from its origin. The ends of the suture were passed through a short length of 2 mm id tubing and coronary artery occlusion effected by placing tension on the suture such that the tube compressed the artery. After initial placement of the suture/occluder, the thoracotomy was closed with a small clamp and opened only to effect occlusion and reperfusion of the artery. A Lead II electrocardiograph (ECG) signal was obtained by placing subdermal platinum leads and continuously monitored. After a baseline period of 20-30 minutes the left coronary artery was occluded for 45 minutes. The period of reperfusion was 3 hours. The caspase inhibitor or vehicle was administered as a first bolus 5 minutes before the onset of ischemia and a second bolus was administered again at the onset of reperfusion. Additionally, an infusion was initiated immediately after the first bolus dose. Control animals received the vehicle alone in equal volumes to the caspase inhibitor treated animals. At the end of reperfusion the animals were euthanized and infarct size determined using a dual staining technique (1.5% w/v triphenyltetrazolium chloride to demarcate infarct tissue and 0.25% w/v Evan’s blue to demarcate the area at risk of infarct. The heart was subsequently cut transversely into 4 slices of equal thickness, and infarct size and area at risk quantified using planimetry.

Using the above procedure, it is demonstrated that administration of a caspase inhibitor reduces infarct size in the rat subjected to 45 minutes of regional ischemia and 3 hours of reperfusion.
WHAT IS CLAIMED IS:

1. A compound represented by formula

   \[
   \text{H} \quad \text{R}_1 \text{N} \quad \text{H} \quad \text{R}_2 \text{R}_3 \text{O} \quad \text{H} \quad \text{R}_4 \text{CO}_2 \text{H}
   \]

   or a pharmaceutically acceptable salt, hydrate or ester thereof, wherein:

   5 \( \text{R}_1 \) represents H, NH\(_2\), NHC\(_1\)-6alkyl, NH\(_{\text{C}}\)O\(_{\text{C}}\)-6alkyl, or NH\(_{\text{C}}\)O\(_{\text{A}}\)aryl, said alkyl and the alkyl and aryl portions of

   which are optionally substituted with 1-3 members selected from the group consisting of:

   CO\(_2\)H, CO\(_2\)C\(_1\)-6alkyl, aryl, NH\(_2\), NH\(_{\text{C}}\)C\(_3\)-6alkyl, NH-aryl, N(C\(_1\)-3alkyl)\(_2\) and

   Hetcy:

   10 \( \text{R}_2 \) is selected from the group consisting of:

   (a) H, OH, halo, NH\(_2\), CN, C\(_1\)-6alkyl, C\(_2\)-6alkenyl, C\(_2\)-6alkynyl,

   CO\(_2\)H, Aryl and Hetcy;

   (b) OC\(_1\)-6alkyl and OC\(_3\)-6alkenyl;

   (c) -S(O)\(_y\)C\(_1\)-6alkyl, -S(O)\(_y\)C\(_3\)-6alkenyl, -S(O)\(_y\)aryl and S(O)\(_y\)Hetcy,

   15 where \( y \) is 0, 1 or 2;

   (d) NH\(_{\text{C}}\)C\(_1\)-6alkyl, NH-aryl and NH-Hetcy;

   (e) C(O)C\(_1\)-6alkyl, C(O)C\(_3\)-6alkenyl and C(O)Hetcy;

   (f) C(O)NH\(_2\), C(O)NH\(_{\text{C}}\)C\(_1\)-6alkyl, C(O)N(C\(_1\)-6alkyl)\(_2\), C(O)NH-aryl

   and C(O)N(C\(_1\)-6alkyl)-aryl;

   20 (g) NH\(_{\text{C}}\)N(C\(_1\)-6alkyl), NH\(_{\text{C}}\)N(C\(_3\)-6alkenyl), N(C\(_1\)-6alkyl)C(O)C\(_1\)-

   6alkyl, N(C\(_1\)-6alkyl)C(O)C\(_3\)-6alkenyl and N(C\(_1\)-6alkyl)C(O)aryl;

   (h) S(O)\(_2\)NH\(_2\), S(O)\(_2\)NH\(_{\text{C}}\)C\(_1\)-6alkyl, SO\(_2\)NH-Hetcy, S(O)\(_2\)NH\(_{\text{C}}\)-

   6alkenyl, S(O)\(_2\)N(C\(_1\)-6alkyl)\(_2\), S(O)\(_2\)N(C\(_1\)-6alkyl)C\(_3\)-6alkenyl, SO\(_2\)NH-aryl,

   SO\(_2\)NH-Hetcy, SO\(_2\)N(C\(_1\)-6alkyl)aryl and SO\(_2\)N(C\(_1\)-6alkyl)Hetcy, and;

   25 (i) NH\(_{\text{SO}}\)S(C\(_1\)-6alkyl), NH\(_{\text{SO}}\)S(C\(_3\)-6alkenyl), N(C\(_1\)-6alkyl)SO\(_2\)C\(_1\)-

   6alkyl and N(C\(_1\)-6alkyl)SO\(_2\)C\(_3\)-6alkenyl,

   said C\(_1\)-6alkyl, C\(_2\)-6alkenyl, C\(_3\)-6alkenyl and C\(_2\)-6alkynyl groups and

   portions in (a) through (i) above being optionally substituted with 1-6 members.

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selected from the group consisting of: halo, OH, NH₂, CN, CO₂H, Hetcy, Aryl,
CO₂C₁₋₆alkyl, OC₁₋₆alkyl, O-Aryl, CO₂C₃₋₄alkenyl, C(O)NH₂, C(O)NHC₁₋₃alkyl,
C(O)N(C₁₋₃alkyl)₂, C(O)NH-Aryl, C(O)N(C₁₋₃alkyl)-Aryl, C(O)C₁₋₃alkyl, C(O)C₃₋₄alkenyl, -S(O)₂C₁₋₃alkyl, -S(O)₂C₃₋₄alkenyl, S(O)y-(C₁₋₃alkyl-aryl), wherein y is
as previously defined; OC₁₋₃alkyl-aryl, NH(C₁₋₃alkyl-aryl), N(C₁₋₃alkyl)C(O)C₁₋₃alkyl,
N(C₁₋₃alkyl)C(O)C₃₋₄alkenyl, N(C₁₋₃alkyl)C(O)Aryl, N(C₁₋₃alkyl)C(O)Hetcy, S(O)₂NH₂, S(O)₂NHC₁₋₃alkyl, S(O)₂NH₃, S(O)₂NH², S(O)₂N(C₁₋₃alkyl)₂, S(O)₂N(C₁₋₃alkyl)C₃₋₄alkenyl, S(O)₂N(C₁₋₃alkyl)Aryl, S(O)₂N(C₁₋₃alkyl)Hetcy, NH₃, NH₂, NHSO₂C₁₋₃alkyl,
NH₂SO₂C₃₋₄alkenyl, NH₂SO₂Aryl, NH₂SO₂Hetcy, N(C₁₋₃alkyl)SO₃H, N(C₁₋₃alkyl)SO₂C₁₋₃alkyl, N(C₁₋₃alkyl)SO₂C₃₋₄alkenyl, N(C₁₋₃alkyl)SO₂Aryl and
N(C₁₋₃alkyl)SO₂Hetcy;

R³ represents H, halo or C₁₋₃alkyl, and
R⁴ is selected from the group consisting of: H, C₁₋₆alkyl, C₂₋₆alkenyl,
C₂₋₆alkynyl and Hetcy, said C₁₋₆alkyl, C₂₋₆alkenyl and C₂₋₆alkynyl groups being
optionally substituted with 1-6 members selected from the group consisting of: halo,
OH, NH₂, NHC₁₋₃alkyl, N(C₁₋₃alkyl)₂, CN, CO₂H, Hetcy, Aryl, CO₂C₁₋₆alkyl,
OC₁₋₆alkyl, O-Aryl, CO₂C₁₋₃alkyl, CO₂C₃₋₄alkenyl, C(O)NH₂, C(O)NHC₁₋₃alkyl,
C(O)N(C₁₋₃alkyl)₂, C(O)NH-Aryl, C(O)N(C₁₋₃alkyl)-Aryl, C(O)C₁₋₃alkyl, C(O)C₃₋₄alkenyl, -S(O)₂C₁₋₃alkyl, -S(O)₂C₃₋₄alkenyl, S(O)y-(C₁₋₃alkyl-aryl), wherein y is
as previously defined; OC₁₋₃alkyl-aryl, NH(C₁₋₃alkyl-aryl), N(C₁₋₃alkyl)C(O)C₁₋₃alkyl,
N(C₁₋₃alkyl)C(O)C₃₋₄alkenyl, N(C₁₋₃alkyl)C(O)Aryl, N(C₁₋₃alkyl)C(O)Hetcy, S(O)₂NH₂, S(O)₂NHC₁₋₃alkyl, S(O)₂NH₃, S(O)₂NH², S(O)₂N(C₁₋₃alkyl)₂, S(O)₂N(C₁₋₃alkyl)Aryl, S(O)₂N(C₁₋₃alkyl)Hetcy, NH₃, NH₂, NHSO₂C₁₋₃alkyl,
NH₂SO₂C₃₋₄alkenyl, NH₂SO₂Aryl, NH₂SO₂Hetcy, N(C₁₋₃alkyl)SO₃H, N(C₁₋₃alkyl)SO₂C₁₋₃alkyl, N(C₁₋₃alkyl)SO₂C₃₋₄alkenyl, N(C₁₋₃alkyl)SO₂Aryl and
N(C₁₋₃alkyl)SO₂Hetcy;

Hetcy represents a 6-14 membered aromatic ring system and
Aryl represents a 5-10 membered ring system, aromatic or non-
atheromatic, containing at least one heteroatom and optionally containing up to 2
additional heteroatoms, said heteroatoms being selected from O, S(O)y with y as
defined above and N,
said Aryl and Hetcy groups and portions thereof being optionally substituted with 1-6 members selected from the group consisting of: -(CH₂)₀⁻⁴-CO₂H, -(CH₂)₀⁻₃-CO₂C₁⁻₃-alkyl, halo, CN, NH₂, phenyl, pyrrolidinyl, NHCH₃, C₁⁻₆-alkyl, SO₂NH₂ and SO₂CH₃.

2. A compound in accordance with claim 1 wherein:
R¹ represents H, NH₂, NHC₁⁻₆-alkyl, NHC(O)C₁⁻₆-alkyl, NHC(O)OC₁⁻₆-alkyl or NHC(O)Aryl, said alkyl and the alkyl and aryl portions of which are optionally substituted with 1-2 members selected from the group consisting of: CO₂H, CO₂C₁⁻₆-alkyl, aryl, NH₂, NHC₁⁻₃-alkyl, NH-Aryl and N(C₁⁻₃-alkyl)₂.

3. A compound in accordance with claim 1 wherein:
R² is selected from the group consisting of:
(a) H, OH, halo, NH₂, CN, C₁⁻₆-alkyl, C₂⁻₆-alkenyl, C₂⁻₆-alkynyl,
CO₂H, Aryl, Hetcy;
(b) OC₁⁻₆-alkyl and OC₃⁻₆-alkenyl;
(c) -S(O)ₓC₁⁻₆-alkyl, -S(O)ₓC₃⁻₆-alkenyl, -S(O)ₓAryl, S(O)ₓHetcy,
wherein x is 0 or 2;
(d) NHC₁⁻₆-alkyl;
(e) C(O)C₁⁻₆-alkyl, C(O)C₂⁻₆-alkenyl or C(O)Hetcy;
(f) C(O)NH₂, C(O)NHC₁⁻₆-alkyl, C(O)N(C₁⁻₆-alkyl)₂, C(O)NH-Aryl, C(O)N(C₁⁻₆-alkyl)-Aryl,
(g) NHC(O)C₁⁻₆-alkyl, NHC(O)C₃⁻₆-alkenyl, N(C₁⁻₆-alkyl)C(O)C₁⁻₆-alkyl, N(C₁⁻₆-alkyl)C(O)Hetcy;
(h) S(O)₂NH₂, S(O)₂NHCC₁⁻₆-alkyl, S(O)₂NHCC₃⁻₆-alkenyl, S(O)₂NHHetcy, S(O)₂N(C₁⁻₆-alkyl)₂, S(O)₂N(C₁⁻₆-alkyl)C₃⁻₆-alkenyl;
(i) NHSO₂C₁⁻₆-alkyl, NHSO₂C₃⁻₆-alkenyl, N(C₁⁻₆-alkyl)SO₂C₁⁻₆-alkyl and N(C₁⁻₆-alkyl)SO₂C₃⁻₆-alkenyl;

30 said C₁⁻₆-alkyl, C₂⁻₆-alkenyl, C₃⁻₆-alkenyl and C₂⁻₆-alkynyl groups and portions in (a) through (i) above being optionally substituted with 1-6 members selected from the group consisting of: halo, OH, NH₂, CN, CO₂H, Hetcy, Aryl, CO₂C₁⁻₆-alkyl, OC₁⁻₆-alkyl, CO₂C₁⁻₃-alkyl, CO₂C₃⁻₄-alkenyl, C(O)NH₂, C(O)NHCC₁⁻₃-alkyl, C(O)N(C₁⁻₃-alkyl)₂, C(O)NH-Aryl, C(O)N(C₁⁻₃-alkyl)-Aryl,
C(O)C₁⁻₃-alkyl, C(O)C₃⁻₄-alkenyl, -S(O)ₓC₁⁻₃-alkyl, -S(O)ₓC₃⁻₄-alkenyl, S(O)ₓ-(C₁⁻₆-alkyl)…
3alkyl-aryl), wherein y is as previously defined; OC1-3alkyl-aryl, NH(C1-3alkyl-aryl), N(C1-3alkyl)C(O)C1-3alkyl, N(C1-3alkyl)C(O)C3-4alkenyl, N(C1-3alkyl)C(O)Aryl, N(C1-3alkyl)C(O)Hetcy, S(O)2NH2, S(O)2NHC1-3alkyl, S(O)2NHC3-4alkenyl, S(O)2NH Aryl, S(O)2NHHetcy, S(O)2N(C1-3alkyl)2, S(O)2N(C1-3alkyl)C3-4alkenyl, S(O)2N(C1-3alkyl)Aryl, S(O)2N(C1-3alkyl)Hetcy, NHSO3H, NHSO2C1-3alkyl, NHSO2C3-4alkenyl, NHSO2Aryl, NHSO2Hetcy, N(C1-3alkyl)SO3H, N(C1-3alkyl)SO2C1-3alkyl, N(C1-3alkyl)SO2C3-4alkenyl, N(C1-3alkyl)SO2Aryl and N(C1-3alkyl)SO2Hetcy,

Aryl represents a 6-14 membered aromatic ring system;
Hetcy represents a 5-14 membered ring system, aromatic, non-aromatic or partially aromatic, containing at least one heteroatom and optionally containing up to 3 additional heteroatoms, said heteroatoms being selected from O, S(O)y with y as defined above and N,

said Aryl and Hetcy groups and portions thereof being optionally substituted with 1-6 members selected from the group consisting of: -(CH2)0-4-CO2H, -(CH2)0-3CO2C1-3alkyl, halo, CN, NH2, phenyl, pyrrolidinyl, NHCH3, C1-6alkyl, SO2NH2 and SO2CH3.

4. A compound in accordance with claim 1 wherein R3 represents H or C1-3alkyl.

5. A compound in accordance with claim 1 wherein R4 is selected from the group consisting of: H, C1-6alkyl, C2-6alkenyl, C2-6alkynyl and Hetcy,
said C1-6alkyl, C2-6alkenyl and C2-6alkynyl groups being optionally substituted with 1-6 members selected from the group consisting of: halo, OH, NH2, CN, CO2H, Hetcy, N(C1-10 alkyl)2, Aroyl, CO2C1-6alkyl, OC1-6alkyl, Oaryl, CO2C1-3alkyl, CO2C3-4alkenyl, C(O)NH2, C(O)NHC1-3alkyl, C(O)N(C1-3alkyl)2, C(O)NH-Aryl, C(O)N(C1-3alkyl)-Aryl, C(O)C1-3alkyl, C(O)C3-4alkenyl, -S(O)yC1-3alkyl, -S(O)yC3-4alkenyl, S(O)y-(C1-3alkyl-aryl), wherein y is as previously defined; OC1-3alkyl-aryl, NH(C1-3alkyl-aryl), N(C1-3alkyl)C(O)C1-3alkyl, N(C1-3alkyl)C(O)C3-4alkenyl, N(C1-3alkyl)C(O)Aryl, N(C1-3alkyl)C(O)Hetcy, S(O)2NH2, S(O)2NHC1-3alkyl, S(O)2NHC3-4alkenyl, S(O)2NH Aryl, S(O)2NHHetcy, S(O)2N(C1-3alkyl)2, S(O)2N(C1-3alkyl)C3-4alkenyl, S(O)2N(C1-
3alkyl)Aryl, S(O)₂N(C₁₋₃alkyl)Hetcy, NHSO₃H, NHSO₂C₁₋₃alkyl, NHSO₂C₃₋₄alkenyl, NHSO₂Aryl, NHSO₂Hetcy, N(C₁₋₃alkyl)SO₃H, N(C₁₋₃alkyl)SO₂C₁₋₃alkyl, N(C₁₋₃alkyl)SO₂C₃₋₄alkenyl, N(C₁₋₃alkyl)SO₂Aryl and N(C₁₋₃alkyl)SO₂Hetcy,

Aryl represents a 6-14 membered aromatic ring system;

Hetcy represents a 5-10 membered ring system, aromatic or non-aromatic, containing at least one heteroatom and optionally containing up to 2 additional heteroatoms, said heteroatoms being selected from O, S(O)y with y as defined above and N,

said Aryl and Hetcy groups and portions thereof being optionally substituted with 1-3 members selected from the group consisting of: -(CH₂)₀₋₄-CO₂H, -(CH₂)₀₋₄CO₂C₁₋₃alkyl, halo, CN, NH₂, phenyl, pyrrolidinyl, NHCH₃, C₁₋₆alkyl, SO₂NH₂ and SO₂CH₃.

6. A compound in accordance with claim 2 wherein:
R¹ is selected from the group consisting of: H, NH₂, NHC₁₋₆alkyl, NHC(O)C₁₋₆alkyl, NHC(O)OC₁₋₆alkyl and NHC(O)Aryl, said alkyl and the alkyl and aryl portions of which are optionally substituted with 1-2 members selected from the group consisting of: CO₂H and CO₂C₁₋₆alkyl.

7. A compound in accordance with claim 3 wherein R² is selected from the group consisting of:
(a) H, OH, halo, NH₂, C₁₋₆alkyl, C₂₋₆alkynyl, CO₂H, Aryl, Hetcy,
(b) -S(O)₁₋₄C₁₋₆alkyl, S(O)₁₋₄Hetcy, wherein y is 0 or 2;
(c) C(O)Hetcy,
(d) C(O)NHC₁₋₆alkyl, C(O)N(C₁₋₆alkyl)₂,
(e) NHC(O)C₁₋₆alkyl,
(f) S(O)₂NHC₁₋₆alkyl, S(O)₂NHHetcy, S(O)₂N(C₁₋₆alkyl)₂,
(g) NHSO₂C₁₋₆alkyl,
said C₁₋₆alkyl and C₂₋₆alkynyl groups and portions in (a) through (g) above being optionally substituted with 1-2 members selected from the group consisting of: CN, CO₂H, Aryl, O-Aryl, CO₂C₁₋₆alkyl, OCN₁₋₆alkyl,

Aryl represents a 6-10 membered aromatic ring system;
Hetcy represents a 5-10 membered ring system, aromatic or non-aromatic, containing at least one heteroatom and optionally containing up to 3 additional heteroatoms, said heteroatoms being selected from O, S and N, said Aryl and Hetcy groups and portions thereof being optionally substituted with 1-6 members selected from the group consisting of: -(CH₂)₀₋₆-CO₂H, -(CH₂)₀₋₆CO₂C₁₋₆alkyl.

8. A compound in accordance with claim 4 wherein R³ represents H.

9. A compound in accordance with claim 5 wherein R⁴ is selected from the group consisting of: H and C₁₋₆alkyl, optionally substituted with a member selected from the group consisting of: Aryl, O-Aryl, OC₁₋₆alkyl, S(O)ₓC₁₋₃alkyl, S(O)ₓ-(C₃₋₃alkyl-aryl), wherein y is 0 or 2, OC₁₋₃alkyl-aryl and NH(C₁₋₃alkyl-aryl), wherein Aryl represents phenyl optionally substituted with 1-3 halo groups.

10. A compound in accordance with claim 1 wherein: R¹ is selected from the group consisting of: H, NH₂, NHC₁₋₆alkyl, NHC(O)C₁₋₆alkyl, NH(O)OC₁₋₆alkyl and NH(O)Aryl, said alkyl and the alkyl and aryl portions of which are optionally substituted with 1-2 members selected from the group consisting of: CO₂H and CO₂C₁₋₆alkyl;

R² is selected from the group consisting of:
(a) H, OH, halo, NH₂, C₁₋₆alkyl, C₂₋₆alkynyl, CO₂H, Aryl, Hetcy,
(b) -S(O)ₓC₁₋₆alkyl, S(O)ₓHetyc, wherein x is 0 or 2;
(c) C(O)Hetyc,
(d) C(O)NH(C₁₋₆alkyl), C(O)N(C₁₋₆alkyl)₂,
(e) NHC(O)C₁₋₆alkyl,
(f) S(O)₂NH(C₁₋₆alkyl), S(O)₂N(Hetyc), S(O)₂N(C₁₋₆alkyl)₂,
(g) NH₄SO₂C₁₋₆alkyl,
said C₁₋₆alkyl and C₂₋₆alkynyl groups and portions in (a) through (g) above being optionally substituted with 1-2 members selected from the group consisting of: CN, CO₂H, Aryl, O-Aryl, CO₂C₁₋₆alkyl, OC₁₋₆alkyl,
Aryl represents a 6-10 membered aromatic ring system;
Hetcy represents a 5-10 membered ring system, aromatic or non-aromatic, containing at least one heteroatom and optionally containing up to 3 additional heteroatoms, said heteroatoms being selected from O, S and N, said Aryl and Hetcy groups and portions thereof being optionally substituted with 1-6 members selected from the group consisting of: -(CH₂)₀-₆-CO₂H, -(CH₂)₀-₆CO₂C₁-₆alkyl;

R³ represents H, and

R⁴ is selected from the group consisting of: H and C₁₄alkyl,

optionally substituted with a member selected from the group consisting of: Hetcy, Aryl, O-Aryl, OC₁-₆alkyl, S(O)yC₁-₃alkyl, N(C₁-₁₀ alkyl)₂, S(O)y-(C₁-₃alkyl-aryl), wherein y is 0 or 2, OC₁-₃alkyl-aryl and NH(C₁-₃alkyl-aryl), wherein Aryl represents phenyl optionally substituted with 1-3 halo groups.

11. A compound in accordance with claim 1 as shown in Table I below:

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</table>
or a pharmaceutically acceptable salt, hydrate or ester thereof.

12. A pharmaceutical composition comprised of a compound in accordance with any one of claims 1 to 11 in combination with a pharmaceutically acceptable carrier.
13. A method of treating or preventing a caspase-3 mediated disease or condition in a mammalian patient in need of such treatment or prevention, comprising administering to said patient a compound in accordance with claim 1 in an amount effective to treat or prevent said caspase-3 mediated disease.

14. A method of treating or preventing a caspase-3 mediated disease or condition in accordance with claim 13 wherein the disease or condition is selected from the group consisting of:
   cardiac or cerebral ischemia or reperfusion injury;
   type I diabetes;
   immune deficiency syndrome, including AIDS;
   cerebral and spinal cord trauma injury;
   organ damage during transplantation;
   alopecia;
   aging;
   Parkinson's disease;
   Alzheimer's disease;
   Down's syndrome;
   spinal muscular atrophy;
   multiple sclerosis and neurodegenerative disorders.

15. A method of treating or preventing a caspase-3 mediated disease or condition in accordance with claim 14 wherein the disease or condition is Alzheimer's disease.
16. Use of a compound of formula I, as defined in any one of claims 1 to 11, or a pharmaceutically acceptable salt, hydrate or ester thereof, in the manufacture of a medicament for treating or preventing a caspase-3 mediated disease or condition in a mammalian patient.

17. A caspase-3 inhibitor pharmaceutical composition comprising an acceptable caspase-3 inhibiting amount of a compound of formula I, as defined in any one of claims 1 to 11, or a pharmaceutically acceptable salt, hydrate or ester thereof, in association with a pharmaceutically acceptable carrier.

18. A compound of formula I, as defined in any one of claims 1 to 11, or a pharmaceutically acceptable salt, hydrate or ester thereof, for use in the treatment or prevention of a caspase-3 mediated disease or condition selected from the group consisting of:

- cardiac or cerebral ischemia or reperfusion injury;
- type I diabetes;
- immune deficiency syndrome, including AIDS;
- cerebral and spinal cord trauma injury;
- organ damage during transplantation;
- alopecia;
- aging;
- Parkinson's disease;
- Alzheimer's disease;
- Down's syndrome;
- spinal muscular atrophy;
- multiple sclerosis and neurodegenerative disorders.
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

IPCs: C07D213/82, C07D413/12, C07D405/04, C07D401/12, A61K31/44, A61P9/10

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

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols):

- IPC 7 C07D

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

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

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

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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<td>WO 98 11109 A (IDUN PHARMACEUTICALS INC) 19 March 1998 (1998-03-19) page 36, line 1 - line 21; claim 1; table 1</td>
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- Special categories of cited documents:
  - **A** document defining the general state of the art which is not considered to be of particular relevance
  - **E** earlier document but published on or after the international filing date
  - **L** document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
  - **O** document referring to an oral disclosure, use, exhibition or other means
  - **P** document published prior to the international filing date but later than the priority date claimed

- **T** later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

- **X** document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

- **Y** document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

- **&** document member of the same patent family

Date of the actual completion of the international search: 11 December 2000

Date of mailing of the international search report: 10.01.01

Name and mailing address of the ISA:

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-3040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer: Seymour, L.
INTERNATIONAL SEARCH REPORT

Box I  Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ✗ Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

   Although claims 13-15 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II  Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet {1}) (July 1998)
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