

HETEROCYCLIC COMPOUNDS AND THEIR USE FOR INHIBITING β -AMYLOID PEPTIDE

BACKGROUND OF THE INVENTION

Field of the Invention

5 This invention relates to compounds which inhibit cellular β -amyloid peptide release and/or its synthesis, and, accordingly, have utility in treating Alzheimer's disease.

References

10 The following publications, patents and patent applications are cited in this application as superscript numbers:

- 15 1 Glenner, et al., "Alzheimer's Disease: Initial Report of the Purification and Characterization of a Novel Cerebrovascular Amyloid Protein", *Biochem. Biophys. Res. Commun.*, 120:885-890 (1984).
- 20 2 Glenner, et al., "Polypeptide Marker for Alzheimer's Disease and its Use for Diagnosis", *U.S. Patent No. 4,666,829* issued May 19, 1987.
- 3 Selkoe, "The Molecular Pathology of Alzheimer's Disease", *Neuron*, 6:487-498 (1991).

- 4 Goate, et al., "Segregation of a Missense Mutation in the
Amyloid Precursor Protein Gene with Familial Alzheimer's
Disease", *Nature*, 349:704-706 (1990).
- 5 5 Chartier-Harlan, et al., "Early-Onset Alzheimer's Disease Caused
by Mutations at Codon 717 of the β -Amyloid Precursor Proteing
Gene", *Nature*, 353:844-846 (1989).
- 6 Murrell, et al., "A Mutation in the Amyloid Precursor Protein
Associated with Hereditary Alzheimer's Disease", *Science*,
10 254:97-99 (1991).
- 7 Mullan, et al., "A Pathogenic Mutation for Probable Alzheimer's
Disease in the APP Gene at the N-Terminus of β -Amyloid,
15 *Nature Genet.*, 1:345-347 (1992).
- 8 Schenk, et al., "Methods and Compositions for the Detection of
Soluble β -Amyloid Peptide", *International Patent Application*
Publication No. WO 94/10569, published 11 May 1994.
- 20 9 Selkoe, "Amyloid Protein and Alzheimer's Disease", *Scientific*
American, pp. 2-8, November, 1991.
- 10 *Tetrahedron Letters*, 34(48), 7685 (1993)
- 25 11 Losse, et al., *Tetrahedron*, 27:1423-1434 (1971)
- 12 Citron, et al., "Mutation of the β -Amyloid Precursor Protein in
Familial Alzheimer's Disease Increases β -Protein Production,
30 *Nature*, 360:672-674 (1992).
- 13 Hansen, et al., "Reexamination and Further Development of a
Precise and Rapid Dye Method for Measuring Cell Growth/Cell
Kill", *J. Immun. Meth.*, 119:203-210 (1989).
- 35

All of the above publications, patents and patent applications are herein
incorporated by reference in their entirety to the same extent as if each
40 individual publication, patent or patent application was specifically and
individually indicated to be incorporated by reference in its entirety.

State of the Art

Alzheimer's Disease (AD) is a degenerative brain disorder characterized clinically by progressive loss of memory, cognition, reasoning, judgment and emotional stability that gradually leads to profound mental deterioration and ultimately death. AD is a very common cause of progressive mental failure (dementia) in aged humans and is believed to represent the fourth most common medical cause of death in the United States. AD has been observed in races and ethnic groups worldwide and presents a major present and future public health problem. The disease is currently estimated to affect about two to three million individuals in the United States alone. AD is at present incurable. No treatment that effectively prevents AD or reverses its symptoms and course is currently known.

The brains of individuals with AD exhibit characteristic lesions termed senile (or amyloid) plaques, amyloid angiopathy (amyloid deposits in blood vessels) and neurofibrillary tangles. Large numbers of these lesions, particularly amyloid plaques and neurofibrillary tangles, are generally found in several areas of the human brain important for memory and cognitive function in patients with AD. Smaller numbers of these lesions in a more restrictive anatomical distribution are also found in the brains of most aged humans who do not have clinical AD. Amyloid plaques and amyloid angiopathy also characterize the brains of individuals with Trisomy 21 (Down's Syndrome) and Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch Type (HCHWA-D). At present, a definitive diagnosis of AD usually requires observing the aforementioned lesions in the brain tissue of patients who have died with the disease or, rarely, in small biopsied samples of brain tissue taken during an invasive neurosurgical procedure.

The principal chemical constituent of the amyloid plaques and vascular amyloid deposits (amyloid angiopathy) characteristic of AD and the other disorders mentioned above is an approximately 4.2 kilodalton (kD) protein of

-- 4 --

about 39-43 amino acids designated the β -amyloid peptide (β AP) or sometimes $A\beta$, $A\beta P$ or $\beta/A4$. β -Amyloid peptide was first purified and a partial amino acid sequence was provided by Glenner, et al.¹ The isolation procedure and the sequence data for the first 28 amino acids are described in U.S. Patent No. 4,666,829².

Molecular biological and protein chemical analyses have shown that the β -amyloid peptide is a small fragment of a much larger precursor protein (APP), that is normally produced by cells in many tissues of various animals, including humans. Knowledge of the structure of the gene encoding the APP has demonstrated that β -amyloid peptide arises as a peptide fragment that is cleaved from APP by protease enzyme(s). The precise biochemical mechanism by which the β -amyloid peptide fragment is cleaved from APP and subsequently deposited as amyloid plaques in the cerebral tissue and in the walls of the cerebral and meningeal blood vessels is currently unknown.

Several lines of evidence indicate that progressive cerebral deposition of β -amyloid peptide plays a seminal role in the pathogenesis of AD and can precede cognitive symptoms by years or decades. See, for example, Selkoe³. The most important line of evidence is the discovery that missense DNA mutations at amino acid 717 of the 770-amino acid isoform of APP can be found in affected members but not unaffected members of several families with a genetically determined (familial) form of AD (Goate, et al.⁴; Chartier Harlan, et al.⁵; and Murrell, et al.⁶) and is referred to as the Swedish variant. A double mutation changing lysine⁵⁹⁵-methionine⁵⁹⁶ to asparagine⁵⁹⁵-leucine⁵⁹⁶ (with reference to the 695 isoform) found in a Swedish family was reported in 1992 (Mullan, et al.⁷). Genetic linkage analyses have demonstrated that these mutations, as well as certain other mutations in the APP gene, are the specific molecular cause of AD in the affected members of such families. In addition, a mutation at amino acid 693 of the 770-amino acid isoform of APP has been identified as the cause of the β -amyloid peptide deposition disease, HCHWA-D,

-- 5 --

and a change from alanine to glycine at amino acid 692 appears to cause a phenotype that resembles AD in some patients but HCHWA-D in others. The discovery of these and other mutations in APP in genetically based cases of AD prove that alteration of APP and subsequent deposition of its β -amyloid peptide fragment can cause AD.

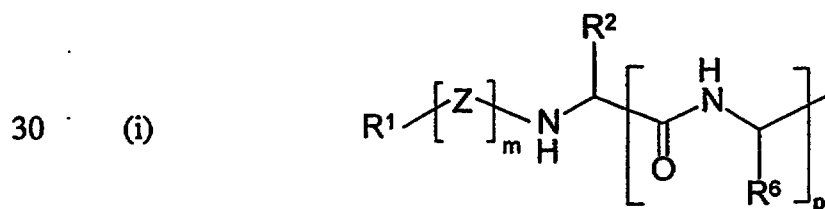
Despite the progress which has been made in understanding the underlying mechanisms of AD and other β -amyloid peptide related diseases, there remains a need to develop methods and compositions for treatment of the disease(s). Ideally, the treatment methods would advantageously be based on drugs which are capable of inhibiting β -amyloid peptide release and/or its synthesis *in vivo*.

SUMMARY OF THE INVENTION

This invention is directed to the discovery of a class of compounds which inhibit β -amyloid peptide release and/or its synthesis and, therefore, are useful in the prevention of AD in patients susceptible to AD and/or in the treatment of patients with AD in order to inhibit further deterioration in their condition. The class of compounds having the described properties are defined by formula I below:

A-B-C

wherein A is selected from the group consisting of:



where R^1 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl,

-- 6 --

substituted alkynyl, substituted cycloalkyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic;

Z is selected from the group consisting of

- 5 (a) a group having the formula $-CX'X''C(O)-$ where X' is hydrogen, hydroxy or fluoro; X'' is hydrogen, hydroxy or fluoro, or X' and X'' together form an oxo group;
- 10 (b) a group having the formula $-T-CX'X''C(O)-$ where T is selected from the group consisting of oxygen, sulfur and $-NR^3$ where R^3 is hydrogen, acyl, alkyl, aryl or heteroaryl group; X' is hydrogen or fluoro, X'' is hydrogen, hydroxy or fluoro, or X' and X'' together form an oxo group; and
- 15 (c) a group having the formula $-CX'X''-T-C(O)-$ where T is selected from the group consisting of oxygen, sulfur and $-NR^3$ where R^3 is hydrogen, acyl, alkyl, aryl or heteroaryl group; X' is hydrogen or fluoro, X'' is hydrogen, hydroxy or fluoro, or X' and X'' together form an oxo group;

R^2 is selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclic;

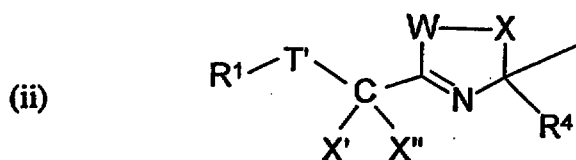
20 R^6 is selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclic;

m is an integer equal to 0 or 1; and

p is an integer equal to 0 or 1;

25

30



where R^1 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl,

-- 7 --

substituted alkynyl, substituted cycloalkyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic;

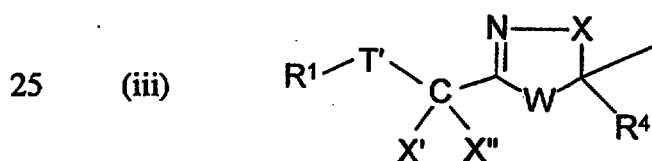
T' is selected from the group consisting of a bond covalently linking R¹ to -CX'X'', oxygen, sulfur and -NR³ where R³ is hydrogen, acyl, alkyl, aryl or heteroaryl group;

W and X are independently selected from the group consisting of -(CR⁷R⁷)_q-, oxygen, sulfur and -NR⁸ where q is an integer equal to one or two, and each R⁷ and R⁸ is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl, acyl, acyloxy, carboxyl, carboxyl esters and heterocyclic and further, when q is 2, an R⁷ group on each of the carbon atoms can optionally be fused to form an aryl, heteroaryl, heterocyclic or cycloalkyl group with the ethylene group with the proviso that when unsaturated, the remaining R⁷ group on each carbon atom participates in the unsaturation;

and with the further proviso that when W is oxygen, then X is not also oxygen;

X' is hydrogen, hydroxy or fluoro, X'' is hydrogen, hydroxy or fluoro, or X' and X'' together form an oxo group;

R⁴ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, heteroaryl and heterocyclic; and



where R¹ is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted cycloalkyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic;

-- 8 --

T' is selected from the group consisting of a bond covalently linking R¹ to -CX'X'', oxygen, sulfur and -NR³ where R³ is hydrogen, acyl, alkyl, aryl or heteroaryl group;

W and X are independently selected from the group consisting of
 5 -(CR⁷R⁷)_q-, oxygen, sulfur and -NR⁸ where q is an integer equal to one or two and each R⁷ and R⁸ is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl, acyl, acyloxy, carboxyl, carboxyl esters, and heterocyclic and further, when q is 2, an R⁷ group on each of the carbon atoms can optionally be fused to form an aryl,
 10 heteroaryl, heterocyclic or cycloalkyl group with the ethylene group with the proviso that when unsaturated, the remaining R⁷ group on each carbon atom participates in the unsaturation;

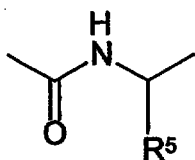
X' is hydrogen, hydroxy or fluoro, X'' is hydrogen, hydroxy or fluoro, or X' and X'' together form an oxo group;

15 R⁴ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, heteroaryl and heterocyclic;

B is selected from the group consisting of:

20

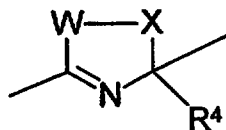
(i)



where R⁵ is selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl,
 25 substituted cycloalkyl, aryl, heteroaryl and heterocyclic;

30

(ii)



W and X are independently selected from the group consisting of

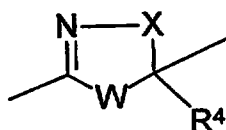
-- 9 --

$-(CR^7R^8)_q-$, oxygen, sulfur and $-NR^8$ where q is an integer equal to one or two, and each R^7 and R^8 is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl, acyl, acyloxy, carboxyl, carboxyl esters, and heterocyclic and further, when q is 2, an R^7 group on each of the carbon atoms can optionally be fused to form an aryl, heteroaryl, heterocyclic or cycloalkyl group with the ethylene group with the proviso that when unsaturated, the remaining R^7 group on each carbon atom participates in the unsaturation;

and with the further proviso that when W is oxygen, then X is not also oxygen;

R^4 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, heteroaryl and heterocyclic;

(iii)



W and X are independently selected from the group consisting of $-(CR^7R^8)_q-$, oxygen, sulfur and $-NR^8$ where q is an integer equal to 1 or 2 and each R^7 and R^8 is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl, acyl, acyloxy, and heterocyclic and further, when q is 2, an R^7 group on each of the carbon atoms can optionally be fused to form an aryl, heteroaryl, heterocyclic or cycloalkyl group with the ethylene group with the proviso that when unsaturated, the remaining R^7 group on each carbon atom participates in the unsaturation;

R^4 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, heteroaryl and heterocyclic; and

(iv) when A is either formula (ii) or (iii) as defined above, then B can also be a covalent bond linking A to C ;

-- 10 --

C is selected from the group consisting of:

(i) $-C(O)Y$ or $-C(S)Y$

where Y is selected from the group consisting of:

5 (a) alkyl or cycloalkyl,

(b) substituted alkyl with the proviso that the substitution on said substituted alkyl do not include α -haloalkyl, α -diazoalkyl, α -OC(O)alkyl, or α -OC(O)aryl groups,

(c) alkoxy or thioalkoxy,

10 (d) substituted alkoxy or substituted thioalkoxy,

(e) hydroxy,

(f) aryl,

(g) heteroaryl,

(h) heterocyclic,

15 (i) $-NR'R''$ where R' and R'' are independently selected from hydrogen, alkyl, alkenyl, alkynyl, substituted alkyl, substituted alkenyl, substituted alkenyl, cycloalkyl, aryl, heteroaryl, heterocyclic, where one of R' or R'' is hydroxy or alkoxy, and where R' and R'' are joined to form a cyclic group having from 2 to 8 carbon atoms optionally containing 1 to 2 additional
20 heteroatoms selected from oxygen, sulfur and nitrogen and optionally substituted with one or more alkyl, alkoxy or carboxylalkyl groups,

(j) $-NHSO_2-R^8$ where R^8 is selected from alkyl, substituted alkyl, alkenyl, substituted alkenyl, cycloalkyl, aryl, heteroaryl and heterocyclic,

(k) $-NR^9NR^{10}R^{10}$ where R^9 is hydrogen or alkyl, and each R^{10} is
25 independently selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, cycloalkyl, aryl, heteroaryl, heterocyclic, and

(l) $-ONR^9[C(O)O]_zR^{10}$ where z is zero or one, R^9 and R^{10} are as defined above;

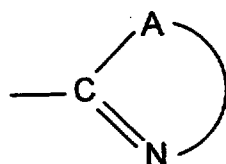
30 (ii) $-CR^{11}R^{11}Y'$

-- 11 --

where each R^{11} is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, heteroaryl and heterocyclic and Y' is selected from the group consisting of hydroxyl, alkoxy, amino, thiol, substituted alkoxy, thioalkoxy, substituted thioalkoxy, $-OC(O)R^9$, $-SSR^9$, and $-SSC(O)R^9$ where R^9 is selected from the group consisting of alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl and heterocyclic; and

10

(iii)



15

20

25

30

where A, together with $-C=N-$, forms a heterocyclic group which is optionally fused to form a bi- or multi-fused ring system (preferably no more than 5 fused rings) with one or more ring structures selected from the group consisting of cycloalkyl, cycloalkenyl, heterocyclic, aryl and heteroaryl group which, in turn, each of such ring structures is optionally substituted with 1 to 4 substituents selected from the group consisting of hydroxyl, halo, alkoxy, substituted alkoxy, thioalkoxy, substituted thioalkoxy, nitro, cyano, carboxyl, carboxyl esters, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, heteroaryl, heterocyclic, $-NHC(O)R^{10}$, $-NHSO_2R^{10}$, $-C(O)NH_2$, $-C(O)NHR^{10}$, $-C(O)NR^{10}R^{10}$, $-S(O)R^{10}$, $-S(O)_2R^{10}$, $-S(O)_2NHR^{10}$ and $-S(O)_2NR^{10}R^{10}$ where each R^{10} is independently selected from the group consisting of alkyl, substituted alkyl, or aryl, amino, N-alkylamino, N,N-dialkylamino, N-substituted alkylamino, N,N-disubstituted alkylamino, N-alkenylamino, N,N-dialkenylamino, N-substituted alkenylamino, N,N-disubstituted alkenylamino, N-cycloalkylamino, N,N-dicycloalkylamino, N-substituted cycloalkylamino, N,N-disubstituted cycloalkylamino, N-arylamino, N,N-diarylamino, N-heteroarylamino, N,N-diheteroarylamino, N-heterocyclic amino, N,N-diheterocyclic amino and mixed N,N-amino groups comprising a first and second substituent on said amino group which

- 12 -

substituents are selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, cycloalkyl, substituted cycloalkyl, aryl, heteroaryl, and heterocyclic provided that said first and second substituents are not the same;

5 with the proviso that when *A* has structure (i) and *B* has structure (i), then *C* does not have structure (i) or (ii);

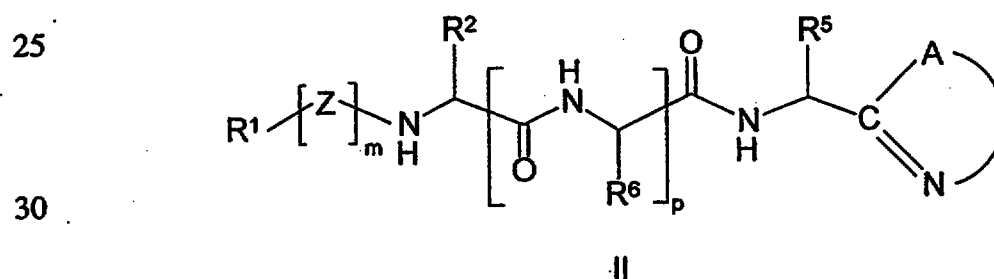
with the further provisos that

A. when *A* has structure (i) with R^1 being phenyl, *Z* being $-\text{CH}_2\text{OC(O)}-$, R^2 being methyl and *p* being zero, *B* has structure (iii) with *W* being $-\text{NH}-$, *X* being $-\text{CH}_2-$, and R^4 being benzyl then *C* is not $-\text{C(O)OCH}_3$;

B. when *A* has structure (i) with R^1 being 3,5-difluorophenyl, *Z* being $-\text{CH}_2\text{C(O)}-$, R^2 being methyl, and *p* being zero, *B* has structure (ii) with *W* being $>\text{NC(O)OC(CH}_3)_3$, *X* being $-\text{CH}_2-$, and R^4 being phenyl, then *C* is not $-\text{C(O)OCH}_3$; and

15 C. when *A* has structure (ii) wherein R^1 is 3,5-difluorophenyl, *T'* is a bond linking R^1 to $-\text{CX}'\text{X}''-$, X' and X'' are hydrogen, *W* is sulfur, *X* is methylene and R^4 is methyl, and *B* is a covalent bond linking *A* to *C*, then *C* is not $-\text{C(O)OCH}_3$.

20 In one preferred embodiment, the compounds of formula I are further characterized by formula II below:



wherein R^1 , R^2 , R^5 , R^6 , *A*, *Z*, *m* and *p* are as defined above.

35

In formula II above, when m is one, Z is preferably $-CX'X''C(O)-$ where X'' is preferably hydrogen, X' is preferably hydrogen or fluoro or X' and X'' form an oxo group.

5 In formula II above, preferred R^1 unsubstituted aryl groups include, for example, phenyl, 1-naphthyl, 2-naphthyl, and the like.

Preferred R^1 substituted aryl groups in formula II include, for example, monosubstituted phenyls (preferably 3 or 5 substituents); disubstituted phenyls
10 (preferably 3,5 substituents); and trisubstituted phenyls (preferably 3,4,5 substituents). Preferably, the substituted phenyl groups do not include more than 3 substituents.

Examples of substituted R^1 phenyls preferred in formula II include, for
15 instance, 2-chlorophenyl, 2-fluorophenyl, 2-bromophenyl, 2-hydroxyphenyl, 2-nitrophenyl, 2-methylphenyl, 2-methoxyphenyl, 2-phenoxyphenyl, 2-trifluoromethylphenyl, 4-fluorophenyl, 4-chlorophenyl, 4-bromophenyl, 4-nitrophenyl, 4-methylphenyl, 4-hydroxyphenyl, 4-methoxyphenyl, 4-ethoxyphenyl, 4-butoxyphenyl, 4-*iso*-propylphenyl, 4-phenoxyphenyl, 4-
20 trifluoromethylphenyl, 4-hydroxymethylphenyl, 3-methoxyphenyl, 3-hydroxyphenyl, 3-nitrophenyl, 3-fluorophenyl, 3-chlorophenyl, 3-bromophenyl, 3-phenoxyphenyl, 3-thiomethoxyphenyl, 3-methylphenyl, 3-trifluoromethylphenyl, 2,3-dichlorophenyl, 2,3-difluorophenyl, 2,4-dichlorophenyl, 2,5-dimethoxyphenyl, 3,4-dichlorophenyl, 3,4-difluorophenyl,
25 3,4-methylenedioxyphenyl, 3,4-dimethoxyphenyl, 3,5-difluorophenyl, 3,5-dichlorophenyl, 3,5-di-(trifluoromethyl)phenyl, 3,5-dimethoxyphenyl, 2,4-dichlorophenyl, 2,4-difluorophenyl, 2,6-difluorophenyl, 3,4,5-trifluorophenyl, 3,4,5-trimethoxyphenyl, 3,4,5-tri-(trifluoromethyl)phenyl, 2,4,6-trifluorophenyl, 2,4,6-trimethylphenyl, 2,4,6-tri-(trifluoromethyl)phenyl, 2,3,5-trifluorophenyl,
30 2,4,5-trifluorophenyl, 2,5-difluorophenyl, 2-fluoro-3-trifluoromethylphenyl,

4-fluoro-2-trifluoromethylphenyl, 2-fluoro-4-trifluoromethylphenyl, 4-benzyloxyphenyl, 2-chloro-6-fluorophenyl, 2-fluoro-6-chlorophenyl, 2,3,4,5,6-pentafluorophenyl, 2,5-dimethylphenyl, 4-phenylphenyl and 2-fluoro-3-trifluoromethylphenyl.

5

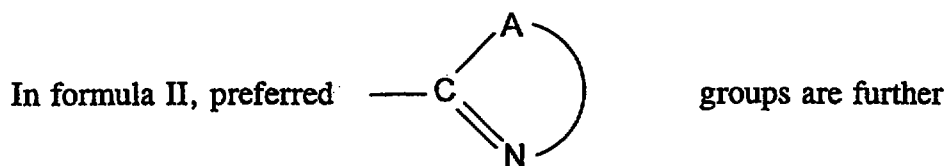
Preferred R¹ alkaryl groups in formula II include, by way of example, benzyl, 2-phenylethyl, 3-phenyl-*n*-propyl, and the like.

Preferred R¹ alkyl, substituted alkyl, alkenyl, cycloalkyl and
10 cycloalkenyl groups in formula II include, by way of example, *iso*-propyl, *n*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *t*-butyl, -CH₂CH=CH₂, -CH₂CH=CH(CH₂)₄CH₃, cyclopropyl, cyclobutyl, cyclohexyl, cyclopentyl, cyclohex-1-enyl, -CH₂-cyclopropyl, -CH₂-cyclobutyl, -CH₂-cyclohexyl, -CH₂-cyclopentyl, -CH₂CH₂-cyclopropyl, -CH₂CH₂-cyclobutyl, -CH₂CH₂-
15 cyclohexyl, -CH₂CH₂-cyclopentyl, and the like.

Preferred R¹ heteroaryls and substituted heteroaryls in formula II include, by way of example, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, fluoropyridyls (including 5-fluoropyrid-3-yl), chloropyridyls (including 5-chloropyrid-3-yl),
20 thiophen-2-yl, thiophen-3-yl, benzothiazol-4-yl, 2-phenylbenzoxazol-5-yl, furan-2-yl, benzofuran-2-yl, thionaphthen-2-yl, 2-chlorothiophen-5-yl, 3-methylisoxazol-5-yl, 2-(thiophenyl)thiophen-5-yl, 6-methoxythionaphthen-2-yl, 3-phenyl-1,2,4-thioxadiazol-5-yl, 2-phenyloxazol-4-yl, and the like.

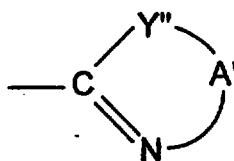
25 Preferably, in formula II, R² is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl and heterocyclic. Particularly preferred R² substituents include, by way of example, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, phenyl, benzyl, cyclohexyl, cyclopentyl, cycloheptyl, -CH₂CH₂SCH₃, and the like. As noted
30 below, R², as well as R⁵ and R⁶ are preferably the side chain of an L-amino acid.

Preferred R⁵ and/or R⁶ substituents in formula II are independently selected from the group consisting of include, for example, hydrogen, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, -CH₂CH(CH₂CH₃)₂, 2-methyl-*n*-butyl, 6-fluoro-*n*-hexyl, phenyl, benzyl, cyclohexyl, cyclopentyl, cycloheptyl, allyl, *iso*-but-2-enyl, 3-methylpentyl, -CH₂-cyclopropyl, -CH₂-cyclohexyl, -CH₂CH₂-cyclopropyl, -CH₂CH₂-cyclohexyl, -CH₂-indol-3-yl, *p*-(phenyl)phenyl, *o*-fluorophenyl, *m*-fluorophenyl, *p*-fluorophenyl, *m*-methoxyphenyl, *p*-methoxyphenyl, phenethyl, benzyl, *m*-hydroxybenzyl, *p*-hydroxybenzyl, *p*-nitrobenzyl, *m*-trifluoromethylphenyl, *p*-(CH₃)₂NCH₂CH₂CH₂O-benzyl, *p*-(CH₃)₃COC(O)CH₂O-benzyl, *p*-(HOOCCH₂O)-benzyl, 2-aminopyrid-6-yl, *p*-(N-morpholino-CH₂CH₂O)-benzyl, -CH₂CH₂C(O)NH₂, -CH₂-imidazol-4-yl, -CH₂-(3-tetrahydrofuranyl), -CH₂-thiophen-2-yl, -CH₂-(1-methyl)cyclopropyl, -CH₂-thiophen-3-yl, thiophen-3-yl, thiophen-2-yl, -CH₂-C(O)O-*t*-butyl, -CH₂-C(CH₃)₃, -CH₂CH(CH₂CH₃)₂, 2-methylcyclopentyl, -cyclohex-2-enyl, -CH[CH(CH₃)₂]COOCH₃, -CH₂CH₂N(CH₃)₂, -CH₂C(CH₃)=CH₂, -CH₂CH=CHCH₃ (cis and trans), -CH₂OH, -CH(OH)CH₃, -CH(O-*t*-butyl)CH₃, -CH₂OCH₃, -(CH₂)₄NH-Boc, -(CH₂)₄NH₂, -CH₂-pyridyl (e.g., 2-pyridyl, 3-pyridyl and 4-pyridyl), pyridyl (2-pyridyl, 3-pyridyl and 4-pyridyl), -CH₂-naphthyl (e.g., 1-naphthyl and 2-naphthyl), -CH₂-(N-morpholino), *p*-(N-morpholino-CH₂CH₂O)-benzyl, benzo[b]thiophen-2-yl, 5-chlorobenzo[b]thiophen-2-yl, 4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl, benzo[b]thiophen-3-yl, 5-chlorobenzo[b]thiophen-3-yl, benzo[b]thiophen-5-yl, 6-methoxynaphth-2-yl, -CH₂CH₂SCH₃, thien-2-yl, thien-3-yl, and the like.



characterized by the following structures:

-- 16 --



5

where Y'' is a heteroatom selected from oxygen, sulfur and $>NR^8$ where R^8 is as defined above and A', together with $-Y''-C=N-$, forms a heterocyclic group which is optionally fused to form a bi- or multi-fused ring system (preferably no more than 5 fused rings) with one or more ring structures selected from the group consisting of cycloalkyl, cycloalkenyl, heterocyclic, aryl and heteroaryl group which, in turn, each of such ring structures are optionally substituted with 1 to 4 substituents selected from the group consisting of hydroxyl, halo, alkoxy, substituted alkoxy, thioalkoxy, substituted thioalkoxy, nitro, cyano, carboxyl, carboxyl esters, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, amino, N-alkylamino, N,N-dialkylamino, N-substituted alkylamino, N-alkyl N-substituted alkylamino, N,N-disubstituted alkylamino, aryl, heteroaryl, heterocyclic, $-NHC(O)R^{10}$, $-NHSO_2R^{10}$, $-C(O)NH_2$, $-C(O)NHR^{10}$, $-C(O)NR^{10}R^{10}$, $-S(O)R^{10}$, $-S(O)_2R^{10}$, $-S(O)_2NHR^{10}$ and $-S(O)_2NR^{10}R^{10}$ where each R^{10} is independently selected from the group consisting of alkyl, substituted alkyl, or aryl.

Preferred heterocyclic structures include, by way of example, 3-methyl-1,2,4-oxadiazol-5-yl, thiazolin-2-yl, 3-phenyl-1,2,4-oxadiazol-5-yl, 3-(p-methoxy-benzyl)-1,2,4-oxadiazol-5-yl, and the like.

Preferred compounds of formula II include the following:

(S)-5-[1-N-[N-(3,5-difluorophenylacetyl)-L-alaninyl]amino]ethyl-3-ethyl-1,2,4-oxadiazole

(S)-5-[1-N-[N-(3,5-difluorophenylacetyl)-L-alaninyl]amino-2-phenylethyl]-3-methyl-1,2,4-oxadiazole

35

-- 17 --

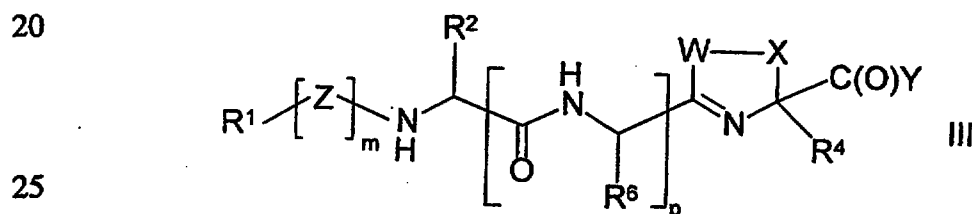
2-[1-*N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]amino-1-phenyl]methyl-2-thiazoline

5 (S)-5-[1-*N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]amino-1-phenyl]methyl-3-methyl-1,2,4-oxadiazole

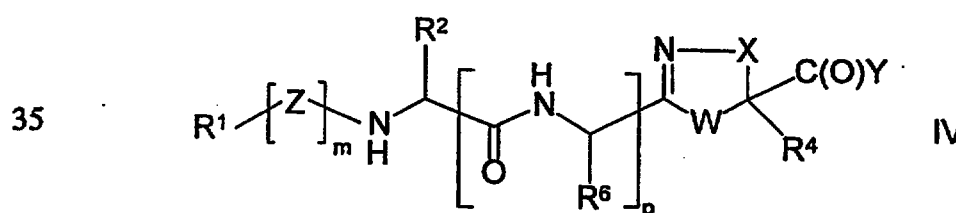
(S)-5-[1-*N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]amino-1-phenyl]methyl-3-phenyl-1,2,4-oxadiazole

10 (S)-5-[1-*N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]amino-1-phenyl]methyl-3-(4-methoxyphenylmethyl)-1,2,4-oxadiazole

15 In another preferred embodiment, the compounds of formula I are further characterized by formula III and IV below:



and



40

wherein R^1 , R^2 , R^4 , R^6 , W, X, Y, Z, m and p are as defined above.

45 In formula III and IV above, when m is one, Z is preferably -CX'X''C(O)- where X'' is preferably hydrogen, X' is preferably hydrogen or fluoro and where X' and X'' form an oxo group.

In formula III and IV above, preferred R¹ unsubstituted aryl groups include, for example, phenyl, 1-naphthyl, 2-naphthyl, and the like.

Preferred R¹ substituted aryl groups in formula III and IV include, for example, monosubstituted phenyls (preferably 3 or 5 substituents); disubstituted phenyls (preferably 3,5 substituents); and trisubstituted phenyls (preferably 3,4,5 substituents). Preferably, the substituted phenyl groups do not include more than 3 substituents.

Examples of substituted R¹ phenyls preferred in formula III and IV include, for instance, 2-chlorophenyl, 2-fluorophenyl, 2-bromophenyl, 2-hydroxyphenyl, 2-nitrophenyl, 2-methylphenyl, 2-methoxyphenyl, 2-phenoxyphenyl, 2-trifluoromethylphenyl, 4-fluorophenyl, 4-chlorophenyl, 4-bromophenyl, 4-nitrophenyl, 4-methylphenyl, 4-hydroxyphenyl, 4-methoxyphenyl, 4-ethoxyphenyl, 4-butoxyphenyl, 4-*iso*-propylphenyl, 4-phenoxyphenyl, 4-trifluoromethylphenyl, 4-hydroxymethylphenyl, 3-methoxyphenyl, 3-hydroxyphenyl, 3-nitrophenyl, 3-fluorophenyl, 3-chlorophenyl, 3-bromophenyl, 3-phenoxyphenyl, 3-thiomethoxyphenyl, 3-methylphenyl, 3-trifluoromethylphenyl, 2,3-dichlorophenyl, 2,3-difluorophenyl, 2,4-dichlorophenyl, 2,5-dimethoxyphenyl, 3,4-dichlorophenyl, 3,4-difluorophenyl, 3,4-methylenedioxyphenyl, 3,4-dimethoxyphenyl, 3,5-difluorophenyl, 3,5-dichlorophenyl, 3,5-di(trifluoromethyl)phenyl, 3,5-dimethoxyphenyl, 2,4-dichlorophenyl, 2,4-difluorophenyl, 2,6-difluorophenyl, 3,4,5-trifluorophenyl, 3,4,5-trimethoxyphenyl, 3,4,5-tri(trifluoromethyl)phenyl, 2,4,6-trifluorophenyl, 2,4,6-trimethylphenyl, 2,4,6-tri(trifluoromethyl)phenyl, 2,3,5-trifluorophenyl, 2,4,5-trifluorophenyl, 2,5-difluorophenyl, 2-fluoro-3-trifluoromethylphenyl, 4-fluoro-2-trifluoromethylphenyl, 2-fluoro-4-trifluoromethylphenyl, 4-benzyloxyphenyl, 2-chloro-6-fluorophenyl, 2-fluoro-6-chlorophenyl, 2,3,4,5,6-pentafluorophenyl, 2,5-dimethylphenyl, 4-phenylphenyl and 2-fluoro-3-trifluoromethylphenyl.

Preferred R¹ alkaryl groups in formula III and IV include, by way of example, benzyl, 2-phenylethyl, 3-phenyl-*n*-propyl, and the like.

Preferred R¹ alkyl, substituted alkyl, alkenyl, cycloalkyl and
5 cycloalkenyl groups in formula III and IV include, by way of example,
iso-propyl, *n*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *t*-butyl, -CH₂CH=CH₂,
-CH₂CH=CH(CH₂)₄CH₃, cyclopropyl, cyclobutyl, cyclohexyl, cyclopentyl,
cyclohex-1-enyl, -CH₂-cyclopropyl, -CH₂-cyclobutyl, -CH₂-cyclohexyl,
-CH₂-cyclopentyl, -CH₂CH₂-cyclopropyl, -CH₂CH₂-cyclobutyl, -CH₂CH₂-
10 cyclohexyl, -CH₂CH₂-cyclopentyl, and the like.

Preferred R¹ heteroaryls and substituted heteroaryls in formula III and
IV include, by way of example, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl,
fluoropyridyls (including 5-fluoropyrid-3-yl), chloropyridyls (including 5-
15 chloropyrid-3-yl), thiophen-2-yl, thiophen-3-yl, benzothiazol-4-yl,
2-phenylbenzoxazol-5-yl, furan-2-yl, benzofuran-2-yl, thionaphthen-2-yl,
2-chlorothiophen-5-yl, 3-methylisoxazol-5-yl, 2-(thiophenyl)thiophen-5-yl,
6-methoxythionaphthen-2-yl, 3-phenyl-1,2,4-thioxadiazol-5-yl, 2-phenyloxazol-
4-yl, and the like.

20
Preferably, in formula III and IV, R² is selected from the group
consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl and
heterocyclic. Particularly preferred R² substituents include, by way of example,
methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, phenyl,
25 benzyl, cyclohexyl, cyclopentyl, cycloheptyl, -CH₂CH₂SCH₃, and the like. As
noted below, R² (as well as R⁶) are preferably the side chain of an L-amino
acid.

Preferred R⁶ substituents in formula III and IV include, for example,
30 hydrogen, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl,

- $tert$ -butyl, $-CH_2CH(CH_2CH_3)_2$, 2-methyl- n -butyl, 6-fluoro- n -hexyl, phenyl,
 benzyl, cyclohexyl, cyclopentyl, cycloheptyl, allyl, iso -but-2-enyl,
 3-methylpentyl, $-CH_2$ -cyclopropyl, $-CH_2$ -cyclohexyl, $-CH_2CH_2$ -cyclopropyl,
 $-CH_2CH_2$ -cyclohexyl, $-CH_2$ -indol-3-yl, p -(phenyl)phenyl, o -fluorophenyl,
 5 m -fluorophenyl, p -fluorophenyl, m -methoxyphenyl, p -methoxyphenyl,
 phenethyl, benzyl, m -hydroxybenzyl, p -hydroxybenzyl, p -nitrobenzyl,
 m -trifluoromethylphenyl, p -(CH_3)₂NCH₂CH₂CH₂O-benzyl,
 p -(CH_3)₃COC(O)CH₂O-benzyl, p -(HOOCCH₂O)-benzyl, 2-aminopyrid-6-yl,
 p -(N -morpholino-CH₂CH₂O)-benzyl, $-CH_2CH_2C(O)NH_2$, $-CH_2$ -imidazol-4-yl,
 10 $-CH_2$ -(3-tetrahydrofuranyl), $-CH_2$ -thiophen-2-yl, $-CH_2$ -(1-methyl)cyclopropyl,
 $-CH_2$ -thiophen-3-yl, thiophen-3-yl, thiophen-2-yl, $-CH_2$ -C(O)O- t -butyl,
 $-CH_2$ -C(CH_3)₃, $-CH_2CH(CH_2CH_3)_2$, 2-methylcyclopentyl, cyclohex-2-enyl,
 $-CH[CH(CH_3)_2]COOCH_3$, $-CH_2CH_2N(CH_3)_2$, $-CH_2C(CH_3)=CH_2$,
 $-CH_2CH=CHCH_3$ (cis and trans), $-CH_2OH$, $-CH(OH)CH_3$, $-CH(O-t-butyl)CH_3$,
 15 $-CH_2OCH_3$, $-(CH_2)_4NH$ -Boc, $-(CH_2)_4NH_2$, $-CH_2$ -pyridyl (e.g., 2-pyridyl,
 3-pyridyl and 4-pyridyl), pyridyl (2-pyridyl, 3-pyridyl and 4-pyridyl),
 $-CH_2$ -naphthyl (e.g., 1-naphthyl and 2-naphthyl), $-CH_2$ -(N -morpholino),
 p -(N -morpholino-CH₂CH₂O)-benzyl, benzo[b]thiophen-2-yl,
 5-chlorobenzo[b]thiophen-2-yl, 4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl,
 20 benzo[b]thiophen-3-yl, 5-chlorobenzo[b]thiophen-3-yl, benzo[b]thiophen-5-yl,
 6-methoxynaphth-2-yl, $-CH_2CH_2SCH_3$, thien-2-yl, thien-3-yl, and the like.

- Preferably Y in Formula III or IV is hydroxy, alkoxy, substituted alkoxy
 and $-NR'R''$ where R' and R'' are as defined above. Preferred alkoxy and
 25 substituted alkoxy groups include methoxy, ethoxy, n -propoxy, iso -propoxy,
 n -butoxy, iso -butoxy, t -butoxy, neo -pentoxy, benzyloxy, 2-phenylethoxy, 3-
 phenyl- n -propoxy, 3-iodo- n -propoxy, 4-bromo- n -butoxy, and the like.
 Preferred $-NR'R''$ groups include, by way of example, amino ($-NH_2$),
 $-NH(iso-butyl)$, $-NH(sec-butyl)$, N -methylamino, N,N -dimethylamino,
 30 N -benzylamino, N -morpholino, azetidino, N -thiomorpholino, N -piperidinyl,
 N -hexamethyleneimino, N -heptamethylene-imino, N -pyrrolidinyl,

-NH-methallyl, -NHCH₂-(furan-2-yl), -NHCH₂-cyclopropyl, -NH(*t*-butyl),
 -NH(*p*-methylphenyl), -NHCH₂-(*p*-fluorophenyl), -NHCH₂CH₂OCH₃,
 -NH-cyclohexyl, -NHCH₂CH₂N(CH₃)₂, -NHCH₂C(CH₃)₃, -NHCH₂-(pyrid-2-yl),
 -NHCH₂-(pyrid-3-yl), -NHCH₂-(pyrid-4-yl), N-thiazolindinyl,
 5 -N(CH₂CH₂CH₃)₂, -NHOH, -NH(*p*-NO₂-φ), -NHCH₂(*p*-NO₂-φ),
 -NHCH₂(*m*-NO₂-φ), -N(CH₃)OCH₃, -N(CH₃)CH₂-φ, -NHCH₂-(3,5-di-
 fluorophenyl), -NHCH₂CH₂F, -NHCH₂(*p*-CH₃O-φ), -NHCH₂(*m*-CH₃O-φ),
 -NHCH₂(*p*-CF₃-φ), -N(CH₃)CH₂CH₂OCH₃, -NHCH₂CH₂φ, -NHCH(CH₃)φ,
 -NHCH₂-(*p*-F-φ), -N(CH₃)CH₂CH₂N(CH₃)₂, -NHCH₂-(tetrahydrofuran-2-yl),
 10 and the like.

Still another preferred Y group is an alkyl group such as
 -CH₂CH₂CH(CH₃)₂, and the like.

15 Preferred heterocyclic structures defined by W and X include, by way of
 example, 4,5-dihydrothiazoles, 3,4-dihydro-1,3-isodiazoles, 3,4-dihydro-3-N-t-
 butoxy-3-isodiazoles, 4,5-dihydrooxazoles, and the like.

Preferred compounds of formula III and IV include the following:

- 20 (S)-2-[1-(3,5-difluorophenylacetamido)ethyl]-4-ethoxycarbonyl-2-
 thiazoline
- 25 1-*tert*-butoxycarbonyl-2-[1-(*N*-carbobenzyloxy)aminoethyl]-4-
 methoxycarbonyl-4-phenylmethyl-2-imidazoline
- 1-*tert*-butoxycarbonyl-2-[1-(3,5-difluorophenylacetamido)ethyl]-4-
 methoxycarbonyl-4-phenylmethyl-2-imidazoline
- 30 2-[1-(3,5-difluorophenylacetamido)ethyl]-4-methoxycarbonyl-4-
 phenylmethyl-2-imidazoline
- 2-[1-(3,5-difluorophenylacetamido)ethyl]-4-methoxycarbonyl-4-phenyl-2-
 imidazoline
- 35 2-[1-(3,5-difluorophenylacetamido)-1-phenyl]methyl-4-ethoxycarbonyl-2-
 thiazoline

-- 22 --

1-*tert*-butoxycarbonyl-2-[1-(*N*-carbobenzyloxy)aminoethyl]-4-methoxycarbonyl-4-phenyl-2-imidazoline

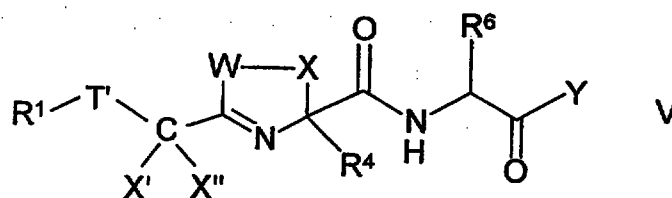
2-[(*S*)-1-(3,5-dichloroanilino)ethyl]-(*S*)-4-methoxycarbonyl-2-oxazolidine

(*S*)-2-[1-(3,5-difluorophenylacetamido)ethyl]-5(*R,S*)-ethoxycarbonyl-2-oxazoline

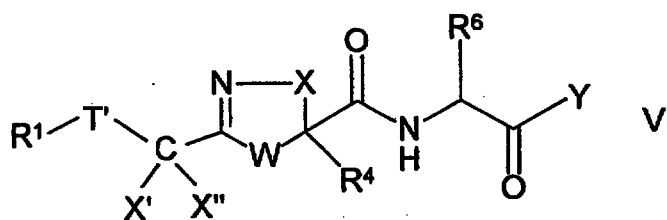
2-[1-(3,5-difluorophenylacetamido)-1-phenyl]methyl-4-methoxycarbonyl-2-thiazoline

[1-(*N*-carbobenzyloxy)aminoethyl]-4-methoxycarbonyl-4-phenyl-2-imidazoline

In another preferred embodiment, the compounds of formula I are further characterized by formula V and VI below:



and



where R^1 , R^4 , R^6 , T' , X' , X'' , W , X , and Y are as defined above.

In formula V and VI above, when m is one, Z is preferably - $CX'X''C(O)$ - where X'' is preferably hydrogen, X' is preferably hydrogen or fluoro or where X' and X'' form an oxo group.

In formula V and VI above, preferred R¹ unsubstituted aryl groups include, for example, phenyl, 1-naphthyl, 2-naphthyl, and the like.

5 Preferred R¹ substituted aryl groups in formula V and VI include, for example, monosubstituted phenyls (preferably 3 or 5 substituents); disubstituted phenyls (preferably 3,5 substituents); and trisubstituted phenyls (preferably 3,4,5 substituents). Preferably, the substituted phenyl groups do not include more than 3 substituents.

10 Examples of substituted R¹ phenyls preferred in formula IV and VI include, for instance, 2-chlorophenyl, 2-fluorophenyl, 2-bromophenyl, 2-hydroxyphenyl, 2-nitrophenyl, 2-methylphenyl, 2-methoxyphenyl, 2-phenoxyphenyl, 2-trifluoromethylphenyl, 4-fluorophenyl, 4-chlorophenyl, 4-bromophenyl, 4-nitrophenyl, 4-methylphenyl, 4-hydroxyphenyl, 15 4-methoxyphenyl, 4-ethoxyphenyl, 4-butoxyphenyl, 4-*iso*-propylphenyl, 4-phenoxyphenyl, 4-trifluoromethylphenyl, 4-hydroxymethylphenyl, 3-methoxyphenyl, 3-hydroxyphenyl, 3-nitrophenyl, 3-fluorophenyl, 3-chlorophenyl, 3-bromophenyl, 3-phenoxyphenyl, 3-thiomethoxyphenyl, 3-methylphenyl, 3-trifluoromethylphenyl, 2,3-dichlorophenyl, 20 2,3-difluorophenyl, 2,4-dichlorophenyl, 2,5-dimethoxyphenyl, 3,4-dichlorophenyl, 3,4-difluorophenyl, 3,4-methylenedioxyphenyl, 3,4-dimethoxyphenyl, 3,5-difluorophenyl, 3,5-dichlorophenyl, 3,5-di-(trifluoromethyl)phenyl, 3,5-dimethoxyphenyl, 2,4-dichlorophenyl, 2,4-difluorophenyl, 2,6-difluorophenyl, 3,4,5-trifluorophenyl, 25 3,4,5-trimethoxyphenyl, 3,4,5-tri-(trifluoromethyl)phenyl, 2,4,6-trifluorophenyl, 2,4,6-trimethylphenyl, 2,4,6-tri-(trifluoromethyl)phenyl, 2,3,5-trifluorophenyl, 2,4,5-trifluorophenyl, 2,5-difluorophenyl, 2-fluoro-3-trifluoromethylphenyl, 4-fluoro-2-trifluoromethylphenyl, 2-fluoro-4-trifluoromethylphenyl, 4-benzyloxyphenyl, 2-chloro-6-fluorophenyl, 2-fluoro-6-chlorophenyl, 30 2,3,4,5,6-pentafluorophenyl, 2,5-dimethylphenyl, 4-phenylphenyl and 2-fluoro-3-trifluoromethylphenyl.

Preferred R¹ alkaryl groups in formula IV and VI include, by way of example, benzyl, 2-phenylethyl, 3-phenyl-*n*-propyl, and the like.

Preferred R¹ alkyl, substituted alkyl, alkenyl, cycloalkyl and
5 cycloalkenyl groups in formula V and VI include, by way of example,
iso-propyl, *n*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *t*-butyl, -CH₂CH=CH₂,
-CH₂CH=CH(CH₂)₄CH₃, cyclopropyl, cyclobutyl, cyclohexyl, cyclopentyl,
cyclohex-1-enyl, -CH₂-cyclopropyl, -CH₂-cyclobutyl, -CH₂-cyclohexyl,
-CH₂-cyclopentyl, -CH₂CH₂-cyclopropyl, -CH₂CH₂-cyclobutyl, -CH₂CH₂-
10 cyclohexyl, -CH₂CH₂-cyclopentyl, and the like.

Preferred R¹ heteroaryls and substituted heteroaryls in formula III and
IV include, by way of example, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl,
fluoropyridyls (including 5-fluoropyrid-3-yl), chloropyridyls (including 5-
15 chloropyrid-3-yl), thiophen-2-yl, thiophen-3-yl, benzothiazol-4-yl,
2-phenylbenzoxazol-5-yl, furan-2-yl, benzofuran-2-yl, thionaphthen-2-yl,
2-chlorothiophen-5-yl, 3-methylisoxazol-5-yl, 2-(thiophenyl)thiophen-5-yl,
6-methoxythionaphthen-2-yl, 3-phenyl-1,2,4-thioxadiazol-5-yl, 2-phenyloxazol-
4-yl, and the like.

20

Preferred R⁴ substituents in formula III and IV include, for example,
hydrogen, methyl, phenyl, benzyl and the like.

Preferred R⁶ substituents in formula V and VI include, for example,
25 hydrogen, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl,
tert-butyl, -CH₂CH(CH₂CH₃)₂, 2-methyl-*n*-butyl, 6-fluoro-*n*-hexyl, phenyl,
benzyl, cyclohexyl, cyclopentyl, cycloheptyl, allyl, *iso*-but-2-enyl,
3-methylpentyl, -CH₂-cyclopropyl, -CH₂-cyclohexyl, -CH₂CH₂-cyclopropyl,
-CH₂CH₂-cyclohexyl, -CH₂-indol-3-yl, *p*-(phenyl)phenyl, *o*-fluorophenyl,
30 *m*-fluorophenyl, *p*-fluorophenyl, *m*-methoxyphenyl, *p*-methoxyphenyl,
phenethyl, benzyl, *m*-hydroxybenzyl, *p*-hydroxybenzyl, *p*-nitrobenzyl,

- m -trifluoromethylphenyl, p -(CH₃)₂NCH₂CH₂CH₂O-benzyl,
 p -(CH₃)₃COC(O)CH₂O-benzyl, p -(HOOCCH₂O)-benzyl, 2-aminopyrid-6-yl,
 p -(N-morpholino-CH₂CH₂O)-benzyl, -CH₂CH₂C(O)NH₂, -CH₂-imidazol-4-yl,
-CH₂-(3-tetrahydrofuranyl), -CH₂-thiophen-2-yl, -CH₂-(1-methyl)cyclopropyl,
5 -CH₂-thiophen-3-yl, thiophen-3-yl, thiophen-2-yl, -CH₂-C(O)O-*t*-butyl,
-CH₂-C(CH₃)₃, -CH₂CH(CH₂CH₃)₂, -2-methylcyclopentyl, -cyclohex-2-enyl,
-CH[CH(CH₃)₂]COOCH₃, -CH₂CH₂N(CH₃)₂, -CH₂C(CH₃)=CH₂,
-CH₂CH=CHCH₃ (cis and trans), -CH₂OH, -CH(OH)CH₃, -CH(O-*t*-butyl)CH₃,
-CH₂OCH₃, -(CH₂)₄NH-Boc, -(CH₂)₄NH₂, -CH₂-pyridyl (e.g., 2-pyridyl,
10 3-pyridyl and 4-pyridyl), pyridyl (2-pyridyl, 3-pyridyl and 4-pyridyl),
-CH₂-naphthyl (e.g., 1-naphthyl and 2-naphthyl), -CH₂-(N-morpholino),
 p -(N-morpholino-CH₂CH₂O)-benzyl, benzo[b]thiophen-2-yl,
5-chlorobenzo[b]thiophen-2-yl, 4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl,
benzo[b]thiophen-3-yl, 5-chlorobenzo[b]thiophen-3-yl, benzo[b]thiophen-5-yl,
15 6-methoxynaphth-2-yl, -CH₂CH₂SCH₃, thien-2-yl, thien-3-yl, and the like.

- Preferably Y in Formula V or VI is hydroxy, alkoxy, substituted alkoxy
and -NR'R'' where R' and R'' are as defined above. Preferred alkoxy and
substituted alkoxy groups include methoxy, ethoxy, *n*-propoxy, *iso*-propoxy,
20 *n*-butoxy, *iso*-butoxy, *t*-butoxy, *neo*-pentoxy, benzyloxy, 2-phenylethoxy, 3-
phenyl-*n*-propoxy, 3-iodo-*n*-propoxy, 4-bromo-*n*-butoxy, and the like.
Preferred -NR'R'' groups include, by way of example, amino (-NH₂),
-NH(*iso*-butyl), -NH(*sec*-butyl), N-methylamino, N,N-dimethylamino,
N-benzylamino, N-morpholino, azetidino, N-thiomorpholino, N-piperidinyl,
25 N-hexamethyleneimino, N-heptamethylene-imino, N-pyrrolidinyl,
-NH-methallyl, -NHCH₂-(furan-2-yl), -NHCH₂-cyclopropyl, -NH(*t*-butyl),
-NH(*p*-methylphenyl), -NHCH₂-(*p*-fluorophenyl), -NHCH₂CH₂OCH₃,
-NH-cyclohexyl, -NHCH₂CH₂N(CH₃)₂, -NHCH₂C(CH₃)₃, -NHCH₂-(pyrid-2-yl),
-NHCH₂-(pyrid-3-yl), -NHCH₂-(pyrid-4-yl), N-thiazolindinyl,
30 -N(CH₂CH₂CH₃)₂, -NHOH, -NH(*p*-NO₂-φ), -NHCH₂(*p*-NO₂-φ),

-- 26 --

-NHCH₂(*m*-NO₂-φ), -N(CH₃)OCH₃, -N(CH₃)CH₂-φ, -NHCH₂-(3,5-di-fluorophenyl), -NHCH₂CH₂F, -NHCH₂(*p*-CH₃O-φ), -NHCH₂(*m*-CH₃O-φ), -NHCH₂(*p*-CF₃-φ), -N(CH₃)CH₂CH₂OCH₃, -NHCH₂CH₂φ, -NHCH(CH₃)φ, -NHCH₂-(*p*-F-φ), -N(CH₃)CH₂CH₂N(CH₃)₂, -NHCH₂-(tetrahydrofuran-2-yl), and the like.

Still another preferred Y group is an alkyl group such as -CH₂CH₂CH(CH₃)₂, and the like.

Preferred heterocyclic structures defined by W and X include, by way of example, 4-methylthiazolin-4-yl.

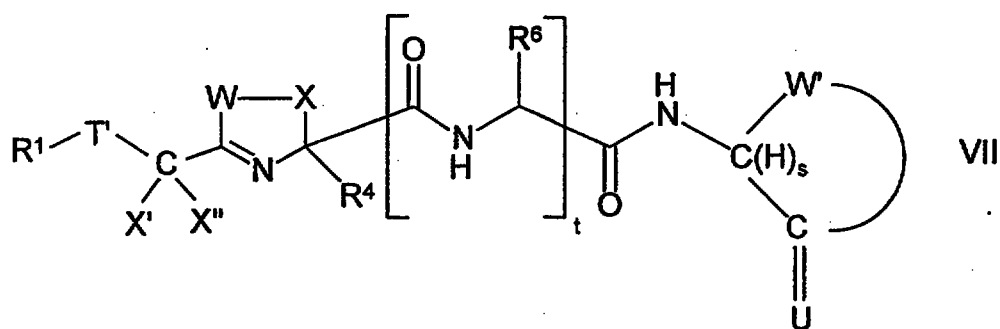
Preferred compounds of formula V and VI include the following:

(4R)-4-[N-(1S)-(1-methoxycarbonyl-1-phenyl)methyl]carbamoyl-2-(3,5-difluorophenylmethyl)-4-methyl-2-thiazoline

4-[N-(S)-(1-methoxycarbonyl-1-phenyl)methyl]carbamoyl-2-(3,5-difluorophenylmethyl)-2-thiazoline

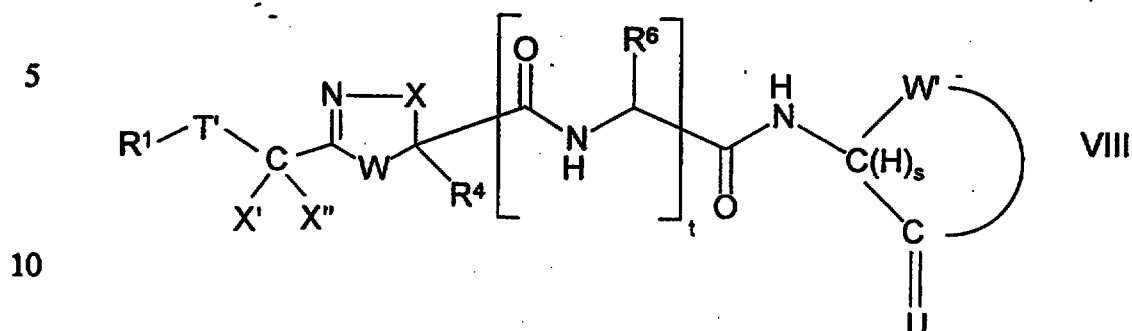
4-[N-(S)-(1-methoxycarbonyl-1-phenyl)methyl]carbamoyl-2-(3,5-difluorophenylmethyl)-4-methyl-2-imidazoline

Yet another preferred compound of this invention includes lactams and related compounds of formula VII and VIII



-- 27 --

and



15 wherein R^1 , R^4 , R^6 , T' , X' , X'' , W and X are as defined above;

W' , together with $-C(H)_sC(=U)-$, forms a cycloalkyl, cycloalkenyl, heterocyclic, substituted cycloalkyl, or substituted cycloalkenyl group wherein each of said cycloalkyl, cycloalkenyl, heterocyclic, substituted cycloalkyl or substituted cycloalkenyl group is optionally fused to form a bi- or multi-fused ring system (preferably no more than 5 fused rings) with one or more ring structures selected from the group consisting of cycloalkyl, cycloalkenyl, heterocyclic, aryl and heteroaryl group which, in turn, each of such ring structures is optionally substituted with 1 to 4 substituents selected from the group consisting of hydroxyl, halo, alkoxy, substituted alkoxy, thioalkoxy, substituted thioalkoxy, aryl, heteroaryl, heterocyclic, nitro, cyano, carboxyl, carboxyl esters, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, amino, N-alkylamino, N,N-dialkylamino, N-substituted alkylamino, N-alkyl N-substituted alkylamino, N,N-disubstituted alkylamino, $-NHC(O)R^{10}$, $-NH SO_2 R^{10}$, $-C(O)NH_2$, $-C(O)NHR^{10}$, $-C(O)NR^{10}R^{10}$, $-S(O)R^{10}$, $-S(O)_2R^{10}$, $-S(O)_2NHR^{10}$ and $-S(O)_2NR^{10}R^{10}$ where each R^{10} is independently selected from the group consisting of alkyl, substituted alkyl, or aryl;

20

25

30

U is selected from the group consisting of oxo ($=O$), thiooxo ($=S$), hydroxyl ($-H$, $-OH$), thiol (H , $-SH$) and hydro (H , H);

s is an integer equal to 0 or 1; and

35 t is an integer equal to 0 or 1.

In formula VII and VIII above, X" is preferably hydrogen, X' is preferably hydrogen or fluoro or X' and X" form an oxo group, and T' is preferably a covalent bond linking R¹ to -CX'X"-.

- 5 In formula VII and VIII above, preferred R¹ unsubstituted aryl groups include, for example, phenyl, 1-naphthyl, 2-naphthyl, and the like.

10 Preferred R¹ substituted aryl groups in formula VII and VIII include, for example, monosubstituted phenyls (preferably 3 or 5 substituents); disubstituted phenyls (preferably 3,5 substituents); and trisubstituted phenyls (preferably 3,4,5 substituents). Preferably, the substituted phenyl groups do not include more than 3 substituents.

15 Examples of substituted R¹ phenyls preferred in formula VII and VIII include 2-chlorophenyl, 2-fluorophenyl, 2-bromophenyl, 2-hydroxyphenyl, 2-nitrophenyl, 2-methylphenyl, 2-methoxyphenyl, 2-phenoxyphenyl, 2-trifluoromethylphenyl, 4-fluorophenyl, 4-chlorophenyl, 4-bromophenyl, 4-nitrophenyl, 4-methylphenyl, 4-hydroxyphenyl, 4-methoxyphenyl, 4-ethoxyphenyl, 4-butoxyphenyl, 4-*iso*-propylphenyl, 20 4-phenoxyphenyl, 4-trifluoromethylphenyl, 4-hydroxymethylphenyl, 3-methoxyphenyl, 3-hydroxyphenyl, 3-nitrophenyl, 3-fluorophenyl, 3-chlorophenyl, 3-bromophenyl, 3-phenoxyphenyl, 3-thiomethoxyphenyl, 3-methylphenyl, 3-trifluoromethylphenyl, 2,3-dichlorophenyl, 2,3-difluorophenyl, 2,4-dichlorophenyl, 2,5-dimethoxyphenyl, 25 3,4-dichlorophenyl, 3,4-difluorophenyl, 3,4-methylenedioxyphenyl, 3,4-dimethoxyphenyl, 3,5-difluorophenyl, 3,5-dichlorophenyl, 3,5-di-(trifluoromethyl)phenyl, 3,5-dimethoxyphenyl, 2,4-dichlorophenyl, 2,4-difluorophenyl, 2,6-difluorophenyl, 3,4,5-trifluorophenyl, 3,4,5-trimethoxyphenyl, 3,4,5-tri-(trifluoromethyl)phenyl, 2,4,6-trifluorophenyl, 30 2,4,6-trimethylphenyl, 2,4,6-tri-(trifluoromethyl)phenyl, 2,3,5-trifluorophenyl, 2,4,5-trifluorophenyl, 2,5-difluorophenyl, 2-fluoro-3-trifluoromethylphenyl,

4-fluoro-2-trifluoromethylphenyl, 2-fluoro-4-trifluoromethylphenyl, 4-benzyloxyphenyl, 2-chloro-6-fluorophenyl, 2-fluoro-6-chlorophenyl, 2,3,4,5,6-pentafluorophenyl, 2,5-dimethylphenyl, 4-phenylphenyl and 2-fluoro-3-trifluoromethylphenyl.

5

Preferred R¹ alkaryl groups in formula VII and VIII include, by way of example, benzyl, 2-phenylethyl, 3-phenyl-*n*-propyl, and the like.

10

Preferred R¹ alkyl, substituted alkyl, alkenyl, cycloalkyl and cycloalkenyl groups in formula VII and VIII include, by way of example, *iso*-propyl, *n*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *t*-butyl, -CH₂CH=CH₂, -CH₂CH=CH(CH₂)₄CH₃, cyclopropyl, cyclobutyl, cyclohexyl, cyclopentyl, cyclohex-1-enyl, -CH₂-cyclopropyl, -CH₂-cyclobutyl, -CH₂-cyclohexyl, -CH₂-cyclopentyl, -CH₂CH₂-cyclopropyl, -CH₂CH₂-cyclobutyl, -CH₂CH₂-cyclohexyl, -CH₂CH₂-cyclopentyl, and the like.

15

Preferred R¹ heteroaryls and substituted heteroaryls in formula VII and VIII include, by way of example, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, fluoropyridyls (including 5-fluoropyrid-3-yl), chloropyridyls (including 5-chloropyrid-3-yl), thiophen-2-yl, thiophen-3-yl, benzothiazol-4-yl, 2-phenylbenzoxazol-5-yl, furan-2-yl, benzofuran-2-yl, thionaphthen-2-yl, 2-chlorothiophen-5-yl, 3-methylisoxazol-5-yl, 2-(thiophenyl)thiophen-5-yl, 6-methoxythionaphthen-2-yl, 3-phenyl-1,2,4-thioxadiazol-5-yl, 2-phenyloxazol-4-yl, and the like.

25

Preferred R⁴ substituents in formula VII and VIII include, for example, hydrogen, methyl, phenyl, benzyl and the like.

30

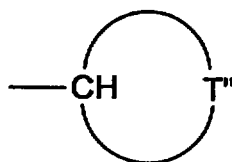
Preferred R⁶ substituents in formula VII and VIII include, for example, hydrogen, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl,

-- 30 --

- $tert$ -butyl, $-CH_2CH(CH_2CH_3)_2$, 2-methyl- n -butyl, 6-fluoro- n -hexyl, phenyl,
 benzyl, cyclohexyl, cyclopentyl, cycloheptyl, allyl, iso -but-2-enyl,
 3-methylpentyl, $-CH_2$ -cyclopropyl, $-CH_2$ -cyclohexyl, $-CH_2CH_2$ -cyclopropyl,
 $-CH_2CH_2$ -cyclohexyl, $-CH_2$ -indol-3-yl, p -(phenyl)phenyl, o -fluorophenyl,
 5 m -fluorophenyl, p -fluorophenyl, m -methoxyphenyl, p -methoxyphenyl,
 phenethyl, benzyl, m -hydroxybenzyl, p -hydroxybenzyl, p -nitrobenzyl,
 m -trifluoromethylphenyl, p -(CH_3)₂NCH₂CH₂CH₂O-benzyl,
 p -(CH_3)₃COC(O)CH₂O-benzyl, p -(HOOCCH₂O)-benzyl, 2-aminopyrid-6-yl,
 p -(N -morpholino-CH₂CH₂O)-benzyl, $-CH_2CH_2C(O)NH_2$, $-CH_2$ -imidazol-4-yl,
 10 $-CH_2$ -(3-tetrahydrofuranyl), $-CH_2$ -thiophen-2-yl, $-CH_2$ (1-methyl)cyclopropyl,
 $-CH_2$ -thiophen-3-yl, thiophen-3-yl, thiophen-2-yl, $-CH_2$ -C(O)O- t -butyl,
 $-CH_2$ -C(CH₃)₃, $-CH_2CH(CH_2CH_3)_2$, 2-methylcyclopentyl, cyclohex-2-enyl,
 $-CH[CH(CH_3)_2]COOCH_3$, $-CH_2CH_2N(CH_3)_2$, $-CH_2C(CH_3)=CH_2$,
 $-CH_2CH=CHCH_3$ (cis and trans), $-CH_2OH$, $-CH(OH)CH_3$, $-CH(O-t\text{-butyl})CH_3$,
 15 $-CH_2OCH_3$, $-(CH_2)_4NH$ -Boc, $-(CH_2)_4NH_2$, $-CH_2$ -pyridyl (e.g., 2-pyridyl,
 3-pyridyl and 4-pyridyl), pyridyl (2-pyridyl, 3-pyridyl and 4-pyridyl),
 $-CH_2$ -naphthyl (e.g., 1-naphthyl and 2-naphthyl), $-CH_2$ -(N -morpholino),
 p -(N -morpholino-CH₂CH₂O)-benzyl, benzo[b]thiophen-2-yl,
 5-chlorobenzo[b]thiophen-2-yl, 4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl,
 20 benzo[b]thiophen-3-yl, 5-chlorobenzo[b]thiophen-3-yl, benzo[b]thiophen-5-yl,
 6-methoxynaphth-2-yl, $-CH_2CH_2SCH_3$, thien-2-yl, thien-3-yl, and the like.

- Preferred cyclic groups defined by W' and $-C(H)_5C(=U)-$ include
 cycloalkyl, lactone, lactam, benzazepinone, dibenzazepinone and
 25 benzodiazepine groups. In one preferred embodiment, the cyclic group defined
 by W' and $-C(H)_5C(=U)-$, forms a cycloalkyl group of the formula:

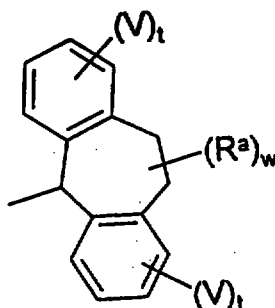
30



wherein T'' is selected from the group consisting of alkylene and substituted alkylene.

A preferred cycloalkyl group is represented by the formula:

5



10

wherein each V is independently selected from the group consisting of hydroxy, acyl, acyloxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, amino, aminoacyl, alkaryl, aryl, aryloxy, carboxyl, carboxylalkyl, cyano, halo, nitro, heteroaryl, thioalkoxy, substituted thioalkoxy, trihalomethyl and the like; R^a is selected from the group consisting of alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, carboxyl, carboxyl alkyl, cyano, halo, and the like; *t* is an integer from 0 to 4; and *w* is an integer from 0 to 3.

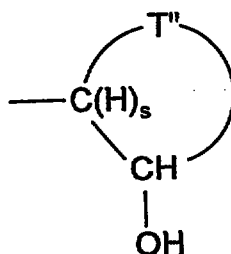
20

Preferably *t* is an integer from 0 to 2 and, more preferably, is an integer equal to 0 or 1.

25

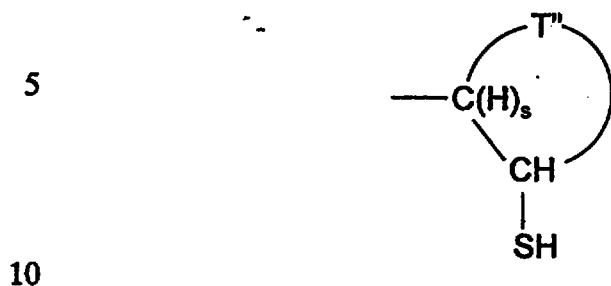
In another preferred embodiment, the cyclic group defined by W', together with -C(H)_sC(=U)- is a ring of the formula:

30



-- 32 --

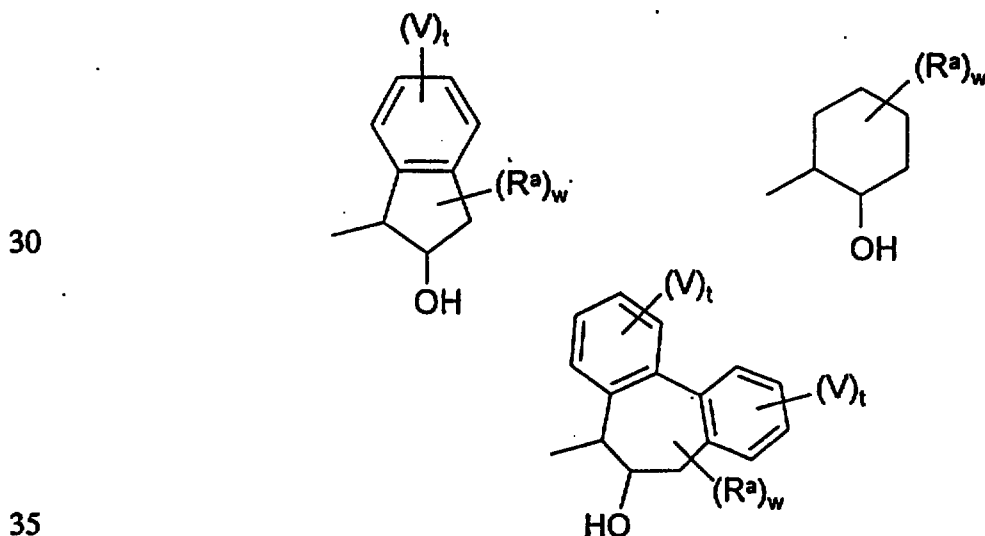
or



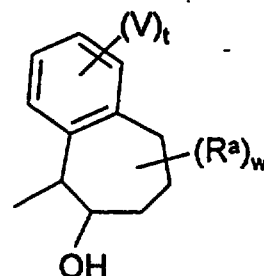
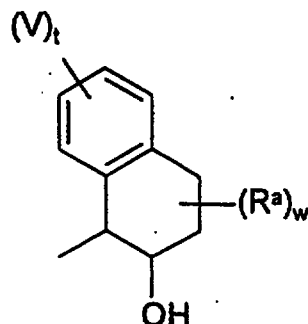
wherein s is zero or one, T'' is selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene, $-(R^{13}Z)_qR^{13}-$ and $-ZR^{13}-$,
 15 where Z is a substituent selected from the group consisting of $-O-$, $-S-$ and $>NR^{12}$, each R^{12} is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, aryl, heteroaryl and heterocyclic, each R^{13} is independently alkylene, substituted alkylene, alkenylene and substituted alkenylene with the
 20 proviso that when Z is $-O-$ or $-S-$, any unsaturation in the alkenylene and substituted alkenylene does not involve participation of the $-O-$ or $-S-$, and q is an integer of from 1 to 3.

Particularly preferred alcohol or thiol substituted groups include

25



5



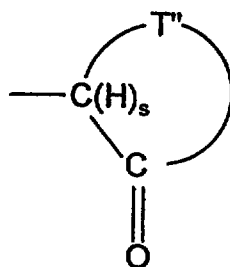
wherein each V is independently selected from the group consisting of hydroxy,
 10 acyl, acyloxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, alkenyl,
 substituted alkenyl, alkynyl, substituted alkynyl, amino, aminoacyl, alkaryl,
 aryl, aryloxy, carboxyl, carboxylalkyl, cyano, halo, nitro, heteroaryl,
 thioalkoxy, substituted thioalkoxy, trihalomethyl and the like; R^a is selected
 from the group consisting of alkyl, substituted alkyl, alkoxy, substituted alkoxy,
 15 amino, carboxyl, carboxyl alkyl, cyano, halo, and the like; t is an integer from
 0 to 4; and w is an integer from 0 to 3.

Preferably t is an integer from 0 to 2 and, more preferably, is an integer
 equal to 0 or 1.

20

Yet another preferred embodiment of the cyclic group defined by W' ,
 together with $-C(H)_sC(=U)-$, is a ring of the formula:

25

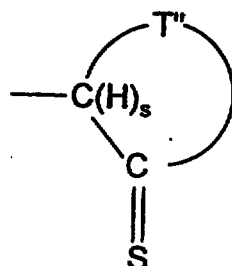


30

or

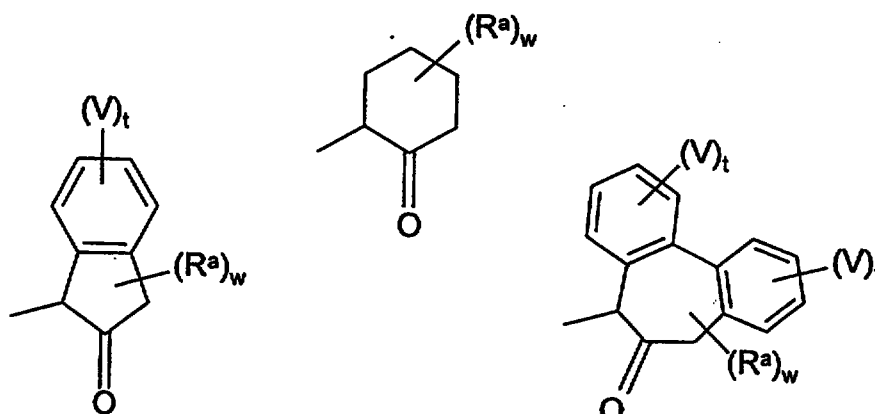
35

-- 34 --



wherein s is zero or one, T'' is selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene, $-(R^{13}Z)_qR^{13}-$ and $-ZR^{13}-$ where Z is a substituent selected from the group consisting of $-O-$, $-S-$ and $>NR^{12}$, each R^{12} is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, aryl, heteroaryl and heterocyclic, each R^{13} is independently alkylene, substituted alkylene, alkenylene and substituted alkenylene with the proviso that when Z is $-O-$ or $-S-$, any unsaturation in the alkenylene and substituted alkenylene does not involve participation of the $-O-$ or $-S-$, and q is an integer of from 1 to 3.

Particularly preferred cyclic ketone and thioketone groups include:

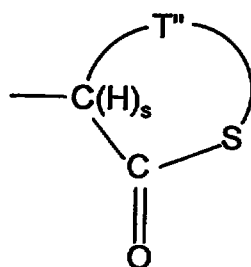
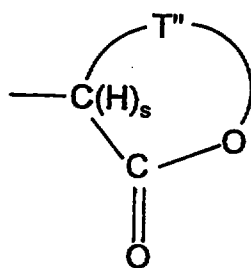


-- 35 --

wherein each V is independently selected from the group consisting of hydroxy, acyl, acyloxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, amino, aminoacyl, alkaryl, aryl, aryloxy, carboxyl, carboxylalkyl, cyano, halo, nitro, heteroaryl, thioalkoxy, substituted thioalkoxy, trihalomethyl and the like; R^a is selected from the group consisting of alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, carboxyl, carboxyl alkyl, cyano, halo, and the like; *t* is an integer from 0 to 4; and *w* is an integer from 0 to 3.

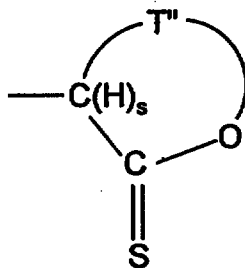
Preferably *t* is an integer from 0 to 2 and, more preferably, is an integer equal to 0 or 1.

In another preferred embodiment, the cyclic group defined by W', together with -C(H)_sC(=U)-, forms a ring of the formula:



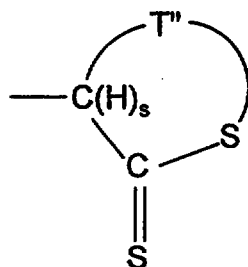
-- 36 --

5



10 or

15

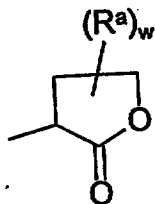


20

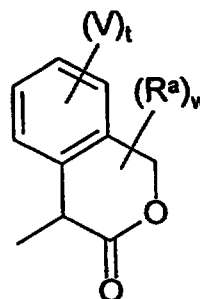
wherein s is zero or one, T'' is selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene, $-(R^{13}Z)_qR^{13}-$ and $-ZR^{13}-$ where Z is a substituent selected from the group consisting of $-O-$, $-S-$ and $>NR^{12}$, each R^{12} is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, aryl, heteroaryl and heterocyclic, each R^{13} is independently alkylene, substituted alkylene, alkenylene and substituted alkenylene with the proviso that when Z is $-O-$ or $-S-$, any unsaturation in the alkenylene and substituted alkenylene does not involve participation of the $-O-$ or $-S-$, and q is an integer of from 1 to 3.

Particularly preferred lactone and thiolactone groups include:

35



and

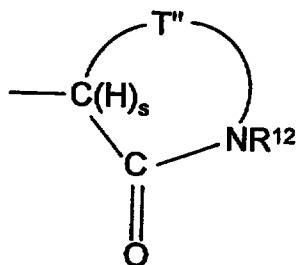


- 37 -

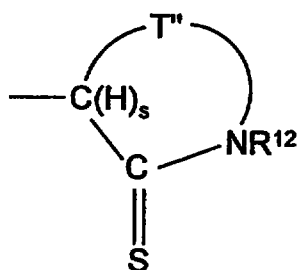
wherein each V is independently selected from the group consisting of hydroxy, acyl, acyloxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, amino, aminoacyl, alkaryl, aryl, aryloxy, carboxyl, carboxylalkyl, cyano, halo, nitro, heteroaryl, thioalkoxy, substituted thioalkoxy, trihalomethyl and the like; R^a is selected from the group consisting of alkyl, substituted alkyl, alkoxy, substituted alkoxy, amino, carboxyl, carboxyl alkyl, cyano, halo, and the like; t is an integer from 0 to 4; and w is an integer from 0 to 3.

Preferably t is an integer from 0 to 2 and, more preferably, is an integer equal to 0 or 1.

In another preferred embodiment, the cyclic group defined by W' and $-C(H)_sC(=O)-$, forms a lactam ring of the formula:



or a thiolactam ring of the formula:

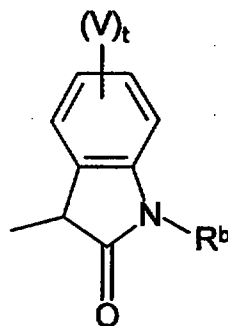
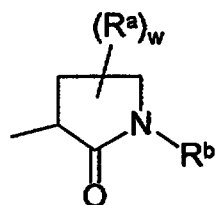


-- 38 --

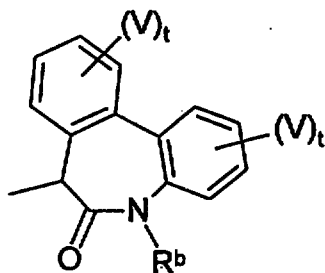
wherein s is zero or one, T'' is selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene, $-(R^{13}Z)_qR^{13}-$ and $-ZR^{13}-$ where Z is a substituent selected from the group consisting of $-O-$, $-S-$ and $>NR^{12}$, each R^{12} is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, aryl, heteroaryl and heterocyclic, each R^{13} is independently alkylene, substituted alkylene, alkenylene and substituted alkenylene with the proviso that when Z is $-O-$ or $-S-$, any unsaturation in the alkenylene and substituted alkenylene does not involve participation of the $-O-$ or $-S-$, and q is an integer of from 1 to 3.

Particularly preferred lactam and thiolactam groups include:

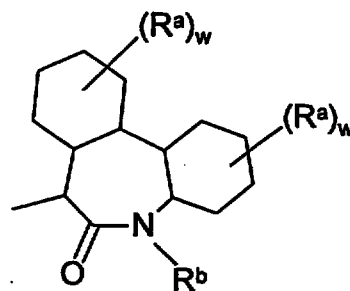
15



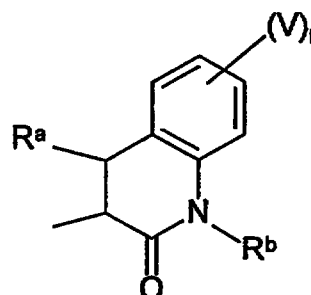
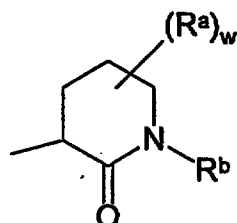
20



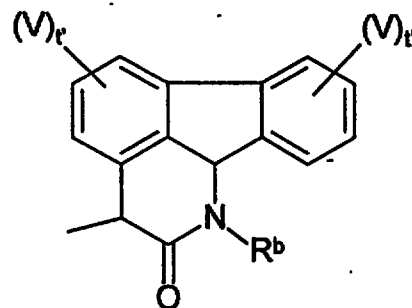
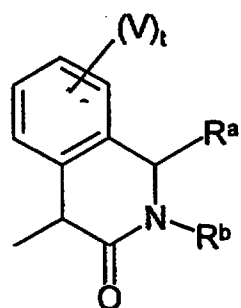
25



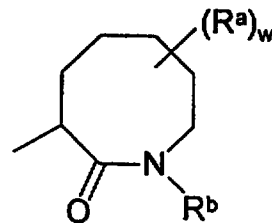
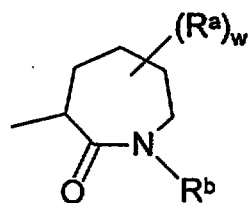
30



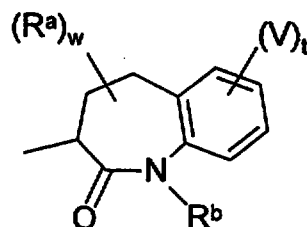
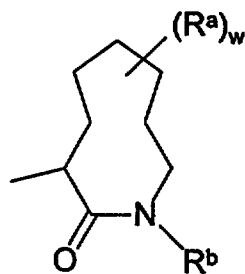
5



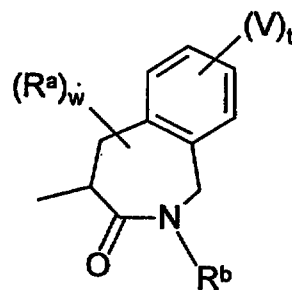
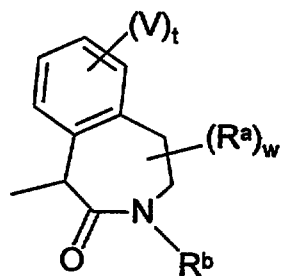
10



15

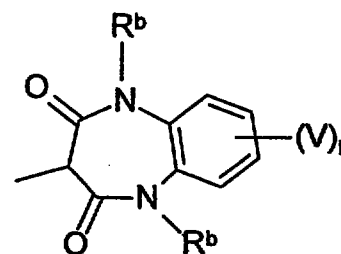
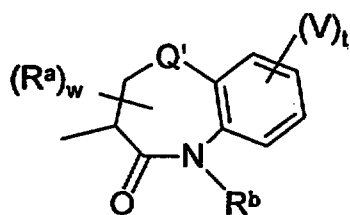


20



25

30

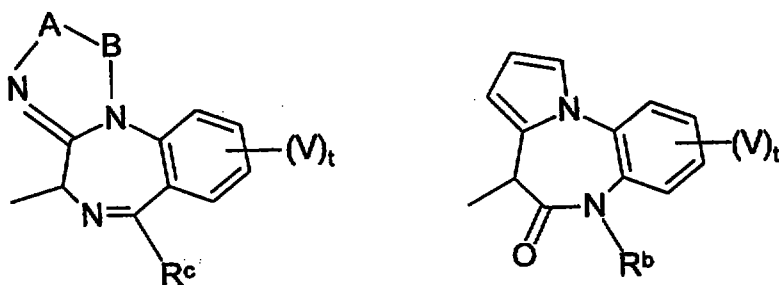
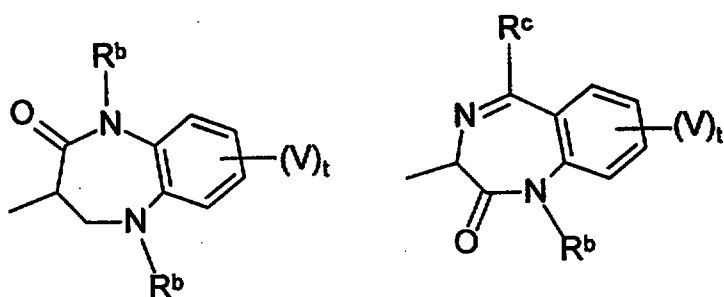


5

10

15

20



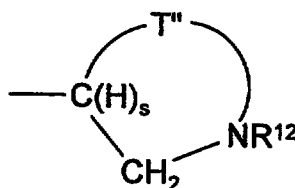
wherein A-B is selected from the group consisting of alkylene, alkenylene,
 25 substituted alkylene, substituted alkenylene and -N=CH-; Q' is oxygen or
 sulfur; each V is independently selected from the group consisting of hydroxy,
 acyl, acyloxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, alkenyl,
 substituted alkenyl, alkynyl, substituted alkynyl, amino, aminoacyl, alkaryl,
 aryl, aryloxy, carboxyl, carboxylalkyl, cyano, halo, nitro, heteroaryl,
 30 thioalkoxy, substituted thioalkoxy, trihalomethyl and the like; R^a is selected
 from the group consisting of alkyl, substituted alkyl, alkoxy, substituted alkoxy,

-- 41 --

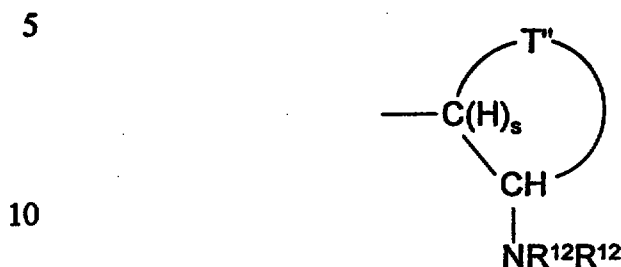
amino, carboxyl, carboxyl alkyl, cyano, halo, and the like; R^b is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, acyl, aryl, heteroaryl, heterocyclic, and the like; R^c is selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, aryl, heteroaryl, heterocyclic, cycloalkyl, and substituted cycloalkyl; t is an integer from 0 to 4; t' is an integer from 0 to 3; and w is an integer from 0 to 3.

Preferably t is an integer from 0 to 2 and, more preferably, is an integer equal to 0 or 1.

In another preferred embodiment, the cyclic group defined by W' , together with $-C(H)_sC(=U)-$, forms a ring of the formula:

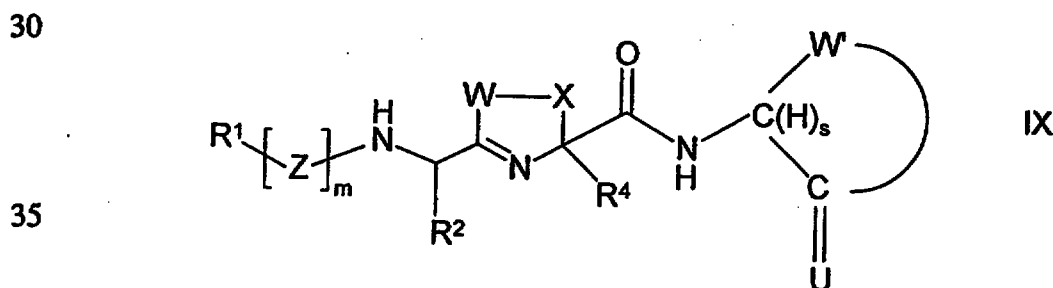


wherein s is zero or one, T'' is selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene, $-(R^{13}Z)_qR^{13}-$ and $-ZR^{13}-$ where Z is a substituent selected from the group consisting of $-O-$, $-S-$ and $>NR^{12}$, each R^{12} is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, aryl, heteroaryl and heterocyclic, each R^{13} is independently alkylene, substituted alkylene, alkenylene and substituted alkenylene with the proviso that when Z is $-O-$ or $-S-$, any unsaturation in the alkenylene and substituted alkenylene does not involve participation of the $-O-$ or $-S-$, and q is an integer of from 1 to 3.



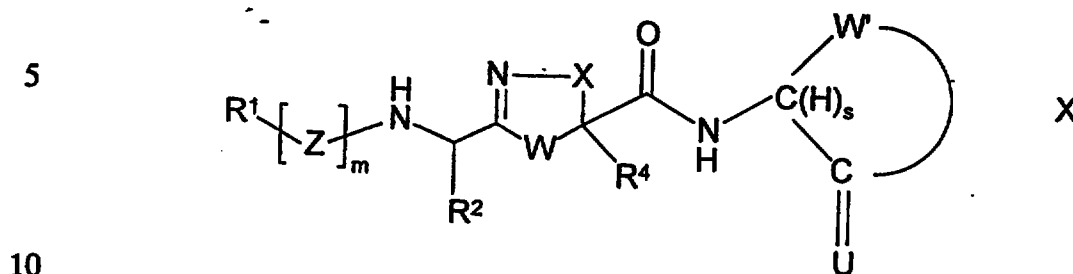
15 wherein s is zero or one, T'' is selected from the group consisting of alkylene, substituted alkylene, alkenylene, substituted alkenylene, $-(R^{13}Z)_qR^{13}-$ and $-ZR^{13}-$ where Z is a substituent selected from the group consisting of $-O-$, $-S-$ and $>NR^{12}$, each R^{12} is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, 20 substituted alkynyl, aryl, heteroaryl and heterocyclic, each R^{13} is independently alkylene, substituted alkylene, alkenylene and substituted alkenylene with the proviso that when Z is $-O-$ or $-S-$, any unsaturation in the alkenylene and substituted alkenylene does not involve participation of the $-O-$ or $-S-$, and q is an integer of from 1 to 3.

Yet another preferred compound of this invention includes lactams and related compounds of formula IX and X:



-- 43 --

and



wherein R^1 , R^2 , R^4 , Z , U , W , W' , X , m and s are as defined above.

Preferred R^1 , R^2 , R^4 , Z , W and W' are also as defined above.

In one of its method aspects, this invention is directed to a method for inhibiting β -amyloid peptide release and/or its synthesis in a cell which method comprises administering to such a cell an amount of a compound or a mixture of compounds of formula I, VII and VIII above effective in inhibiting the cellular release and/or synthesis of β -amyloid peptide.

Because the *in vivo* generation of β -amyloid peptide is associated with the pathogenesis of AD^{8,9}, the compounds of formula I, VII and VIII can also be employed in conjunction with a pharmaceutical composition to prophylactically and/or therapeutically prevent and/or treat AD. Accordingly, in another of its method aspects, this invention is directed to a prophylactic method for preventing the onset of AD in a patient at risk for developing AD which method comprises administering to said patient a pharmaceutical composition comprising a pharmaceutically inert carrier and an effective amount of a compound or a mixture of compounds of formula I, VII and VIII above.

In yet another of its method aspects, this invention is directed to a therapeutic method for treating a patient with AD in order to inhibit further deterioration in the condition of that patient which method comprises administering

-- 44 --

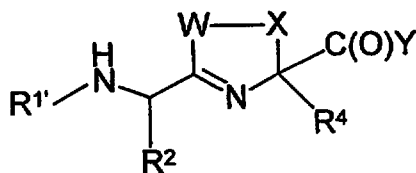
to said patient a pharmaceutical composition comprising a pharmaceutically inert carrier and an effective amount of a compound or a mixture of compounds of formula I, VII and VIII above.

5 This invention also provides for novel pharmaceutical compositions comprising a pharmaceutically inert carrier and a compound of the formula I, VII or VIII above.

10 Still further, this invention provides for novel compounds of formula I, VII or VIII.

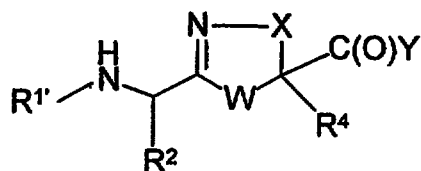
Further preferred compounds of formula I are represented in the following Tables I-IV which illustrate preferred subsets of these structures:

TABLE I



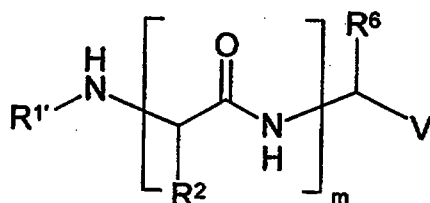
R ¹	R ²	R ⁴	Y	W	X
3,5-di-F- ϕ -CH ₂ C(O)-	-CH ₃	H	-OCH ₂ CH ₃	S	-CH ₂ -
ϕ -CH ₂ -OC(O)-	-CH ₃	-CH ₂ ϕ	-OCH ₃	-N- <i>t</i> -Boc	-CH ₂ -
3,5-di-F- ϕ -CH ₂ C(O)-	-CH ₃	-CH ₂ ϕ	-OCH ₃	-N- <i>t</i> -Boc	-CH ₂ -
3,5-di-F- ϕ -CH ₂ C(O)-	-CH ₃	-CH ₂ ϕ	-OCH ₃	NH	-CH ₂ -
ϕ -CH ₂ OC(O)-	-CH ₃	- ϕ	-OCH ₃	-N- <i>t</i> -Boc	-CH ₂ -
3,5-di-F- ϕ -CH ₂ C(O)-	-CH ₃	- ϕ	-OCH ₃	NH	-CH ₂ -
3,5-di-F- ϕ -CH ₂ C(O)-	-CH ₃	H	-OCH ₃	O	-CH ₂ -
3,5-di-Cl- ϕ -CH ₂ C(O)-	-CH ₃	H	-OCH ₃	O	-CH ₂ -
3,5-di-F- ϕ -CH ₂ C(O)-	- ϕ	H	-OCH ₃	S	-CH ₂ -

TABLE II



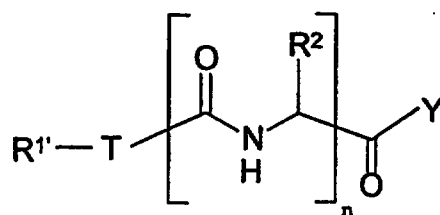
R ¹	R ²	R ⁴	Y	W	X
3,5-difluoro- ϕ -CH ₂ -C(O)-	-CH ₃	H	-OCH ₂ CH ₃	O	-CH ₂ -
3,5-difluoro- ϕ -CH ₂ -C(O)-	-CH ₃	-CH ₂ ϕ	-OCH ₃	NH	-CH ₂ -
3,5-difluoro- ϕ -CH ₂ -C(O)-	-CH ₃	- ϕ	-OCH ₃	NH	-CH ₂ -

TABLE III



R ^{1'}	R ²	m	R ⁶	V
3,5-di-F- ϕ -CH ₂ C(O)-	-CH ₃	1	-CH ₃	3-ethyl-1,2,4-oxadiazol-5-yl
3,5-di-F- ϕ -CH ₂ C(O)-	-CH ₃	1	-CH ₂ ϕ	3-methyl-1,2,4-oxadiazol-5-yl
3,5-di-F- ϕ -CH ₂ C(O)-	--	0	-CH ₃	1-(methylhexano-2-yl)-tetrazol-5-yl
3,5-di-F- ϕ -CH ₂ C(O)-	-CH ₃	1	- ϕ	thiazolin-2-yl
3,5-di-F- ϕ -CH ₂ C(O)-	-CH ₃	1	- ϕ	3-methyl-1,2,4-oxadiazol-5-yl
3,5-di-F- ϕ -CH ₂ C(O)-	-CH ₃	1	- ϕ	3-phenyl-1,2,4-oxadiazol-5-yl
3,5-di-F- ϕ -CH ₂ C(O)-	-CH ₃	1	- ϕ	3-(p-methoxy-benzyl)-1,2,4-oxadiazol-5-yl

TABLE IV



R ¹	T	n	R ²	Y
3,5-di-F-φ-CH ₂ -	2-R ¹ -thiazolin-4-yl	1	-φ	-OCH ₃
3,5-di-F-φ-CH ₂ -	2-R ¹ -4-methyl-thiazolin-4-yl	1	-φ	-OCH ₃
3,5-di-F-φ-CH ₂ -	2-R ¹ -4-methyl-imidazolin-4-yl	1	-φ	-OCH ₃

DETAILED DESCRIPTION OF THE INVENTION

As above, this invention relates to compounds which inhibit β -amyloid peptide release and/or its synthesis, and, accordingly, have utility in treating Alzheimer's disease. However, prior to describing this invention in further detail,
5 the following terms will first be defined.

Definitions

The term " β -amyloid peptide" refers to a 39-43 amino acid peptide having a molecular weight of about 4.2 kD, which peptide is substantially homologous to
10 the form of the protein described by Glenner, et al.¹ including mutations and post-translational modifications of the normal β -amyloid peptide. In whatever form, the β -amyloid peptide is an approximate 39-43 amino acid fragment of a large membrane-spanning glycoprotein, referred to as the β -amyloid precursor protein (APP). Its 43-amino acid sequence is:

15
1
Asp Ala Glu Phe Arg His Asp Ser Gly Tyr

20 11
Glu Val His His Gln Lys Leu Val Phe Phe

21
Ala Glu Asp Val Gly Ser Asn Lys Gly Ala

25 31
Ile Ile Gly Leu Met Val Gly Gly Val Val

30 41
Ile Ala Thr (SEQ ID NO: 1)

or a sequence which is substantially homologous thereto.

"Alkyl" refers to monovalent alkyl groups preferably having from 1 to 10
35 carbon atoms and more preferably 1 to 6 carbon atoms. This term is exemplified by groups such as methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *n*-hexyl, and the like.

-- 50 --

"Substituted alkyl" refers to an alkyl group, preferably of from 1 to 10 carbon atoms, having from 1 to 3 substituents selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, amino, aminoacyl, aminocarboxy esters, cyano, cycloalkyl, halogen, hydroxyl, carboxyl, carboxylalkyl, oxyacyl, oxyacylamino, thiol, thioalkoxy, substituted thioalkoxy, aryl, heteroaryl, heterocyclic, aryloxy, thioaryloxy, heteroaryloxy, thioheteroaryloxy, nitro, and mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-heteroarylamino, mono- and di-heterocyclic amino, and unsymmetric di-substituted amines having different substituents selected from alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic.

"Alkylene" refers to divalent alkylene groups preferably having from 1 to 10 carbon atoms and more preferably 1 to 6 carbon atoms. This term is exemplified by groups such as methylene ($-\text{CH}_2-$), ethylene ($-\text{CH}_2\text{CH}_2-$), the propylene isomers (e.g., $-\text{CH}_2\text{CH}_2\text{CH}_2-$ and $-\text{CH}(\text{CH}_3)\text{CH}_2-$), and the like.

"Alkaryl" refers to -alkylene-aryl groups preferably having from 1 to 10 carbon atoms in the alkylene moiety and from 6 to 10 carbon atoms in the aryl moiety. Such alkaryl groups are exemplified by benzyl, phenethyl and the like.

"Alkoxy" refers to the group "alkyl-O-". Preferred alkoxy groups include, by way of example, methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *tert*-butoxy, *sec*-butoxy, *n*-pentoxy, *n*-hexoxy, 1,2-dimethylbutoxy, and the like.

"Substituted alkoxy" refers to the group "substituted alkyl-O-" where substituted alkyl is as defined above.

"Alkenyl" refers to alkenyl groups preferably having from 2 to 10 carbon atoms and more preferably 2 to 6 carbon atoms and having at least 1 and

preferably from 1-2 sites of alkenyl unsaturation. Preferred alkenyl groups include ethenyl ($-\text{CH}=\text{CH}_2$), *n*-propenyl ($-\text{CH}_2\text{CH}=\text{CH}_2$), *iso*-propenyl ($-\text{C}(\text{CH}_3)=\text{CH}_2$), but-2-enyl ($-\text{CH}_2\text{CH}=\text{CHCH}_3$), and the like.

- 5 "Substituted alkenyl" refers to an alkenyl group as defined above having from 1 to 3 substituents selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, amino, aminoacyl, aminocarboxy esters, cyano, halogen, hydroxyl, carboxyl, carboxylalkyl, cycloalkyl, oxyacyl, oxyacylamino, thiol, thioalkoxy, substituted thioalkoxy, aryl, heteroaryl, heterocyclic, nitro, and mono-
10 and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-heteroarylamino, mono- and di-heterocyclic amino, and unsymmetric di-substituted amines having different substituents selected from alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic.
- 15 "Alkenylene" refers to divalent alkenylene groups preferably having from 2 to 8 carbon atoms and more preferably 2 to 6 carbon atoms. This term is exemplified by groups such as ethenylene ($-\text{CH}=\text{CH}-$), the propenylene isomers (e.g., $-\text{CH}_2\text{CH}=\text{CH}-$ and $-\text{C}(\text{CH}_3)=\text{CH}-$) and the like.
- 20 "Substituted alkenylene" refers to an alkenylene group, preferably of from 2 to 8 carbon atoms, having from 1 to 3 substituents selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, aminoacyl, aminoacyloxy, cyano, halogen, hydroxyl, carboxyl, carboxylalkyl, thiol, thioalkoxy, substituted thioalkoxy, aryl, heteroaryl, heterocyclic, nitro, and mono-
25 and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-heteroarylamino, mono- and di-heterocyclic amino, and unsymmetric di-substituted amines having different substituents selected from alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic. Additionally, such substituted alkylene groups include those where 2 substituents on the alkylene group are fused to form
30 one or more cycloalkyl, aryl, heterocyclic or heteroaryl groups fused to the alkylene group.

"Alkynyl" refers to alkynyl groups preferably having from 2 to 10 carbon atoms and more preferably 2 to 6 carbon atoms and having at least 1 and preferably from 1-2 sites of alkynyl unsaturation. Preferred alkynyl groups include ethynyl ($-C\equiv CH$), propargyl ($-CH_2C\equiv CH$) and the like.

5

"Substituted alkynyl" refers to an alkynyl group as defined above having from 1 to 3 substituents selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, amino, aminoacyl, aminocarboxy esters, cyano, halogen, hydroxyl, carboxyl, carboxylalkyl, cycloalkyl, oxyacyl, oxyacylamino, thiol, thioalkoxy, substituted thioalkoxy, aryl, heteroaryl, heterocyclic, nitro, and mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-heteroarylamino, mono- and di-heterocyclic amino, and unsymmetric di-substituted amines having different substituents selected from alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic.

10

"Acyl" refers to the groups alkyl-C(O)-, substituted alkyl-C(O)-, cycloalkyl-C(O)-, aryl-C(O)-, heteroaryl-C(O)- and heterocyclic-C(O)- where alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl and heterocyclic are as defined herein.

15

"Acylamino" refers to the group $-C(O)NRR$ where each R is independently hydrogen, alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclic and where each of alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl and heterocyclic are as defined herein.

20

"Aminoacyl" refers to the group $-NRC(O)R$ where each R is independently hydrogen, alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclic and where each of alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl and heterocyclic are as defined herein.

25

-- 53 --

"Oxyacyl" refers to the groups -OC(O)-alkyl, -OC(O)-aryl, -C(O)O-heteroaryl-, and -C(O)O-heterocyclic where alkyl, aryl, heteroaryl and heterocyclic are as defined herein.

5 "Oxyacylamino" refers to the groups -OC(O)NR-alkyl, -OC(O)NR-substituted alkyl, -OC(O)NR-aryl, -OC(O)NR-heteroaryl-, and -OC(O)NR-heterocyclic where R is hydrogen, alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclic and where each of alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl and heterocyclic are as defined herein.

10

"Aminocarboxy esters" refers to the groups -NRC(O)O-alkyl, -NRC(O)O-substituted alkyl, -NRC(O)O-aryl, -NRC(O)O-heteroaryl, and -NRC(O)O-heterocyclic where R is hydrogen, alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclic and where each of alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl and heterocyclic are as defined herein.

15

"Aryl" refers to an unsaturated aromatic carbocyclic group of from 6 to 14 carbon atoms having a single ring (e.g., phenyl) or multiple condensed rings (e.g., naphthyl or anthryl). Preferred aryls include phenyl, naphthyl and the like.

20

Unless otherwise constrained by the definition for the aryl substituent, such aryl groups can optionally be substituted with from 1 to 3 substituents selected from the group consisting of hydroxy, acyl, alkyl, alkoxy, alkenyl, alkynyl, substituted alkyl, substituted alkoxy, substituted alkenyl, substituted alkynyl, amino, aminoacyl, aminocarboxy esters, alkaryl, aryl, aryloxy, carboxyl, carboxylalkyl, acylamino, cyano, halo, nitro, heteroaryl, heterocyclic, oxyacyl, oxyacylamino, thioalkoxy, substituted thioalkoxy, trihalomethyl, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-heteroarylamino, mono- and di-heterocyclic amino, and unsymmetric di-substituted amines having different substituents selected from alkyl, substituted alkyl, aryl,

30

heteroaryl and heterocyclic, and the like. Preferred substituents include alkyl, alkoxy, halo, cyano, nitro, trihalomethyl, and thioalkoxy.

5 "Aryloxy" refers to the group aryl-O- wherein the aryl group is as defined above including optionally substituted aryl groups as also defined above.

"Carboxyalkyl" refers to the groups -C(O)O-alkyl and -C(O)O-substituted alkyl where alkyl and substituted alkyl are as defined above.

10 "Cycloalkyl" refers to cyclic alkyl groups of from 3 to 8 carbon atoms having a single cyclic ring or multiple condensed rings which can be optionally substituted with from 1 to 3 alkyl groups. Such cycloalkyl groups include, by way of example, single ring structures such as cyclopropyl, cyclobutyl, cyclopentyl, cyclooctyl, 1-methylcyclopropyl, 2-methylcyclopentyl, 2-methylcyclooctyl, and the
15 like, or multiple ring structures such as adamantanyl, and the like.

"Substituted cycloalkyl" refers to cycloalkyl groups having from 1 to 5 (preferably 1 to 3) substituents selected from the group consisting of hydroxy, acyl, acyloxy, alkyl, substituted alkyl, alkoxy, substituted alkoxy, alkenyl, substituted
20 alkenyl, alkynyl, substituted alkynyl, amino, aminoacyl, alkaryl, aryl, aryloxy, carboxyl, carboxylalkyl, cyano, halo, nitro, heteroaryl, thioalkoxy, substituted thioalkoxy, trihalomethyl and the like.

"Cycloalkenyl" refers to cyclic alkenyl groups of from 4 to 8 carbon atoms
25 having a single cyclic ring and at least one point of internal unsaturation which can be optionally substituted with from 1 to 3 alkyl groups. Examples of suitable cycloalkenyl groups include, for instance, cyclobut-2-enyl, cyclopent-3-enyl, cyclooct-3-enyl and the like.

30 "Substituted cycloalkenyl" refers to cycloalkenyl groups having from 1 to 5 substituents selected from the group consisting of hydroxy, acyl, acyloxy, alkyl,

substituted alkyl, alkoxy, substituted alkoxy, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, amino, aminoacyl, alkaryl, aryl, aryloxy, carboxyl, carboxylalkyl, cyano, halo, nitro, heteroaryl, thioalkoxy, substituted thioalkoxy, trihalomethyl and the like.

5

"Halo" or "halogen" refers to fluoro, chloro, bromo and iodo and preferably is either chloro or bromo.

10

"Heteroaryl" refers to a monovalent aromatic carbocyclic group of from 2 to 10 carbon atoms and 1 to 4 heteroatoms selected from oxygen, nitrogen and sulfur within the ring.

15

Unless otherwise constrained by the definition for the heteroaryl substituent, such heteroaryl groups can be optionally substituted with 1 to 3 substituents selected from the group consisting of hydroxy, acyl, alkyl, alkoxy, alkenyl, alkynyl, substituted alkyl, substituted alkoxy, substituted alkenyl, substituted alkynyl, amino, aminoacyl, aminocarboxy esters, alkaryl, aryl, aryloxy, carboxyl, carboxylalkyl, aminoacyl, cyano, halo, nitro, heteroaryl, heterocyclic, oxyacyl, oxyacylamino, thioalkoxy, substituted thioalkoxy, trihalomethyl, mono- and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino, mono- and di-heteroarylamino, mono- and di-heterocyclic amino, and unsymmetric di-substituted amines having different substituents selected from alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic, and the like. Preferred substituents include alkyl, alkoxy, halo, cyano, nitro, trihalomethyl, and thioalkoxy.

25

Such heteroaryl groups can have a single ring (e.g., pyridyl or furyl) or multiple condensed rings (e.g., indoliziny or benzothienyl). Preferred heteroaryls include pyridyl, pyrrolyl and furyl.

30

"Heterocycle" or "heterocyclic" refers to a monovalent saturated or unsaturated group having a single ring or multiple condensed rings, from 1 to 8

-- 56 --

carbon atoms and from 1 to 4 hetero atoms selected from nitrogen, sulfur or oxygen within the ring.

Unless otherwise constrained by the definition for the heterocyclic
5 substituent, such heterocyclic groups can be optionally substituted with 1 to 3
substituents selected from the group consisting of hydroxy, acyl, alkyl, alkoxy,
alkenyl, alkynyl, substituted alkyl, substituted alkoxy, substituted alkenyl,
substituted alkynyl, amino, aminoacyl, aminocarboxy esters, alkaryl, aryl, aryloxy,
carboxyl, carboxylalkyl, aminoacyl, cyano, halo, nitro, heteroaryl, heterocyclic,
10 oxyacyl, oxyacylamino, thioalkoxy, substituted thioalkoxy, trihalomethyl, mono-
and di-alkylamino, mono- and di-(substituted alkyl)amino, mono- and di-arylamino,
mono- and di-heteroarylamino, mono- and di-heterocyclic amino, and unsymmetric
di-substituted amines having different substituents selected from alkyl, substituted
alkyl, aryl, heteroaryl and heterocyclic, and the like. Such heterocyclic groups can
15 have a single ring or multiple condensed rings. Preferred heterocyclics include
morpholino, piperidinyl, and the like.

Examples of heterocycles and heteroaryls include, but are not limited to,
pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine,
20 isoindole, indole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine,
naphthylpyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole,
carboline, phenanthridine, acridine, phenanthroline, isothiazole, phenazine,
isoxazole, phenoxazine, phenothiazine, imidazolidine, imidazoline, piperidine,
piperazine, indoline, phthalimide, 1,2,3,4-tetrahydroisoquinoline, 4,5,6,7-
25 tetrahydrobenzo[b]thiophene, thiazole, thiazolidine, thiophene, benzo[b]thiophene,
morpholino, piperidinyl, pyrrolidine, tetrahydrofuranlyl, and the like.

"Oxyacyl" refers to the groups -OC(O)-alkyl, -OC(O)-aryl, -C(O)O-
heteroaryl-, and -C(O)O-heterocyclic where alkyl, aryl, heteroaryl and heterocyclic
30 are as defined herein.

"Oxyacylamino" refers to the groups -OC(O)NH-alkyl, -OC(O)NH-substituted alkyl, -OC(O)NH-aryl, -OC(O)NH-heteroaryl-, and -OC(O)NH-heterocyclic where alkyl, aryl, heteroaryl and heterocyclic are as defined herein.

5 "Thiol" refers to the group -SH.

"Thioalkoxy" refers to the group -S-alkyl.

10 "Substituted thioalkoxy" refers to the group -S-substituted alkyl.

"Thioaryloxy" refers to the group aryl-S- wherein the aryl group is as defined above including optionally substituted aryl groups also defined above.

15 "Thioheteroaryloxy" refers to the group heteroaryl-S- wherein the heteroaryl group is as defined above including optionally substituted aryl groups as also defined above.

"Pharmaceutically acceptable salt" refers to pharmaceutically acceptable salts of a compound of formula I, VII or VIII which salts are derived from a variety of organic and inorganic counter ions well known in the art and include, by way of example only, sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium, and the like; and when the molecule contains a basic functionality, salts of organic or inorganic acids, such as hydrochloride, hydrobromide, tartrate, mesylate, acetate, maleate, oxalate and the like.

25

Compound Preparation

The compounds of formula I are readily prepared via several divergent synthetic routes with the particular route selected relative to the ease of compound preparation, commercial availability of starting materials, etc.

30

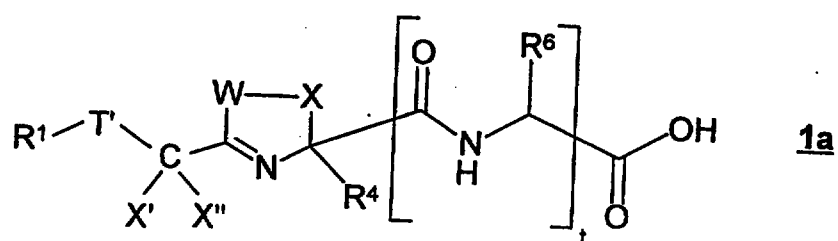
-- 58 --

The heterocyclic ring(s) in the compounds of formula I above can be prepared by use or adaptation of known chemical syntheses and methods, which synthesis and methods are well known in the art. For example, the synthesis of various heterocycles is illustrated in detail in the examples set forth below. Using these procedures, other suitable heterocycles can be prepared by modifying the starting materials employed in these procedures.

In certain cases, the compounds of formula I above are prepared by coupling a suitable heterocycle having one or more pendant functional groups to the other components necessary to form the *A-B-C* structure of formula I. Typical functional groups used for such couplings include, by way of example, carboxylic acid and amino groups. The coupling reaction is generally conducted using conventional coupling reagents such as carbodiimides with or without the use of well known additives such as N-hydroxysuccinimide, 1-hydroxybenzotriazole, etc. can be used to facilitate coupling. The reaction is typically conducted in an inert aprotic polar diluent such as dimethylformamide, dichloromethane, chloroform, acetonitrile, tetrahydrofuran and the like.

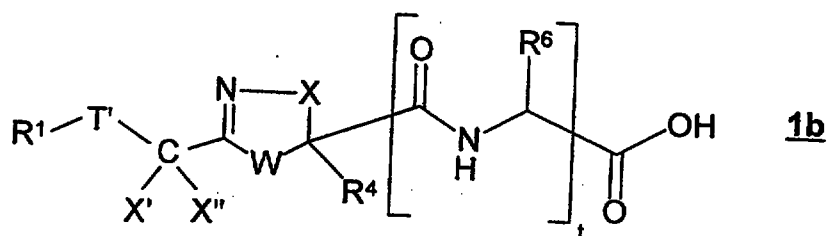
The compounds of formula VII and VIII are readily prepared by conventional amidation of a carboxylic acid as shown in reaction (1) below:

5



10

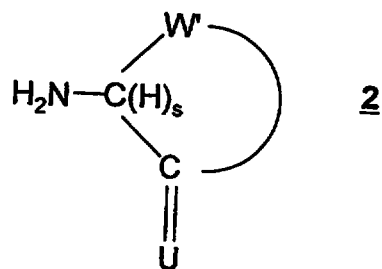
or



15

+

20



25

Reaction 1

VII (for 1a) or VIII (for 1b)

30

wherein R^1 , R^4 , R^6 , T' , X' , X'' , W , X , W' , U , t and s are as defined above.

-- 60 --

The reaction is conventionally conducted by using at least a stoichiometric amount of carboxylic acid 1a or 1b and amine 2. This reaction is conventionally conducted for peptide synthesis and synthetic methods used therein can also be employed to prepare compounds VII and VIII. For example, well known coupling reagents such as carbodiimides with or without the use of well known additives such as N-hydroxysuccinimide, 1-hydroxybenzotriazole, etc. can be used to facilitate coupling. The reaction is conventionally conducted in an inert aprotic polar diluent such as dimethylformamide, dichloromethane, chloroform, acetonitrile, tetrahydrofuran and the like. Alternatively, the acid halide of compound 1a or 1b can be employed in reaction (1) and, when so employed, it is typically employed in the presence of a suitable base to scavenge the acid generated during the reaction. Suitable bases include, by way of example, triethylamine, diisopropylethylamine, N-methylmorpholine and the like.

Synthesis of Carboxylic Acid Starting materials

Carboxylic acids 1a and 1b can be prepared by several divergent synthetic routes with the particular route selected relative to the ease of compound preparation, commercial availability of starting materials, whether t is zero or one. One method for preparing these compounds (when t is one) is the hydrolysis of esters of compounds of formula V and VI above. Similar methods can be employed to prepare related compounds when t is zero.

Carboxylic acids 1 having m equal to 1 and n equal to 1 or 2 can also be prepared by use of polymer supported forms of carbodiimide peptide coupling reagents. A polymer supported form of EDC, for example, has been described (*Tetrahedron Letters*, 34(48), 7685 (1993))¹⁰. Additionally, a new carbodiimide coupling reagent, PEPC, and its corresponding polymer supported forms have been discovered and are very useful for the preparation of such compounds.

-- 61 --

Polymers suitable for use in making a polymer supported coupling reagent are either commercially available or may be prepared by methods well known to the artisan skilled in the polymer arts. A suitable polymer must possess pendant sidechains bearing moieties reactive with the terminal amine of the carbodiimide. Such reactive moieties include chloro, bromo, iodo and methanesulfonyl. Preferably, the reactive moiety is a chloromethyl group. Additionally, the polymer's backbone must be inert to both the carbodiimide and reaction conditions under which the ultimate polymer bound coupling reagents will be used.

10

Certain hydroxymethylated resins may be converted into chloromethylated resins useful for the preparation of polymer supported coupling reagents. Examples of these hydroxylated resins include the 4-hydroxymethylphenylacetamidomethyl resin (Pam Resin) and 4-benzyloxybenzyl alcohol resin (Wang Resin) available from Advanced Chemtech of Louisville, Kentucky, USA (see Advanced Chemtech 1993-1994 catalog, page 115). The hydroxymethyl groups of these resins may be converted into the desired chloromethyl groups by any of a number of methods well known to the skilled artisan.

20

Preferred resins are the chloromethylated styrene/divinylbenzene resins because of their ready commercial availability. As the name suggests, these resins are already chloromethylated and require no chemical modification prior to use. These resins are commercially known as Merrifield's resins and are available from Aldrich Chemical Company of Milwaukee, Wisconsin, USA (see Aldrich 1994-1995 catalog, page 899). Methods for the preparation of PEPC and its polymer supported forms are outlined in the following scheme.

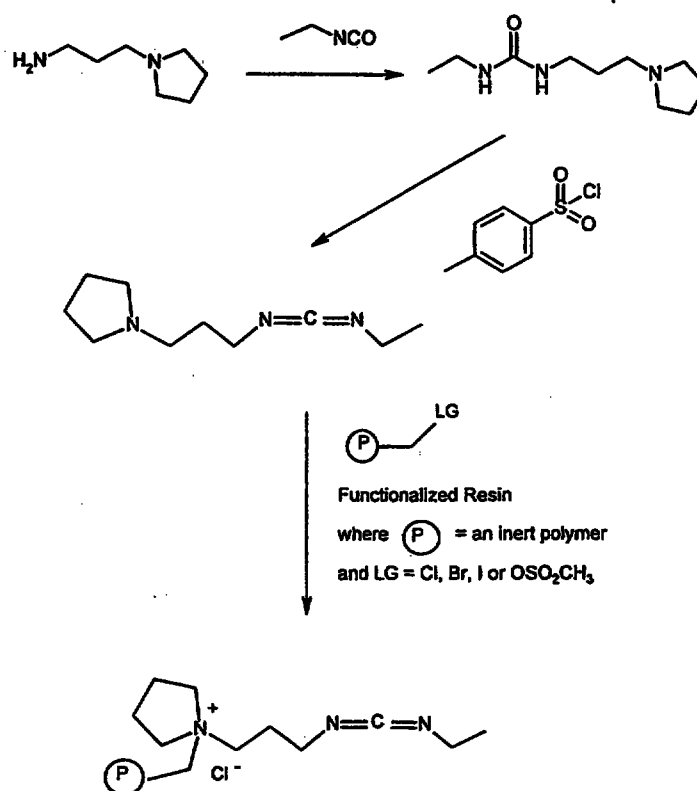
25

5

10

15

20



25

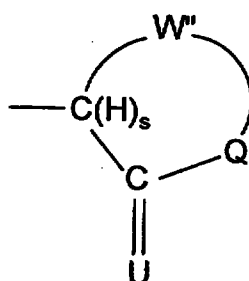
30

Such methods are described more fully in U.S. Patent Application Serial No. 60/019,790 filed June 14, 1996 which application is incorporated herein by reference in its entirety. Briefly, PEPC is prepared by first reacting ethyl isocyanate with 1-(3-aminopropyl)pyrrolidine. The resulting urea is treated with 4-toluenesulfonyl chloride to provide PEPC. The polymer supported form is prepared by reaction of PEPC with an appropriate resin under standard conditions to give the desired reagent.

The carboxylic acid coupling reactions employing these reagents are performed at about ambient to about 45°C, for from about 3 to 120 hours. Typically, the product may be isolated by washing the reaction with CHCl₃ and concentrating the remaining organics under reduced pressure. As discussed *supra*, isolation of products from reactions where a polymer bound reagent has been used is greatly simplified, requiring only filtration of the reaction mixture and then concentration of the filtrate under reduced pressure.

Preparation of Cyclic Amino Compounds

Cyclic amino compounds 2 employed in reaction (1) above are generally aminolactams, aminolactones, aminothiolactones and aminocycloalkyl compounds which can be represented by the formula:



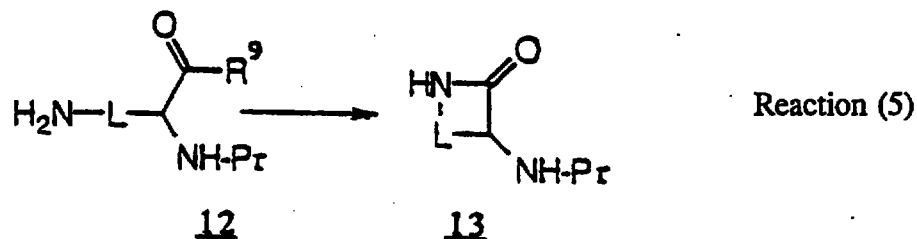
where U and s are as defined above, Q is preferably selected from the group consisting of -O-, -S-, >NR¹⁶, and >CR¹⁷R¹⁸ where each of R¹⁶, R¹⁷ and R¹⁸ are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, heteroaryl and heterocyclic with the proviso that if Q is -O-, -S- or >NR¹⁶, then X is oxo or dihydro.

The aminolactams, aminolactones and aminothiolactones of the formula above can be prepared by use or adaptation of known chemical syntheses which syntheses are well described in the literature. See, e.g., Ogliaruso and Wolfe, *Synthesis of Lactones and Lactams*, Patai, et al. Editor, J. Wiley & Sons, New York, New York, USA, pp. 1085 et seq. (1993).

-- 64 --

Specifically, 3-amino substituted lactams **13** with 5, 6 or 7 ring atoms may be prepared by the direct cyclization of a suitable alpha, omega-diamino acid ester **12** as shown in reaction (5) below:

5



10

wherein L is a linking group (typically an alkylene group) of from 2-4 atoms, Pr is a suitable protecting group such as *t*-butoxycarbonyl, carbobenzyloxy, or the like and R^{19} is an alkoxy or aryloxy group such as methoxy, ethoxy, *p*-nitrophenoxy, *N*-succinimidoxy, and the like. The reaction may be carried out in a solvent such as water, methanol, ethanol, pyridine, and the like. Such reactions are exemplified by cyclization of a lysine ester to a caprolactam as described by Ugi, et al., *Tetrahedron*, **52**(35):11657-11664 (1996).

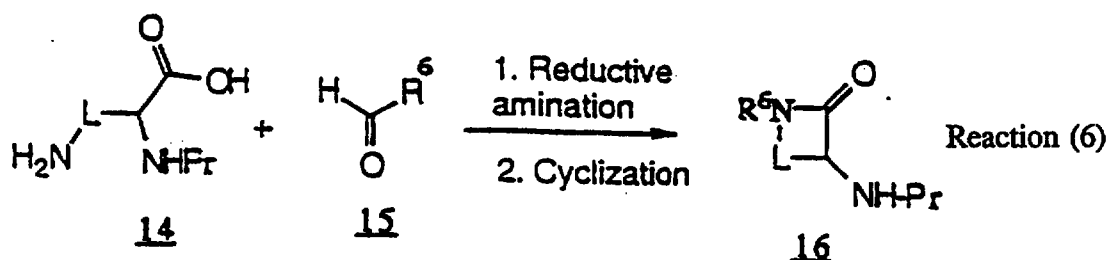
15

Alternatively, such a cyclization can also be conducted in the presence of dehydrating agents such as alumina or silica to form lactams as described by Blade-Font, *Tetrahedron Lett.*, **21**:2443 (1980).

20

The preparation of aminolactams alkylated on the amino group of the cyclic lactam is described by Freidinger, et al., *J. Org. Chem.*, **47**:104-109 (1982) and illustrated in reaction (6) below:

25

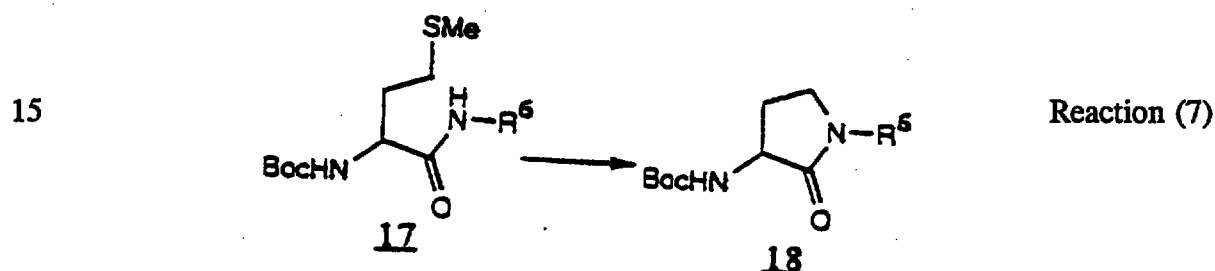


30

wherein L and R¹⁶ are as defined above.

In reaction (6), reductive amination of 14 with aldehyde 15 and subsequent ring closure by methods using, for example, EDC provides for aminolactam 16. The preparation of six-membered lactams using this general procedure is described by Semple, et al., *J. Med. Chem.*, 39:4531-4536 (1996).

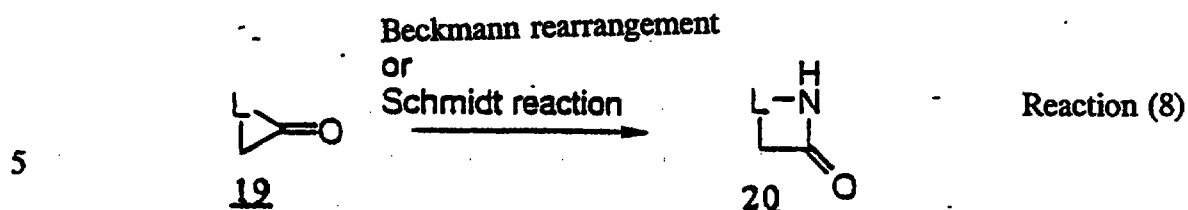
The internal cyclization of an amide anion with a halide or equivalent thereof can sometimes be used to particular advantage in the synthesis of smaller ring lactams where the stereochemistry of the amino-lactam center is available from the standard amino-acid pool. This approach is illustrated in reaction (7) below:



where R¹⁶ is as defined above.

The approach of reaction (7) is presented by Semple, et al., *supra.*, and Freidinger, et al., *J. Org. Chem.*, 47:104-109 (1982) where a dimethylsulfonium leaving group is generated from methyl iodide treatment of an alkyl methyl sulfide 17 to provide for lactam 18. A similar approach using a Mitsunobu reaction on an omega alcohol is found Holladay, et al., *J. Org. Chem.*, 56:3900-3905 (1991).

In another method, lactams 20 can be prepared from cyclic ketones 19 using either the well known Beckmann rearrangement (e.g., Donaruma, et al., *Organic Reactions*, 11:1-156 (1960)) or the well known Schmidt reaction (Wolff, *Organic Reactions*, 3:307-336 (1946)) as shown in reaction (8) below:



wherein L is as defined above.

10 Application of these two reactions leads to a wide variety of lactams especially lactams having two hydrogen atoms on the carbon alpha to the lactam carbonyl which lactams form a preferred group of lactams in the synthesis of the compounds of formula I above. In these reactions, the L group can be highly variable including, for example, alkylene, substituted alkylene and hetero

15 containing alkylene with the proviso that a heteroatom is not adjacent to the carbonyl group of compound 19. Additionally, the Beckmann rearrangement can be applied to bicyclic ketones as described in Krow, et al., *J. Org. Chem.*, 61:5574-5580 (1996).

20 The preparation of lactones can be similarly conducted using peracids in a Baeyer-Villiger reaction on ketones. Alternatively, thiolactones can be prepared by cyclization of an omega -SH group to a carboxylic acid and thiolactams can be prepared by conversion of the oxo group to the thiooxo group by P₂S₅ or by use of the commercially available Lawesson's Reagent,

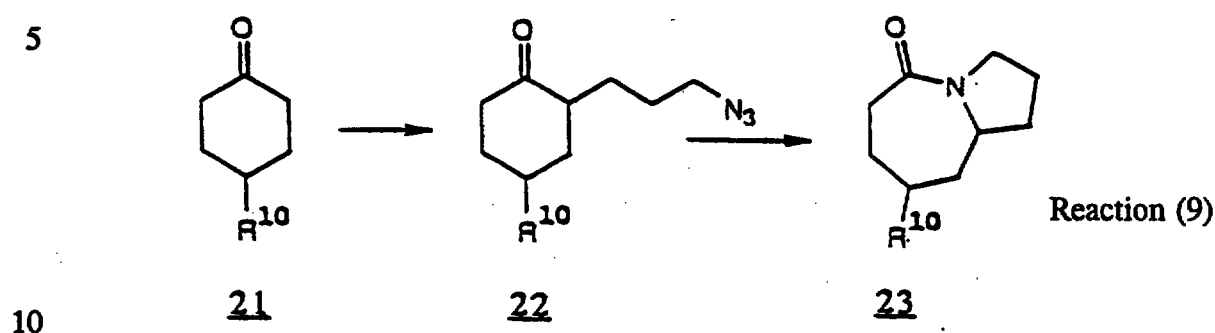
25 *Tetrahedron*, 35:2433 (1979).

 One recently reported route for lactam synthesis is a variation of the Schmidt reaction through the use of an alkyl azide, either intermolecularly or intramolecularly, through a tethered alkylazide function that attacks a ketone

30 under acidic conditions. Gracias, et al., *J. Am. Chem. Soc.*, 117:8047-8048 (1995) describes the intermolecular version whereas Milligan, et al., *J. Am.*

Chem. Soc., 117:10449-10459 (1995) describes the intramolecular version.

One example of the intramolecular version is illustrated in reaction (9) below:



where R^{10} is exemplified by alkyl, substituted alkyl, alkoxy, substituted alkoxy, aryl, heteroaryl, cycloalkyl and heterocyclic.

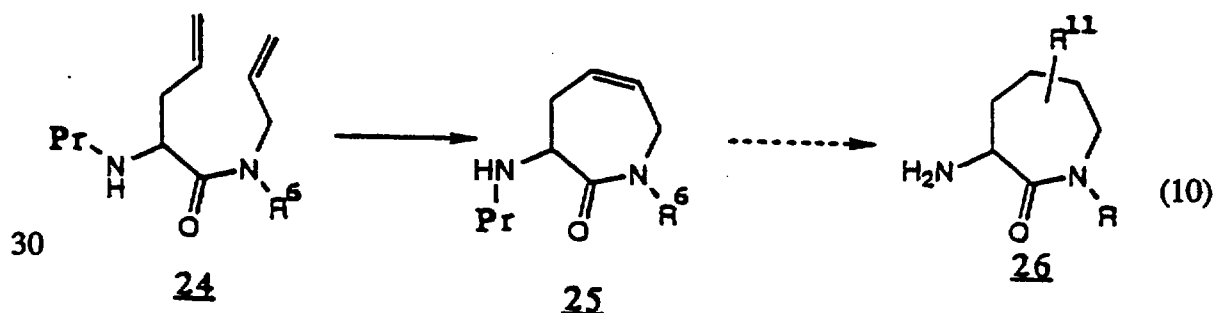
15

In this reaction, ketone 21 is converted to an α -(ω -alkyl)ketone 22 which is cyclized to form bicyclic lactam 23. Such intramolecular reactions are useful in forming bicyclic lactams having 5-7 members and the lactam ring of 6-13 members. The use of hetero atoms at non-reactive sites in these rings is feasible in preparing heterobicyclic lactams.

20

Still another recent approach to the synthesis of lactams is described by Miller, et al., *J. Am. Chem. Soc.*, 118:9606-9614 (1996) and references cited and is illustrated in reaction (10) below:

25



-- 68 --

where R^6 and Pr are as defined above and R^{11} is exemplified by halo, alkyl, substituted alkyl, alkoxy, substituted alkoxy, aryl, heteroaryl, cycloalkyl and heterocyclic wherein the aryl, heteroaryl, cycloalkyl and heterocyclic group is optionally fused to the lactam ring structure.

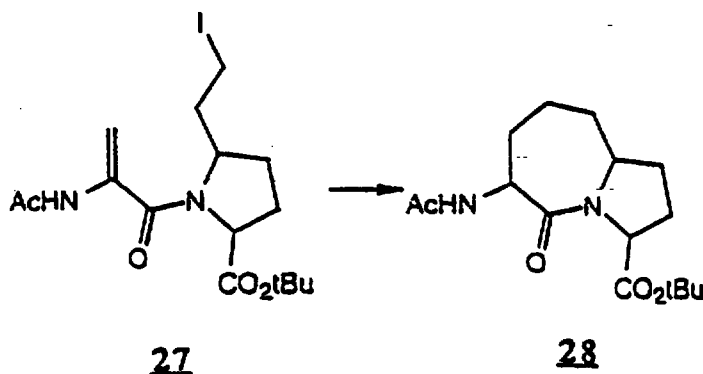
5

Specifically, in reaction (10), lactam 26 is formed from an appropriate unsaturated amide (e.g., 24) through a ruthenium or molybdenum complexes catalysed olefin metathesis reaction to form unsaturated lactam 25 which can be used herein without further modification. However, the unsaturation in 25 permits a myriad of techniques such as hydroboration, Sharpless or Jacobsen epoxidations, Sharpless dihydroxylations, Diels-Alder additions, dipolar cycloaddition reactions and many more chemistries to provide for a wide range of substituents on the lactam ring. Moreover, subsequent transformations of the formed substitution leads to other additional substituents (e.g., mesylation of an alcohol followed by nucleophilic substitution reactions). See, for example, March, et al. *Advanced Organic Chemistry, Reaction Mechanisms and Structure*, 2nd Edition, McGraw-Hill Book Company, New York, New York, USA (1977) for a recitation of numerous such possible reactions. Saturated amides used in this reaction are conventional with amide 24 being commercially available.

20

Related chemistry to cyclize amides to form lactams is disclosed by Colombo, et al., *Tetrahedron Lett.*, 35(23):4031-4034 (1994) and is illustrated in reaction (11) below:

25



30

Reaction (11)

In this reaction, proline derivative 27 is cyclized via a tributyltin-radical cyclization to provide for lactam 28.

Some of the lactams described above contain the requisite amino group alpha to the lactam carbonyl whereas others did not. However, the introduction of the required amino group can be achieved by any of several routes delineated below which merely catalogue several recent literature references for this synthesis.

For example, in a first general synthetic procedure, azide or amine displacement of a leaving group alpha to the carbonyl group of the lactam leads to the alpha-aminolactams. Such general synthetic procedures are exemplified by the introduction of a halogen atom followed by displacement with phthalimide anion or azide and subsequent conversion to the amine typically by hydrogenation for the azide as described in Rogriguez, et al., *Tetrahedron*, 52:7727-7736 (1996), Parsons, et al., *Biochem. Biophys. Res. Comm.*, 117:108-113 (1983) and Watthey, et al., *J. Med. Chem.*, 28:1511-1516 (1985). One particular method involves iodination and azide displacement on, for example, benzylactams as described by Armstrong, et al., *Tetrahedron Lett.*, 35:3239 (1994) and by King, et al., *J. Org. Chem.*, 58:3384 (1993).

Another example of this first general procedure for the synthesis of alpha-aminolactams from the corresponding lactam involves displacement of a triflate group by an azido group as described by Hu, et al., *Tetrahedron Lett.*, 36(21):3659-3662 (1995).

Still another example of this first general procedure uses a Mitsunobu reaction of an alcohol and a nitrogen equivalent (either -NH₂ or a phthalimido group) in the presence of an azodicarboxylate and a triarylphosphine as described in Wada, et al., *Bull. Chem. Soc. Japan*, 46:2833-2835 (1973) using an open chain reagent.

Yet another example of this first general procedure involves reaction of alpha-chlorolactams with anilines or alkyl amines in a neat mixture at 120°C to provide for 2-(N-aryl or N-alkyl)lactams as described by Gaetzi, *Chem. Abs.*, 66:28690m.

5

In a second general synthetic procedure, reaction of an enolate with an alkyl nitrite ester to prepare the alpha oxime followed by reduction yields the alpha-aminolactam compound. This general synthetic procedure is exemplified by Wheeler, et al., *Organic Syntheses*, Coll. Vol. VI, p. 840 which describes the reaction of isoamyl nitrite with a ketone to prepare the desired oxime. The reduction of the oxime methyl ester (prepared from the oxime by reaction with methyl iodide) is described in the *J. Med. Chem.*, 28(12):1886 (1985) and the reduction of alpha-oximino caprolactams by Raney-nickel and palladium catalysts is described by Brenner, et al., U.S. Patent No. 2,938,029.

10

15

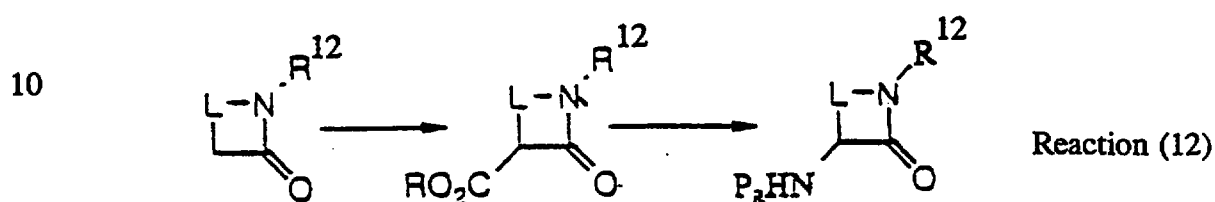
In a third general synthetic procedure, direct reaction of an enolate with an electrophilic nitrogen transfer agent can be used. The original reaction employed toluenesulfonyl azide but was improved as described by Evans, et al., *J. Am. Chem. Soc.*, 112:4011-4030 (1990). Specifically, direct introduction of an azido group which can be reduced to the amine by hydrogenation is described by Micouin, et al., *Tetrahedron*, 52:7719-7726 (1996). Likewise, the use of triisopropylbenzenesulfonyl azide as the azide transferring agent for reaction with an enolate is described by Evans, et al., *supra*. The use of triphenylphosphine to reduce the alpha-azidolactams to the corresponding aminolactams in the benzodiazepine series is disclosed by Butcher, et al., *Tetrahedron Lett.*, 37(37):6685-6688 (1996). Lastly, diazo transfer of beta-diketones and subsequent reduction of the diazo group to the amino group is exemplified by Hu, et al., *Tetrahedron Lett.*, 36(21):3659-3662 (1995) who used Raney-nickel and hydrogen in acetic acid and acetic anhydride as the solvent.

20

25

30

In a fourth general procedure, *N*-substituted lactams are first converted to the 3-alkoxycarbonyl derivatives by reaction with a dialkyl carbonate and a base such as sodium hydride. See, for example, M.L. Reupple, et al., *J. Am. Chem. Soc.*, 93:7021 et seq. (1971) The resulting esters serve as starting materials for conversion to the 3-amino derivatives. This conversion is achieved via the Curtius reaction as shown in reaction (12) below:



15 where Pr is as defined above and R¹² is typically hydrogen, an alkyl or an aryl group.

The Curtius reaction is described by P.A.S. Smith, *Organic Reactions*, 3:337-449 (1946). Depending on the reaction conditions chosen, Pr = H or a protecting group such as Boc. For example, when R = H, treatment of the acid with diphenylphosphoryl azide in the presence of *t*-butanol provides the product wherein Pr = Boc.

25 The alpha-aminolactams employed as the cyclic amino compounds 2 in reaction (1) above include ring *N*-substituted lactams in addition to ring *N*-H lactams. Some methods for preparing ring *N*-substituted lactams have been described above. More generally, however, the preparation of these compounds range from the direct introduction of the substituent after lactam formation to essentially introduction before lactam formation. The former methods typically employ a base and an primary alkyl halide although it is

30

-- 72 --

contemplated that a secondary alkyl halide can also be employed although yields may suffer.

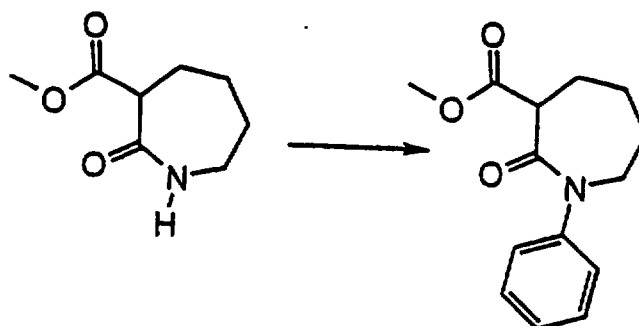
Accordingly, a first general method for preparing N-substituted lactams is achieved via reaction of the lactam with base and alkyl halide (or acrylates in some cases). This reaction is quite well known and bases such as sodamide, sodium hydride, LDA, LiHMDS in appropriate solvents such as THF, DMF, etc. are employed provided that the selected base is compatible with the solvent. See for example: K. Orito, et al., *Tetrahedron*, 36:1017-1021 (1980) and J.E. Semple, et al., *J. Med. Chem.*, 39:4531-4536 (1996) (use of LiHMDS with either R-X or acrylates as electrophiles).

A second general method employs reductive amination on an amino function which is then cyclized to an appropriate ester or other carbonyl function.

A third general method achieves production of the N-substitution during lactam formation. Literature citations report such production from either photolytic or thermal rearrangement of oxaziridines, particularly of N-aryl compounds. See, for example, Krimm, *Chem. Ber.*, 91:1057 (1958) and Suda, et al., *J. Chem. Soc. Chem Comm.*, 949-950, (1994). Also, the use of methyl hydroxylamine for the formation of nitrones and their rearrangement to the N-methyl derivatives is reported by Barton, et al., *J. Chem. Soc.*, 1764-1767 (1975). Additionally, the use of the oxaziridine process in chiral synthesis has been reported by Kitagawa, et al., *J. Am. Chem. Soc.*, 117:5169-5178 (1975).

A more direct route to obtain N-phenyl substituted lactams from the corresponding NH lactams through the use of t-butyltetramethylguanidine and triphenylbismuth dichloride is disclosed by Akhatar, et al., *J. Org. Chem.*, 55:5222-5225 (1990) as shown in reaction (13) below.

5



Reaction (13)

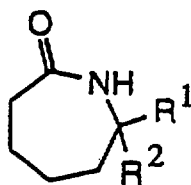
10

Given that numerous methods are available to introduce an alpha-amino group onto a lactam (or lactone) ring, the following lactams (and appropriate corresponding lactones) are contemplated for use in the synthesis of compounds of formula I above. Similar alcohol functions at the carbonyl position are derivative of either amine ring opening of cyclic epoxides, ring opening of aziridines, displacement of appropriate halides with amine or alcohol nucleophiles, or most likely reduction of appropriate ketones. These ketones are also of interest to the present invention.

20

Monocyclic lactams as described by Nedenskov, et al., *Acta Chem. Scand.*, 12:1405-1410 (1958) and represented by the formula:

25

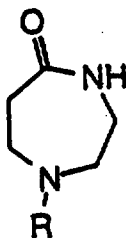


where R¹ and R² are exemplified by alkyl, aryl or alkenyl (e.g., allyl).

-- 74 --

Monocyclic lactams containing a second nitrogen ring atom as described by Sakakida, et al., *Bull. Chem. Soc. Japan*, 44:478-480 (1971) and represented by the formula:

5

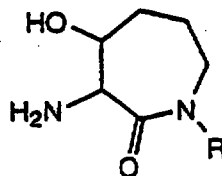


where R is exemplified by CH_3 - or PhCH_2 -.

10

Monocyclic lactams having hydroxyl substitution on the ring as described by Hu, et al., *Tetrahedron Lett.*, 36(21):3659-3662 (1995) and represented by the formula:

15



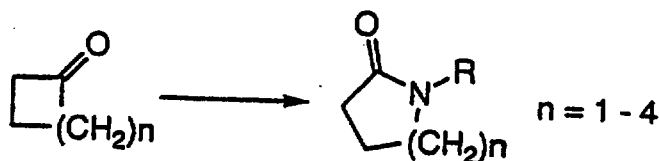
20

where R is exemplified by benzyl (includes both the *cis* and *trans* hydroxy lactams).

25

The direct preparation *N*-substituted lactams of 5-8 members from the corresponding ketones is described by Hoffman, et al., *Tet. Lett.*, 30:4207-4210 (1989). These lactams are represented by the formula:

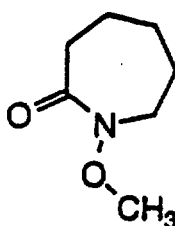
30



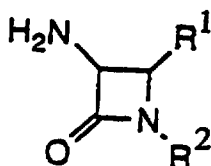
-- 75 --

wherein R is alkyl, alkenyl, alkynyl, cycloalkyl, or benzyl.

N-methoxylactams prepared from cyclohexanone and dimethoxyamine
are described by Vedejs, et al., *Tet. Lett.*, 33:3261-3264 (1992). These
structures are represented by the formula:



Substituted 3-aminoazetidinone derivatives prepared by a variety of
routes including those described by van der Steen, et al., *Tetrahedron*, 47,
7503-7524 (1991)⁵⁶, Hart, et al., *Chem Rev.*, 89:1447-1465 (1989) and
references cited therein are represented by the formula:

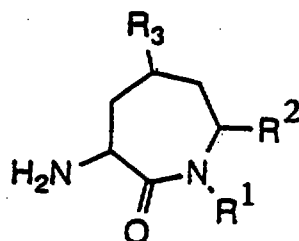


where R¹ and R² are independently selected from alkyl, substituted alkyl,
alkenyl, substituted alkenyl, aryl, heteroaryl, heterocyclic or are fused to form
a cyclic group.

Ring substituted lactams are described by Lowe, et al., *Bioorg. Med.*
Chem. Lett., 4:2877-2882 (1994) and are represented by the formula:

-- 76 --

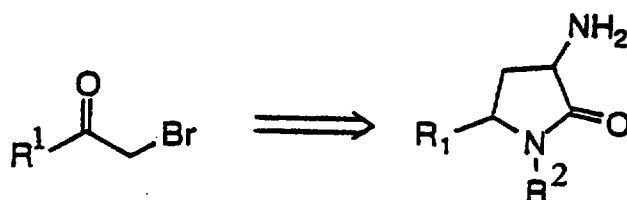
5



- 10 wherein R² and R³ are exemplified by aryl and substituted aryl and R¹ is exemplified by alkyl or hydrogen.

The synthesis of substituted 3-aminopyrrolidones from alpha-bromoketones is described by McKennis, Jr., et al., *J. Org. Chem.*, 28:383-387 (1963). These compounds are represented by the formula:

20



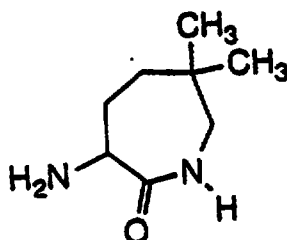
where R¹ is aryl or heteroaryl and R² corresponds to any substituent for which the corresponding amine R²-NH₂ exists.

25 Additional references for the synthesis of alpha aminolactams are as follows:

1. Shirota, et al., *J. Med. Chem.*, 20:1623-1627 (1977) which describes the synthesis of a compound of the formula:

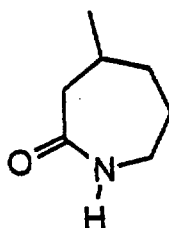
-- 77 --

5



2. Overberger, et al., *J. Am. Chem. Soc.*, 85:3431 (1963) which
10 describes the preparation of optically active β -methylcaprolactam of the
formula:

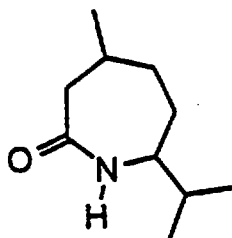
15



20

3. Herschmann, *Helv. Chim. Acta*, 32:2537 (1949) describes the
synthesis of a disubstituted caprolactam from the Beckmann rearrangement of
menthone which is represented by the formula:

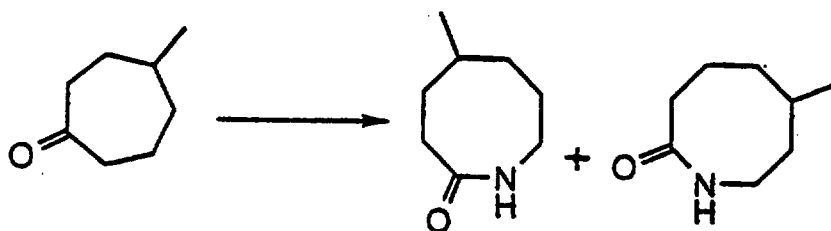
25



-- 78 --

4. Overberger, et al., *Macromolecules*, 1:1 (1968) describes the synthesis of eight-membered lactams from 3-methylcycloheptanone as shown below:

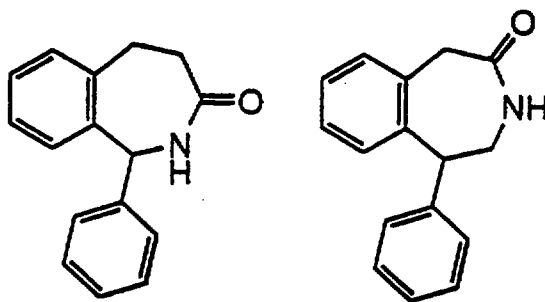
5



10

5. The synthesis of benzolactams (benzazepinones) has been reported by Busacca, et al., *Tet. Lett.*, 33:165-168 (1992):

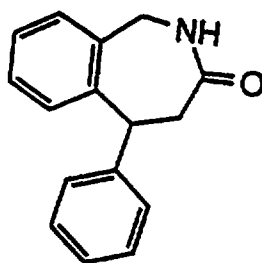
15



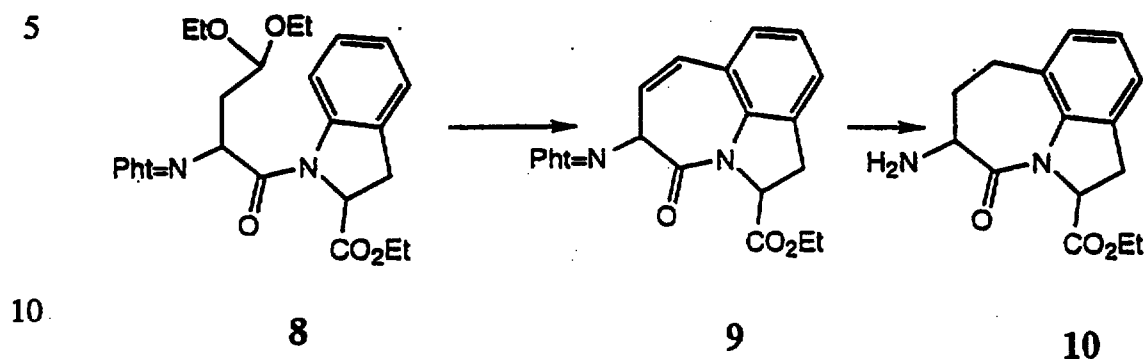
20

by Croisier, et al., U.S. Patent No. 4,080,449:

25



and by J.A. Robl, et al., *Tetrahedron Lett.*, 36(10):1593-1596 (1995) who employed an internal Friedel-Crafts like cyclization to prepare the tricyclic benzylactams shown below where Pht is the phthalimido protecting group:



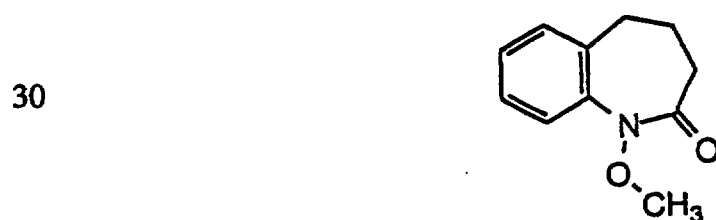
Another tricyclic lactam series is disclosed by Flynn, et al., *J. Med. Chem.*, 36:2420-2423 (1993) and references cited therein.

6. Orito, et al., *Tetrahedron*, 36:1017-1021 (1980) discloses phenyl substituted benzazepinones represented by the formula:

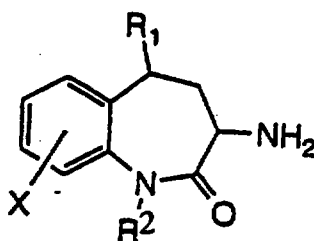


wherein R = H or CH₃;

Kawase, et al., *J. Org. Chem.*, 54:3394-3403 (1989) discloses a N-methoxy benzazepinone represented by the formula:

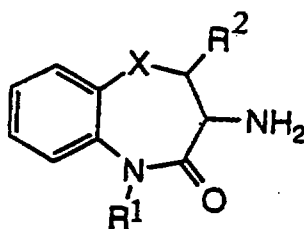


7. Lowe, et al., *J. Med. Chem.*, 37:3789-3811 (1994) describes several synthetic pathways to substituted benzazepinones of the formula:



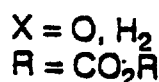
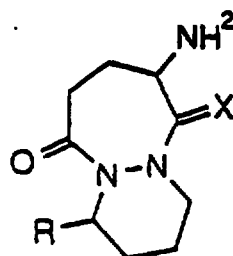
where R^1 is substituted aryl or cyclohexyl, X is a suitable substituent and R^2 can be H or alkyl. The syntheses described in Lowe are, however, adaptable to form numerous R^1 substituents.

8. Robl, et al., *Bioorg. Med. Chem. Lett.*, 4:1789-1794 (1994) and references cited therein as well as Skiles, et al., *Bioorg. Med. Chem. Lett.*, 3:773-778 (1993) disclose benzofused lactams which contain additional heteroatoms in the lactam ring. These compounds are represented by the formula:



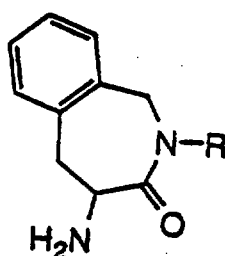
where X is O and $R^2 = H$ or CH_3 , or X = S and $R^2 = H$. In either case, $R^1 = H$ or alkyl. Also, in Skiles, the thio group of the thiolactam can be oxidized to the SO_2 group. These structures are also presented from Beckmann rearrangement in Grunewald, et al., *J. Med. Chem.*, 39(18):3539 (1996).

9. Also syntheses for the benzoheterolactam series is presented in Thomas, et al., *J. Chem. Soc., Perkin II*, 747 (1986) which could lead to compounds of the formula:



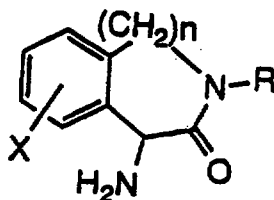
where X is O or H₂ and R is CO₂R.

10. Further examples of benzazepinones are found in Warshawsky, et al., *Bioorg. Med. Chem. Lett.*, 6:957-962 (1996) which discloses compounds of the formula:



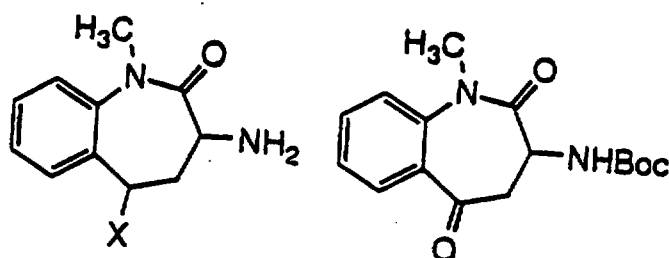
The synthesis can be generalized to produce R = alkyl or aryl.

25 11. Ben-Ishai, et al., *Tetrahedron*, 43:439-450 (1987) describes syntheses which could lead to several benzolactams of the formula:



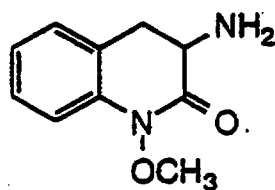
wherein $n = 0, 1, \text{ or } 2$ and $R = -CH_3, PhCH_2-$ and H .

12. van Niel et al., *Bioorg. Med. Chem. Lett.*, 5:1421-1426 (1995)
5 reports the synthesis of compounds of the formulas:



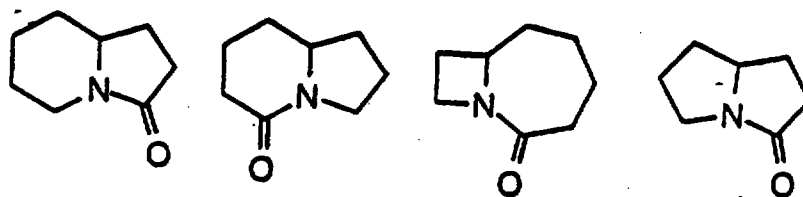
wherein X is $-OH, -NH_2$ or $-NR^6R^6$ where R^6 is as defined above. The
reported ketone is a versatile synthetic intermediate which can be modified by
15 conventional methods such as reductive amination, reduction, etc.

13. Kawase, et al., *J. Org. Chem.*, 54:3394-3403 (1989) describes a
synthetic method for the preparation of:



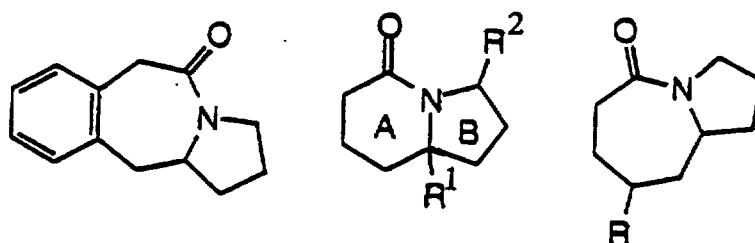
25 In addition to the above, saturated bicyclic alpha-aminolactams are also
contemplated for use in the synthesis of compounds of formula I. Such
saturated bicyclic alpha-aminolactams are well known in the art. For example,
Edwards, et al., *Can. J. Chem.*, 49:1648-1658 (1971) describes several
30 syntheses of bicyclic lactams of the formula:

5



Similarly, Milligan, et al., *J. Am. Chem. Soc.*, 117:10449-10459 (1995) and references cited therein report the synthesis of lactams of the formula:

10



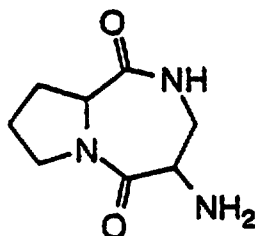
15

wherein R^1 and R^2 are H or $-CH_3$, ring A can have from 6-13 members and ring B can have from 5-7 members. R can be alkyl, aryl, cycloalkyl and the like.

20

The introduction of a heteroatom into the saturated cyclic structure fused to the lactam ring is disclosed by Curran et al., *Tet. Lett.*, 36:191-194 (1995), who describe a synthetic method which can be used to obtain a lactam of the formula:

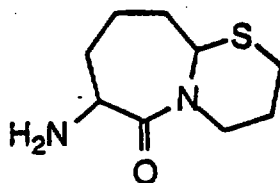
25



30

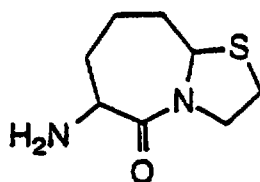
by Shusarchyk, et al., *Bioorg. Med. Chem. Lett.*, 5:753-758 (1995), who describe syntheses which could lead to a lactam of the formula:

5



and by Wyvratt, et al., Eur. Pat. Appl. 61187 (1982), who describe a lactam of the formula:

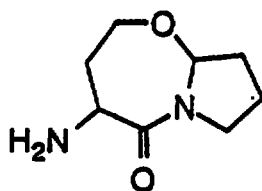
10



15

Lactams having further heteroatom(s) in the cyclic lactam structure (in addition to the nitrogen of the amido group of the lactam) are described by Cornille, et al., *J. Am. Chem. Soc.*, 117:909-917 (1995), who describe lactams of the formula:

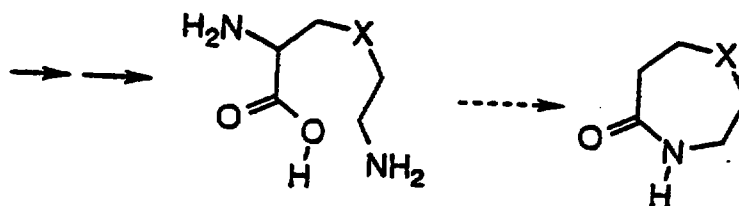
20



25

and J. Kolc, *Coll. Czech. Chem. Comm.*, 34:630 (1969), who describes lysines suitable for cyclization to lactams which have a hetero lactam ring atom as shown by the formula:

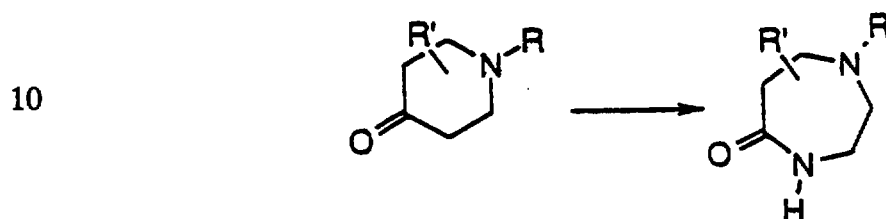
30



-- 85 --

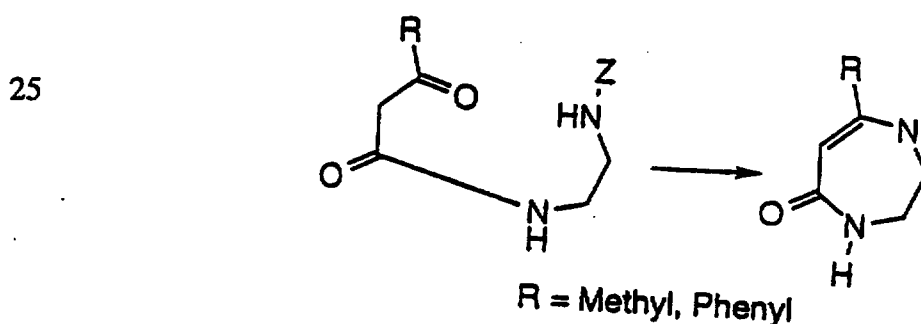
where X=O, S and NR where R is, for example, alkyl, substituted alkyl, aryl, heteroaryl, heterocyclic, and the like.

Similarly, each of Dickerman, et al., *J. Org. Chem.*, 14:530 (1949)⁸⁶,
5 Dickerman, et al., *J. Org. Chem.*, 20:206 (1955), and Dickerman, et al., *J. Org. Chem.*, 19:1855 (1954) used the Schmidt and Beckmann reactions on substituted 4-piperidones to provide for lactams of the formula:



where R is acyl, alkyl, substituted alkyl, aryl, heteroaryl or heterocyclic
15 provided that R is not an acid labile group such as t-Boc; and R' is hydrogen, alkyl, substituted alkyl, alkoxy, substituted alkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocycloxy, halo, cyano, nitro, trihalomethyl, and the like.

20 An internal cyclization of appropriate ethylenediamine amides onto a ketone or aldehyde is described by Hoffman, et al., *J. Org. Chem.*, 27:3565 (1962) as follows:



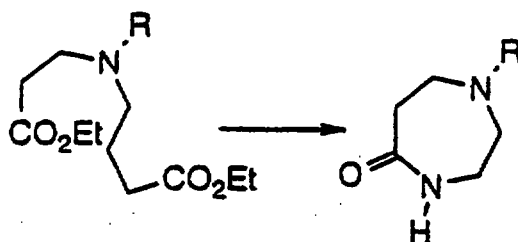
30

Ring expansion methodology based on beta lactams to provide for larger ring lactams containing an aza group has twice been reported in Wasserman, et al., *J. Am. Chem. Soc.*, 103:461-2 (1981) and in Crombie, et al., *Tetrahedron Lett.*, 27(42):5151-5154 (1986).

5

Dieckmann methodology has been used to prepare aza caprolactams from unsymmetrical amines such as shown below by Yokoo, et al., *Bull. Chem. Soc. Jap.*, 29:631 (1956).

10



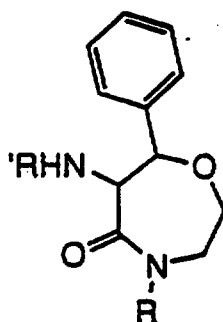
15

where R is as defined in this reference. The disclosure of Yokoo, et al. can be extended to cover R being alkyl, substituted alkyl, aryl, alkoxy, substituted alkoxy, heteroaryl, cycloalkyl, heterocyclic, alkenyl, substituted alkenyl, and the like.

20

The synthesis of various members of the oxalactam series has been reported by Burkholder, et al., *Bioorg. Med. Chem. Lett.*, 2:231 (1993) and references cited therein which oxalactams are represented by the formula:

25

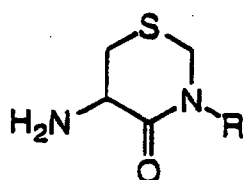


30

where 'R is as defined in the reference and R can be alkyl, substituted alkyl, aryl, alkoxy, substituted alkoxy, heteroaryl, cycloalkyl, heterocyclic, alkenyl, substituted alkenyl, and the like.

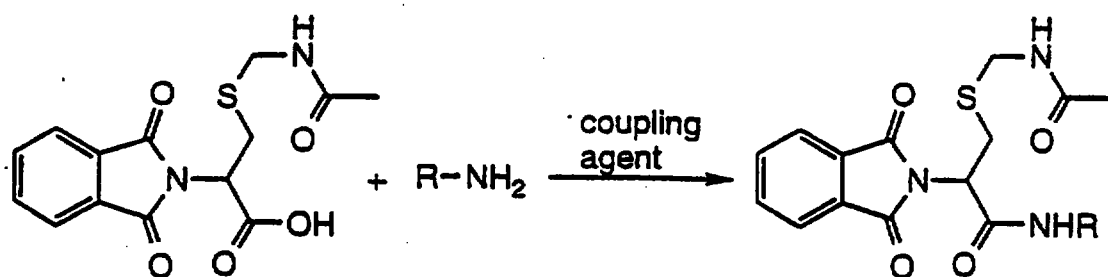
- 5 The synthesis of thialactams (generally oxalactams can be made by the same methodology) has been reported by Freidinger, et al., *J. Org. Chem.*, 47:104-109 (1982), who prepared thialactams of the formula:

10

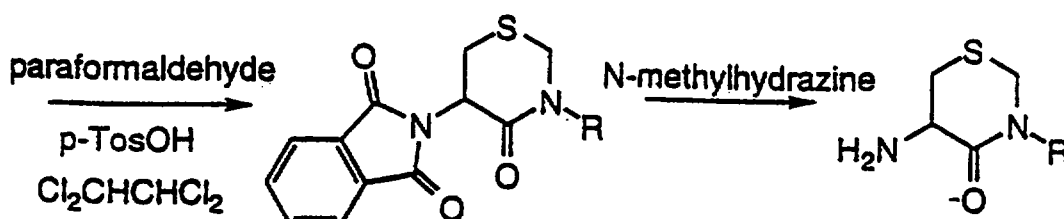


This reference provides a series of procedures having broad application for synthesis of lactams permitting R in the above formula to be derived from any amine (alkyl, aryl, heteroaryl, etc.) with the restriction being that the R-group does not contain any functional groups reactive with formaldehyde (e.g., primary and secondary amines). The general synthetic scheme provided by Freidlinger, et al. is:

20



25



30

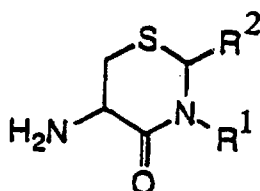
-- 88 --

The coupling agent is any standard reagent used in the formation of typical peptide or amide bonds, for example, carbodiimide reagents. See, also, Karanewsky, U.S. Patent No. 4,460,579 and Kametani, et al., *Heterocycles*, 9:831-840 (1978).

5

The Friedinger procedure can be extended to afford disubstituted thialactams of the following structure:

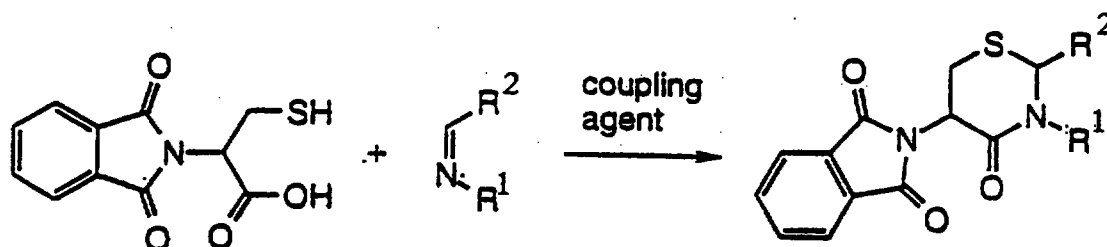
10



In this procedure, the thiolactam ring is prepared as follows:

15

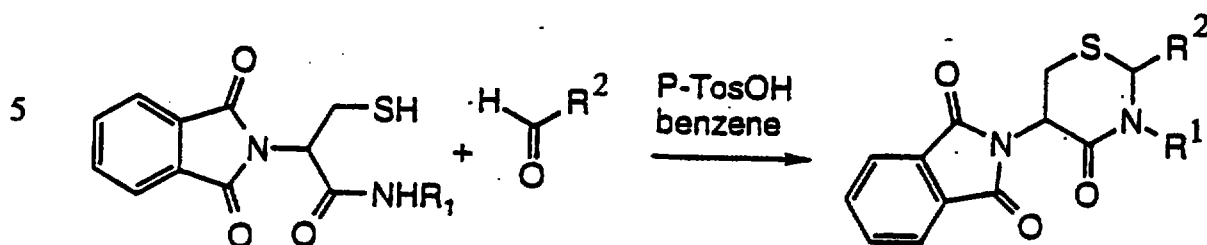
20



25

In practical terms, R^2 will be limited to aryl and heteroaryl groups and sterically hindered alkyl groups such as t-butyl. R^1 can be highly variable and is limited only by subsequent reaction steps.

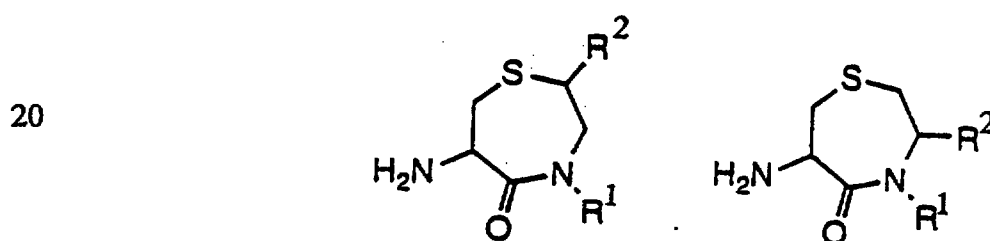
Still further is the Kametani procedure which provides for lactams as follows:



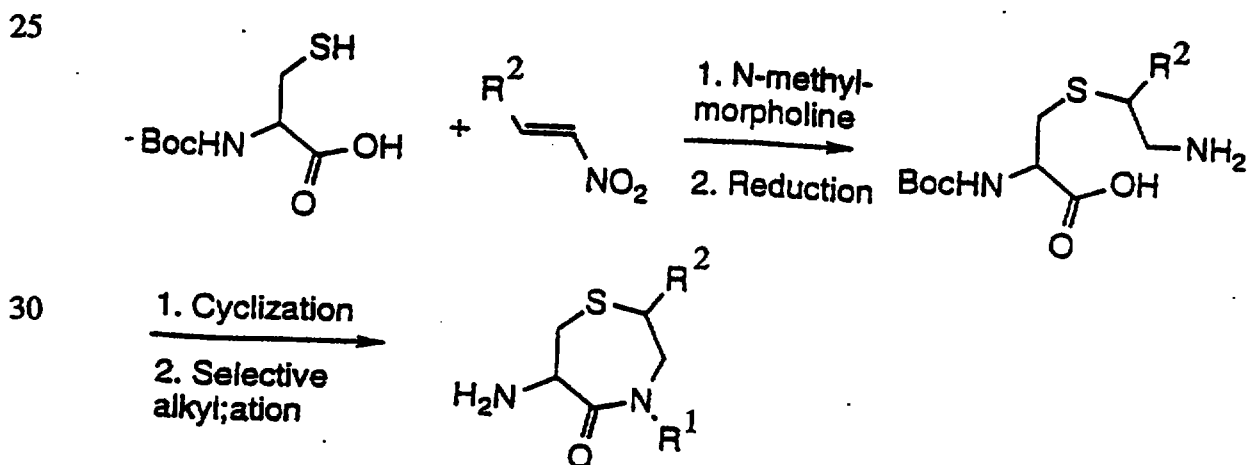
10

In principle, the Kametani procedure allows for a wide selection of R¹ and R² groups limited primarily by stability to the reaction conditions.

See, for example, Yanganasawa, et al., *J. Med. Chem.*, 30:1984-1991 (1987) and J. Das et al., *Biorg. Med. Chem. Lett.*, 4:2193-2198 (1994) which describes general methods for the synthesis of isomeric 7-membered thialactams of the following structure:

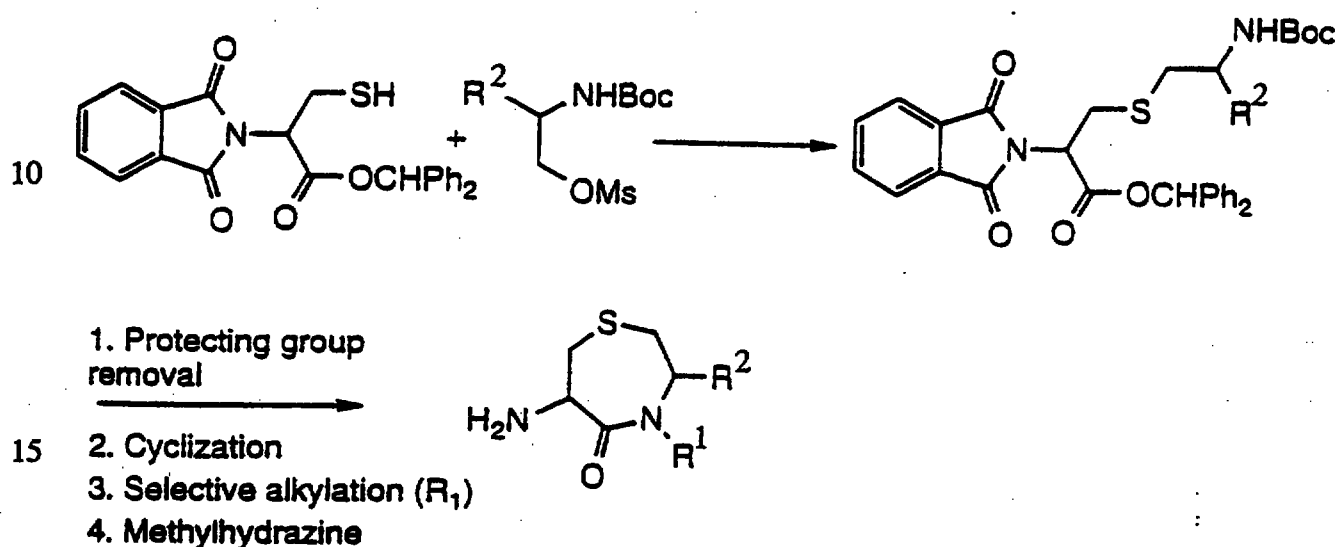


The first synthetic route is:



-- 90 --

R^2 can be highly variable (e.g., alkyl, substituted alkyl, aryl, heteroaryl, heterocyclic and the like) since a number of well documented routes exist for the synthesis of nitroethylene derivatives from aldehydes and nitromethane (Henry reaction) followed by dehydration. R^1 is limited to groups that can
 5 undergo alkylation reactions.



In this procedure, R^2 can be highly variable. The starting component required
 20 to introduce R^2 can be readily derived by the reduction of any known alpha-BOC-amino acid to the alcohol derivative followed by formation of the mesylate.

As noted above, the primary approaches to the preparation of lactams is
 25 the Beckmann/Schmidt ring expansion reaction using either inter- or intramolecular approaches serves to prepare lactams of various ring sizes. The intramolecular approach generates bicyclic materials with the lactam nitrogen incorporated into the ring fusion. Additional approaches set forth above are at the base of the methodology are internal cyclization of omega-amino
 30 acids/esters where the construction of the substituent pattern takes place prior to cyclization, and internal cyclization of an electrophilic center onto a

nucleophilic functional group as in the Friedel-Crafts type cyclization at the center of the Ben-Ishal procedure for making benzazepinones. This latter procedure is applicable to a wide variety of heteroaromatics as well as benzenoid rings, and may also be applied to non-aromatic double or triple
5 bonds to generate a wide array of substituents or ring fusions.

Deoxygenation of the lactam by reagents such as diborane, LiAlH_4 , and the like leads to azaheterocycles ($=\text{X}$ is dihydro).

10 Similarly, for $\text{U} = \text{H}$, OH , such compounds can be prepared by epoxidation of cycloalkenyl groups followed by oxirane opening by, e.g., ammonia. After formation of compounds of formula I, $=\text{U}$ being H , OH can be oxidized to provide for cycloalkylones ($=\text{X}$ being oxo).

15 Additionally, the 5,7-dihydro-6H-diben[b,d]azepin-6-one derivatives employed in this invention can be prepared using conventional procedures and reagents. For example, an appropriately substituted *N-tert*-Boc-2-amino-2'-methylbiphenyl compound can be cyclized to form the corresponding 5,7-dihydro-6H-diben[b,d]azepin-6-one derivative by first treating the biphenyl
20 compound with about 2.1 to about 2.5 equivalents of a strong base, such as *sec*-butyl lithium. This reaction is typically conducted at a temperature ranging from about -80°C to about -60°C in an inert diluent such as THF. The resulting dianion is then treated with dry carbon dioxide at a temperature of about -78°C to afford the 5,7-dihydro-6H-diben[b,d]azepin-6-one. This
25 procedure is described further in R. D. Clark et al., *Tetrahedron*, 49(7), 1351-1356 (1993) and references cited therein.

After forming the 5,7-dihydro-6H-diben[b,d]azepin-6-one, the amide nitrogen can be readily alkylated by first treating the dibenzazepinone with about
30 1.1 to about 1.5 equivalents of a strong base, such as sodium hydride, in an inert diluent, such as DMF. This reaction is typically conducted at a

-- 92 --

temperature ranging from about -10°C to about 80°C for about 0.5 to about 6 hours. The resulting anion is then contacted with an excess, preferably about 1.1 to about 3.0 equivalents, of an alkyl halide, typically an alkyl chloride, bromide or iodide. Generally, this reaction is conducted at a temperature of
5 about 0°C to about 100°C for about 1 to about 48 hours.

An amino group can then be introduced at the 5-position of the 7-alkyl-5,7-dihydro-6H-diben[b,d]azepin-6-one using conventional procedures and reagents. For example, treatment of 7-methyl-5,7-dihydro-6H-
10 diben[b,d]azepin-6-one with an excess of butyl nitrite in the presence of a strong base, such as potassium 1,1,1,3,3,3-hexamethyldisilazane (KHMDs), affords 5-oximo-7-methyl-5,7-dihydro-6H-diben[b,d]azepin-6-one. Subsequent reduction of the oximo group by hydrogenation in the presence of a catalyst, such as palladium on carbon, then provides 5-amino-7-methyl-5,7-dihydro-6H-
15 diben[b,d]azepin-6-one. Other conventional amination procedures, such as azide transfer followed by reduction of the azido group, may also be employed.

Similarly, various benzodiazepine derivatives suitable for use in this invention can be prepared using conventional procedures and reagents. For
20 example, a 2-aminobenzophenone can be readily coupled to α -(isopropylthio)-N-(benzyloxycarbonyl)glycine by first forming the acid chloride of the glycine derivative with oxalyl chloride, and then coupling the acid chloride with the 2-aminobenzophenone in the presence of a base, such as 4-methylmorpholine, to afford the 2-[α -(isopropylthio)-N-(benzyloxycarbonyl)glyciny]-
25 aminobenzophenone. Treatment of this compound with ammonia gas in the presence of an excess, preferably about 1.1 to about 1.5 equivalents, of mercury (II) chloride then affords the 2-[N-(α -amino)-N'-(benzyloxycarbonyl)-glyciny]aminobenzophenone. This intermediate can then be readily cyclized by treatment with glacial acetic acid and ammonium acetate to provide the 3-
30 (benzyloxycarbonyl)amino-2,3-dihydro-5-phenyl-1H-1,4-benzodiazepin-2-one.

Subsequent removal of the Cbz group affords the 3-amino-2,3-dihydro-5-phenyl-1H-1,4-benzodiazepin-2-one.

Alternatively, 2,3-dihydro-5-phenyl-1H-1,4-benzodiazepin-2-ones can be readily aminated at the 3-position using conventional azide transfer reactions followed by reduction of the resulting azido group to form the corresponding amino group. The conditions for these and related reactions are described in the examples set forth below. Additionally, 2,3-dihydro-5-phenyl-1H-1,4-benzodiazepin-2-ones are readily alkylated at the 1-position using conventional procedures and reagents. For example, this reaction is typically conducted by first treating the benzodiazepinone with about 1.1 to about 1.5 equivalents of a base, such as sodium hydride, potassium *tert*-butoxide, potassium 1,1,1,3,3,3-hexamethyldisilazane, cesium carbonate, in an inert diluent, such as DMF. This reaction is typically conducted at a temperature ranging from about -78°C to about 80°C for about 0.5 to about 6 hours. The resulting anion is then contacted with an excess, preferably about 1.1 to about 3.0 equivalents, of an alkyl halide, typically an alkyl chloride, bromide or iodide. Generally, this reaction is conducted at a temperature of about 0°C to about 100°C for about 1 to about 48 hours.

Additionally, the 3-amino-2,4-dioxo-2,3,4,5-tetrahydro-1H-1,5-benzodiazepines employed in this invention are typically prepared by first coupling malonic acid with a 1,2-phenylenediamine. Conditions for this reaction are well known in the art and are described, for example, in PCT Application WO 96-US8400 960603. Subsequent alkylation and amination using conventional procedures and reagents affords various 3-amino-1,5-bis(alkyl)-2,4-dioxo-2,3,4,5-tetrahydro-1H-1,5-benzodiazepines. Such procedures are described in further detail in the example set forth below.

Accordingly, a vast number of lactams, lactones and thiolactones are available by art recognized procedures. Similarly, the art is replete with

examples of aminocycloalkyl compounds for use in the synthesis of compounds of formula I above.

5 In the synthesis of compounds of formula I using the synthetic methods described above, the starting materials can contain a chiral center (e.g., alanine) and, when a racemic starting material is employed, the resulting product is a mixture of R,S enantiomers. Alternatively, a chiral isomer of the starting material can be employed and, if the reaction protocol employed does not racemize this starting material, a chiral product is obtained. Such reaction
10 protocols can involve inversion of the chiral center during synthesis.

Accordingly, unless otherwise indicated, the products of this invention are a mixture of diastereomers or R,S enantiomers. Preferably, however, when a chiral product is desired, the chiral product corresponds to the L-amino acid
15 derivative. Alternatively, chiral products can be obtained via purification techniques which separates diastereomers or enantiomers to provide for one or the other stereoisomer. Such techniques are well known in the art.

Pharmaceutical Formulations

20 When employed as pharmaceuticals, the compounds of formula I are usually administered in the form of pharmaceutical compositions. These compounds can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, and intranasal. These compounds are effective as both injectable and oral compositions. Such
25 compositions are prepared in a manner well known in the pharmaceutical art and comprise at least one active compound.

This invention also includes pharmaceutical compositions which contain, as the active ingredient, one or more of the compounds of formula I above
30 associated with pharmaceutically acceptable carriers. In making the compositions of this invention, the active ingredient is usually mixed with an

excipient, diluted by an excipient or enclosed within such a carrier which can be in the form of a capsule, sachet, paper or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

10

In preparing a formulation, it may be necessary to mill the active compound to provide the appropriate particle size prior to combining with the other ingredients. If the active compound is substantially insoluble, it ordinarily is milled to a particle size of less than 200 mesh. If the active compound is substantially water soluble, the particle size is normally adjusted by milling to provide a substantially uniform distribution in the formulation, e.g. about 40 mesh.

15

Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, sterile water, syrup, and methyl cellulose. The formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxybenzoates; sweetening agents; and flavoring agents. The compositions of the invention can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art.

20

25

30

-- 96 --

The compositions are preferably formulated in a unit dosage form, each dosage containing from about 5 to about 100 mg, more usually about 10 to about 30 mg, of the active ingredient. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and
5 other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient. Preferably, the compound of formula I above is employed at no more than about 20 weight percent of the pharmaceutical composition, more preferably no more than about 15 weight
10 percent, with the balance being pharmaceutically inert carrier(s).

The active compound is effective over a wide dosage range and is generally administered in a pharmaceutically effective amount. It, will be understood, however, that the amount of the compound actually administered
15 will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

For preparing solid compositions such as tablets, the principal active
20 ingredient is mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly
25 throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation is then subdivided into unit dosage forms of the type described above containing from, for example, 0.1 to about 500 mg of the active ingredient of the present invention.

30

-- 97 --

The tablets or pills of the present invention may be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil, or peanut oil, as well as elixirs and similar pharmaceutical vehicles.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described *supra*. Preferably the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably pharmaceutically acceptable solvents may be nebulized by use of inert gases. Nebulized solutions may be breathed directly from the nebulizing device or the nebulizing device may be attached to a face mask tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions may be administered, preferably orally or nasally, from devices which deliver the formulation in an appropriate manner.

30

The following formulation examples illustrate the pharmaceutical compositions of the present invention.

Formulation Example 1

5 Hard gelatin capsules containing the following ingredients are prepared:

	<u>Ingredient</u>	<u>Quantity</u>	
		<u>(mg/capsule)</u>	
	Active Ingredient	30.0	
10	Starch		305.0
	Magnesium stearate	5.0	

15 The above ingredients are mixed and filled into hard gelatin capsules in 340 mg quantities.

Formulation Example 2

A tablet formula is prepared using the ingredients below:

	<u>Ingredient</u>	<u>Quantity</u>	
		<u>(mg/tablet)</u>	
	Active Ingredient	25.0	
	Cellulose, microcrystalline	200.0	
	Colloidal silicon dioxide	10.0	
25	Stearic acid	5.0	

The components are blended and compressed to form tablets, each weighing 240 mg.

30 Formulation Example 3

A dry powder inhaler formulation is prepared containing the following components:

	<u>Ingredient</u>	<u>Weight %</u>	
35	Active Ingredient	5	
	Lactose		95

The active ingredient is mixed with the lactose and the mixture is added to a dry powder inhaling appliance.

Formulation Example 4

5 Tablets, each containing 30 mg of active ingredient, are prepared as follows:

	<u>Ingredient</u>	<u>Quantity</u> <u>(mg/tablet)</u>
10	Active Ingredient	30.0 mg
	Starch	45.0 mg
	Microcrystalline cellulose	35.0 mg
	Polyvinylpyrrolidone (as 10% solution in sterile water)	4.0 mg
15	Sodium carboxymethyl starch	4.5 mg
	Magnesium stearate	0.5 mg
	Talc	<u>1.0 mg</u>
20	Total	120 mg

25 The active ingredient, starch and cellulose are passed through a No. 20 mesh U.S. sieve and mixed thoroughly. The solution of polyvinyl-pyrrolidone is mixed with the resultant powders, which are then passed through a 16 mesh U.S. sieve. The granules so produced are dried at 50° to 60°C and passed through a 16 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 30 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

Formulation Example 5

Capsules, each containing 40 mg of medicament are made as follows:

-- 100 --

	<u>Ingredient</u>	<u>Quantity</u> <u>(mg/capsule)</u>
5	Active Ingredient	40.0 mg
	Starch	109.0 mg
	Magnesium stearate	<u>1.0 mg</u>
	Total	150.0 mg

10

The active ingredient, starch, and magnesium stearate are blended, passed through a No. 20 mesh U.S. sieve, and filled into hard gelatin capsules in 150 mg quantities.

15

Formulation Example 6

Suppositories, each containing 25 mg of active ingredient are made as follows:

20	<u>Ingredient</u>	<u>Amount</u>
	Active Ingredient	25 mg
	Saturated fatty acid glycerides to	2,000 mg

25

The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2.0 g capacity and allowed to cool.

30

Formulation Example 7

Suspensions, each containing 50 mg of medicament per 5.0 ml dose are made as follows:

-- 101 --

	<u>Ingredient</u>	<u>Amount</u>
	Active Ingredient	50.0 mg
5	Xanthan gum	4.0 mg
	Sodium carboxymethyl cellulose (11%)	
	Microcrystalline cellulose (89%)	50.0 mg
	Sucrose	1.75 g
	Sodium benzoate	10.0 mg
10	Flavor and Color	q.v.
	Purified water to	5.0 ml

The active ingredient, sucrose and xanthan gum are blended, passed through a No. 10 mesh U.S. sieve, and then mixed with a previously made solution of the microcrystalline cellulose and sodium carboxymethyl cellulose in water. The sodium benzoate, flavor, and color are diluted with some of the water and added with stirring. Sufficient water is then added to produce the required volume.

20

Formulation Example 8

	<u>Ingredient</u>	<u>Quantity</u> <u>(mg/capsule)</u>
25	Active Ingredient	15.0 mg
	Starch	407.0 mg
	Magnesium stearate	<u>3.0 mg</u>
	Total	425.0 mg

30

The active ingredient, starch, and magnesium stearate are blended, passed through a No. 20 mesh U.S. sieve, and filled into hard gelatin capsules in 560 mg quantities.

-- 102 --

Formulation Example 9

A subcutaneous formulation may be prepared as follows:

	<u>Ingredient</u>	<u>Quantity</u>
5	Active Ingredient corn oil	1.0 mg 1 ml

(Depending on the solubility of the active ingredient in corn oil, up to
10 about 5.0 mg or more of the active ingredient may be employed in this
formulation, if desired).

Formulation Example 10

A topical formulation may be prepared as follows:

15	<u>Ingredient</u>	<u>Quantity</u>
	Active Ingredient	1-10 g
	Emulsifying Wax	30 g
	Liquid Paraffin	20 g
20	White Soft Paraffin	to 100 g

The white soft paraffin is heated until molten. The liquid paraffin and
emulsifying wax are incorporated and stirred until dissolved. The active
25 ingredient is added and stirring is continued until dispersed. The mixture is
then cooled until solid.

Another preferred formulation employed in the methods of the present
invention employs transdermal delivery devices ("patches"). Such transdermal
30 patches may be used to provide continuous or discontinuous infusion of the
compounds of the present invention in controlled amounts. The construction
and use of transdermal patches for the delivery of pharmaceutical agents is well
known in the art. See, e.g., U.S. Patent 5,023,252, issued June 11, 1991,
herein incorporated by reference. Such patches may be constructed for
35 continuous, pulsatile, or on demand delivery of pharmaceutical agents.

Frequently, it will be desirable or necessary to introduce the pharmaceutical composition to the brain, either directly or indirectly. Direct techniques usually involve placement of a drug delivery catheter into the host's ventricular system to bypass the blood-brain barrier. One such implantable delivery system
5 used for the transport of biological factors to specific anatomical regions of the body is described in U.S. Patent 5,011,472 which is herein incorporated by reference.

Indirect techniques, which are generally preferred, usually involve
10 formulating the compositions to provide for drug latentiation by the conversion of hydrophilic drugs into lipid-soluble drugs. Latentiation is generally achieved through blocking of the hydroxy, carbonyl, sulfate, and primary amine groups present on the drug to render the drug more lipid soluble and amenable to transportation across the blood-brain barrier. Alternatively, the delivery of
15 hydrophilic drugs may be enhanced by intra-arterial infusion of hypertonic solutions which can transiently open the blood-brain barrier.

Other suitable formulations for use in the present invention can be found in
20 *Remington's Pharmaceutical Sciences*, Mace Publishing Company, Philadelphia, PA, 17th ed. (1985).

Utility

The compounds and pharmaceutical compositions of the invention are useful in inhibiting β -amyloid peptide release and/or its synthesis, and,
25 accordingly, have utility in diagnosing and treating Alzheimer's disease in mammals including humans.

As noted above, the compounds described herein are suitable for use in a variety of drug delivery systems described above. Additionally, in order to
30 enhance the *in vivo* serum half-life of the administered compound, the compounds may be encapsulated, introduced into the lumen of liposomes,

-- 104 --

prepared as a colloid, or other conventional techniques may be employed which provide an extended serum half-life of the compounds. A variety of methods are available for preparing liposomes, as described in, e.g., Szoka, et al., U.S. Patent Nos. 4,235,871, 4,501,728 and 4,837,028 each of which is incorporated
5 herein by reference.

The amount of compound administered to the patient will vary depending upon what is being administered, the purpose of the administration, such as prophylaxis or therapy, the state of the patient, the manner of administration,
10 and the like. In therapeutic applications, compositions are administered to a patient already suffering from AD in an amount sufficient to at least partially arrest further onset of the symptoms of the disease and its complications. An amount adequate to accomplish this is defined as "therapeutically effective dose." Amounts effective for this use will depend on the judgment of the
15 attending clinician depending upon factors such as the degree or severity of AD in the patient, the age, weight and general condition of the patient, and the like. Preferably, for use as therapeutics, the compounds described herein are administered at dosages ranging from about 1 to about 500 mg/kg/day.

20 In prophylactic applications, compositions are administered to a patient at risk of developing AD (determined for example by genetic screening or familial trait) in an amount sufficient to inhibit the onset of symptoms of the disease. An amount adequate to accomplish this is defined as "prophylactically effective dose." Amounts effective for this use will depend on the judgment of the
25 attending clinician depending upon factors such as the age, weight and general condition of the patient, and the like. Preferably, for use as prophylactics, the compounds described herein are administered at dosages ranging from about 1 to about 500 mg/kg/day.

30 As noted above, the compounds administered to a patient are in the form of pharmaceutical compositions described above. These compositions may be

sterilized by conventional sterilization techniques, or may be sterile-filtered.

The resulting aqueous solutions may be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile aqueous carrier prior to administration. The pH of the compound preparations typically will be

5 between 3 and 11, more preferably from 5 to 9 and most preferably from 7 and 8. It will be understood that use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of pharmaceutical salts.

10 The compounds described herein are also suitable for use in the administration of the compounds to a cell for diagnostic and drug discovery purposes. Specifically, the compounds may be used in the diagnosis of cells releasing and/or synthesizing β -amyloid peptide. In addition the compounds described herein are useful for the measurement and evaluation of the activity of other candidate drugs on the inhibition of the cellular release and/or

15 synthesis of β -amyloid peptide.

The following synthetic and biological examples are offered to illustrate this invention and are not to be construed in any way as limiting the scope of this invention.

20

EXAMPLES

In the examples below, the following abbreviations have the following meanings. If an abbreviation is not defined, it has its generally accepted meaning.

25

BEMP	=	2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine
Boc	=	<i>t</i> -butoxycarbonyl
BOP	=	benzotriazol-1-yloxy-tris(dimethylamino)phosphonium
30		hexafluorophosphate
bd	=	broad doublet
bs	=	broad singlet
d	=	doublet
dd	=	doublet of doublets
35		
DIC	=	diisopropylcarbodiimide

-- 106 --

	DCM	=	dichloromethane
	DMF	=	dimethylformamide
	DMAP	=	dimethylaminopyridine
	DMSO	=	dimethylsulfoxide
5	EDC	=	ethyl-1-(3-dimethylaminopropyl)carbodiimide
	eq.	=	equivalents
	EtOAc	=	ethyl acetate
	EtOH	=	ethanol
	g	=	grams
10	HOBt	=	1-hydroxybenzotriazole hydrate
	Hunig's base	=	diisopropylethylamine
	L	=	liter
	m	=	multiplet
	M	=	molar
15	max	=	maximum
	meq	=	milliequivalent
	mg	=	milligram
	mL	=	milliliter
	mm	=	millimeter
20	mmol	=	millimole
	MOC	=	methoxyoxycarbonyl
	N	=	normal
	N/A	=	not available
	ng	=	nanogram
25	nm	=	nanometers
	OD	=	optical density
	PEPC	=	1-(3-(1-pyrrolidinyl)propyl)-3-ethylcarbodiimide
	PP-HOBt	=	piperidine-piperidine-1-hydroxybenzotriazole
30	psi	=	pounds per square inch
	ϕ	=	phenyl
	q	=	quartet
	quint.	=	quintet
	rpm	=	rotations per minute
35	s	=	singlet
	t	=	triplet
	TFA	=	trifluoroacetic acid
	THF	=	tetrahydrofuran
	tlc	=	thin layer chromatography
40	μ L	=	microliter
	UV	=	ultra-violet

Additionally, the following abbreviations are used to indicate the commercial source for certain compounds and reagents:

-- 107 --

	Aldrich	=	Aldrich Chemical Company, Inc., 1001 West Saint Paul Avenue, Milwaukee, WI 53233 USA
5	Fluka	=	Fluka Chemical Corp., 980 South 2nd Street, Ronkonkoma NY 11779 USA
	Lancaster	=	Lancaster Synthesis, Inc., P.O. Box 100 Windham, NH 03087 USA
10	Sigma	=	Sigma, P.O. Box 14508, St. Louis MO 63178 USA
	Chemservice	=	Chemservice Inc., Westchester, PA
15	Bachem	=	Bachem Biosciences Inc., 3700 Horizon Drive, Renaissance at Gulph Mills, King of Prussia, PA 19406 USA
20	Maybridge	=	Maybridge Chemical Co. Trevillet, Tintagel, Cornwall PL34 OHW United Kingdom
	TCI	=	TCI America, 9211 North Harborside Street, Portland OR 97203
25	Alfa	=	Johnson Matthey Catalog Company, Inc. 30 Bond Street, Ward Hill, MA 01835-0747
30	Novabiochem	=	Calbiochem-Novabiochem Corp. 10933 North Torrey Pines Road, P.O. Box 12087, La Jolla CA 92039-2087
	Oakwood	=	Oakwood, Columbia, South Carolina
35	Advanced Chemtech	=	Advanced Chemtech, Louisville, KY
	Pfaltz & Bauer	=	Pfaltz & Bauer, Waterbury, CT, USA

40 In the examples below, all temperatures are in degrees Celsius (unless otherwise indicated). Each of the compounds set forth in Examples 1-___ was prepared by one of the following General Procedures, unless otherwise indicated.

-- 108 --

GENERAL PROCEDURE A

EDC Coupling -- Procedure I

A carboxylic acid (1.0 eq.), 1-hydroxybenzotriazole hydrate (1.1 eq.) and an amine (1.0 eq.) were stirred in THF under a nitrogen atmosphere. To this mixture was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.1 eq.) followed by a suitable base, such as Hunig's base (1.1 eq. of base if a free amine is used, and 2.1 eq. of base if an amine hydrochloride is used). After stirring from about 4 h to 17 h at room temperature, the solvent was removed under reduced pressure. The residue was partitioned between ethyl acetate and water and the organic layer was separated and washed sequentially with aqueous sodium bicarbonate, dilute aqueous hydrochloric acid and brine. The organic layer was then dried (sodium sulfate) and concentrated under reduced pressure. The product was either used without further purification or was purified using standard procedures, such as silica gel chromatography and/or recrystallization.

GENERAL PROCEDURE B

EDC Coupling -- Procedure II

A carboxylic acid (1 eq.) was stirred in a suitable solvent (such as THF, dioxane or DMF) and an alcohol or oxime (1 - 5 eq.) was added. To this mixture was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.2 eq.) and 1-hydroxybenzotriazole hydrate (1 eq.) followed by a suitable base, such as 4-methylmorpholine, triethylamine, or Hunig's base (0 - 1 eq.). A catalytic amount (0.1 eq.) of 4-dimethylaminopyridine was then added and the mixture was stirred at ambient temperature and under a dry atmosphere of nitrogen. After 20 hours, the mixture was concentrated under reduced pressure and the resulting concentrate was partitioned between ethyl acetate and water. The organic portion was separated and washed with aqueous sodium bicarbonate and brine, and then dried (sodium sulfate) and concentrated under reduced pressure. The crude product was either used without further

purification or was purified using standard procedures, such as silica gel chromatography and/or recrystallization.

GENERAL PROCEDURE C

5

EDC Coupling -- Procedure III

To a solution of the amine (1 eq.) in THF (0.08-0.06 M) at 0°C under an atmosphere of nitrogen was added 3,5-difluorophenylacetic acid (1.10 eq.), 1-hydroxybenzotriazole hydrate (1.15-1.20 eq.), *N,N*-diisopropylethylamine (2.30 eq.), followed by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.15-1.20 eq.). The cooling bath was removed and the mixture allowed to warm to ambient temperature with stirring for 12-14 hours. The solution was then diluted with ethyl acetate, washed with 0.2-0.5 M aqueous HCl (2x), dilute aqueous NaHCO₃ (1x), and brine (1x), and then the organic phase was dried over Na₂SO₄, filtered, concentrated *in vacuo*, and the residue purified by flash chromatography to afford the product.

GENERAL PROCEDURE D

Removal of *N-tert*-BOC Protecting Group -- Procedure I

To the *N*-Boc-protected imidazoline (1 eq.) in a round-bottomed flask, cooled to 0°C, was added trifluoroacetic acid (0.07-0.08 M) followed by anisole (6.2-8.0 eq.). The resulting solution was stirred at 0°C for 1 hour, then allowed to warm to ambient temperature with stirring for 1-1.5 hours. The solution was then concentrated *in vacuo*, Et₂O was added and the mixture again concentrated *in vacuo*. The residue was dissolved in either CH₂Cl₂ or EtOAc and washed with dilute aqueous NaHCO₃ (1 or 2x), and sometimes brine (1x), then the organic phase was dried over Na₂SO₄, filtered, and concentrated *in vacuo* to afford the product.

GENERAL PROCEDURE E

30

Removal of *N-tert*-BOC Protecting Group -- Procedure II

The *N-tert*-Boc-amine was dissolved in a suitable dry solvent (such as 1,4-dioxane or ethyl acetate) and the solution was cooled in an ice bath. Gaseous HCl was introduced into the solution until the mixture was saturated with HCl and the mixture was then stirred until the starting material was consumed. The resulting mixture was concentrated under reduced pressure to yield the amine hydrochloride. The amine hydrochloride was either used without further purification or was triturated in diethyl ether and the resulting solid collected by filtration.

GENERAL PROCEDURE F

Thiazoline Synthesis -- Procedure I

To a stirred solution of a nitrile (1 eq.) in dry ethanol under an atmosphere of nitrogen was added 2-mercaptoethylamine (1 - 3 eq.). The reaction mixture was then heated at reflux until the nitrile was consumed. The mixture was then concentrated under reduced pressure and the resulting product purified by chromatography and/or recrystallization.

GENERAL PROCEDURE G

Thiazoline Synthesis -- Procedure II

To a stirred solution of a nitrile (1 eq.) in dry ethanol under an atmosphere of nitrogen were added L-cysteine ethyl ester hydrochloride (1 - 3 eq.) (Aldrich) and a stoichiometric amount of *N,N*-diisopropylethylamine (based on the L-cysteine ethyl ester hydrochloride). The reaction mixture was heated at reflux for three hours and then concentrated under reduced pressure. The resulting product was purified by chromatography and/or crystallization.

GENERAL PROCEDURE H

Cyclization Using Burgess Reagent

To a solution of *N*-[*N*-(3,5-dichlorophenyl)-L-alaninyl]-L-serine methyl ester (178 mg, 0.5 mmol) in 2.5 mL of THF was added 147 mg (0.62 mmol, 1.2 eq.) of (methoxycarbonylsulfamoyl)triethylammonium hydroxide, inner salt

-- 111 --

(available from Aldrich Chemical Co., Milwaukee, Wisconsin). The solution was refluxed for 5 h and then stirred at room temperature for 36 h. The solvents were then removed and the residue purified by preparative tlc using 3:2 hexanes/ethyl acetate as the eluent to afford 50 mg of 2-[(S)-1-(3,5-dichloroanilino)ethyl]-(S)-4-methoxycarbonyl-2-oxazolidine as a yellow oil. Various other (S)-4-alkoxycarbonyl-2-oxazolidines can be prepared from N-substituted (amino acid)-L-serine esters using this procedure.

GENERAL PROCEDURE I

5-Aminoalkyl-1,2,4-Oxadiazole Synthesis

An *N-tert*-Boc-protected amino acid and an amidoxime are reacted according to General Procedure B above to provide the corresponding O-acyloxime. The O-acyloxime is then heated at reflux in xylenes with the azeotropic removal of water to provide the *N-tert*-Boc-protected 5-aminoalkyl-1,2,4-oxadiazole derivative, which is then typically purified by silica gel chromatography. The *tert*-Boc protecting group is then removed according to General Procedure E above to afford the 5-aminoalkyl-1,2,4-oxadiazole.

The following Examples A-L illustrate the synthesis of heterocyclic intermediates which may be used to prepare the compounds of the present invention.

Example A

Synthesis of

(S)-5-(1-Aminoethyl)-3-ethyl-1,2,4-oxadiazole Hydrochloride

Following General Procedure I above, the title compound was prepared using *N-tert*-Boc-L-alanine (Sigma) and propanamidoxime.

Example B

Synthesis of

(S)-5-(1-Amino-2-phenylethyl)-3-methyl-1,2,4-oxadiazole Hydrochloride

-- 112 --

Following General Procedure I above, the title compound was prepared using *N*-*tert*-Boc-L-phenylalanine (Sigma) and acetamidoxime.

Example C

5

Synthesis of (S)-5-(1-Amino-1-phenylmethyl)-3-methyl-1,2,4-oxadiazole Hydrochloride

Following General Procedure I above, the title compound was prepared using *N*-*tert*-Boc-L-phenylglycine (Sigma) and acetamidoxime.

10

Example D

Synthesis of (S)-5-(1-Amino-1-phenylmethyl)-3-phenyl-1,2,4-oxadiazole Hydrochloride

Following General Procedure I above, the title compound was prepared using *N*-*tert*-Boc-L-phenylglycine (Sigma) and benzamidoxime.

15

Example E

Synthesis of (S)-5-(1-Amino-1-phenylmethyl)- 3-(4-methoxyphenylmethyl)-1,2,4-oxadiazole Hydrochloride

Following General Procedure I above, the title compound was prepared using *N*-*tert*-Boc-L-phenylglycine (Sigma) and 4-methoxyphenylacetamidoxime.

20

Example F

Synthesis of (2S)-2-(1-Aminoethyl)-5(R,S)-ethoxycarbonyl-2-oxazoline

25 **Step A -- Synthesis of *N*-Carbobenzyloxy-L-alanine-D,L-isoserine Ethyl Ester**

Following General Procedure A above and using *N*-carbobenzyloxy-L-alanine (Sigma) and D,L-isoserine ethyl ester hydrochloride, the title compound was prepared.

30

Step B -- Synthesis of (2S)-2-[1-(*N*-Carbobenzyloxy)aminoethyl]-5(R,S)-ethoxycarbonyl-2-oxazoline

-- 113 --

To a solution of *N*-carbobenzyloxy-L-alanine-D,L-isoserine ethyl ester from Step A above in dry THF was added triphenylphosphine (2 eq.). The mixture was cooled to 0°C and a solution of diethyl azodicarboxylate (2 eq.) in THF was added dropwise. The resulting mixture was allowed to warm to room temperature and, after 20 hours, the mixture was concentrated under reduced pressure. The resulting oil was purified by silica gel chromatography to yield the title compound as an oil which was used without further purification.

Step C -- Synthesis of (2S)-2-(1-Aminoethyl)-5(R,S)-ethoxycarbonyl-2-oxazoline

The crude oil from Step B above was dissolved in ethanol and the solution was degassed and stirred under an atmosphere of nitrogen. Palladium on carbon (10%) was added and the atmosphere of nitrogen was replaced with hydrogen under balloon pressure. The mixture was stirred for 2 hours and then filtered through Celite. The filtrate was concentrated and the residue purified by silica gel chromatography to provide the title compound as an oil.

Example G

Synthesis of

(S)-2-(1-Aminoethyl)-4(R,S)-ethoxycarbonyl-2-thiazoline Hydrochloride

Step A -- Synthesis of (S)-2-[1-(*N*-tert-Butoxycarbonyl)aminoethyl]-4-ethoxycarbonyl-2-thiazoline

The title compound was prepared according to the procedures described in C. D. J. Boden, et al., *Synlett*, 5, 417 (1995).

Step B -- Synthesis of (S)-2-(1-Aminoethyl)-4(R,S)-ethoxycarbonyl-2-thiazoline Hydrochloride

The *N*-tert-Boc protecting group was removed from the product of Step A above using General Procedure E above to afford the title compound.

Example H

Synthesis of

2-(3,5-Difluorophenylmethyl)-4-carboxy-2-thiazoline

-- 114 --

Step A -- Synthesis of 2-(3,5-Difluorophenylmethyl)-5-ethoxycarbonyl-2-thiazoline

Following General Procedure G and using 3,5-difluorophenylacetonitrile and L-cysteine ethyl ester hydrochloride (Aldrich), the title compound was prepared.

Step B -- Synthesis of 2-(3,5-Difluorophenylmethyl)-5-carboxy-2-thiazoline

The title compound was prepared by hydrolysis of the product from Step A above using 1 equivalent of LiOH in wet dioxane as described in General Procedure II-A, Method B.

Example I**Synthesis of****N-(3,5-Difluorophenylacetyl)phenylglycinonitrile**

Following General Procedure A above and using 3,5-difluorophenylacetic acid (Aldrich) and 2-phenylglycinonitrile hydrochloride (Lancaster), the title compound was prepared. The crude product was purified by silica gel chromatography using 1:1 ethyl acetate/hexanes as the eluent, followed by crystallization from 1-chlorobutane/acetonitrile.

NMR data was as follows:

¹H-nmr (CDCl₃, 250 MHz): δ = 3.61 (s, 2H), 6.13 (d, 1H), 6.98 (m, 2H), 7.12 (m, 1H), 7.46 (m, 5H), 9.40 (d, 1H).

C₁₆H₁₂F₂N₂O (MW = 286.28); mass spectroscopy (M⁺) 286.

Example J**Synthesis of 2-(1-Aminoethyl)-1-tert-butoxycarbonyl-4-methoxycarbonyl-4-phenylmethyl-2-imidazoline****Step A -- Synthesis of 1-[2-(N-carbobenzyloxy)amino-thiopropionyl]piperidine**

Following the procedures described in Gilbert, et al., *Tetrahedron*, 1995 51, 6315-6336 and using N-carbobenzyloxy-D,L-alanine (Sigma), the title compound was prepared in two steps (51% overall yield) as a solid having a melting point

of 68-69°C. The final reaction was monitored by tlc ($R_f = 0.59$ in 24:1 DCM/EtOAc) and the product was purified by flash column chromatography.

NMR data was as follows:

^1H -nmr (CDCl_3 , 250 MHz): $\delta = 7.37\text{--}7.29$ (m, 5H), 6.46 (bd, 1H, $J = 8.26$ Hz), 5.10 (AB_q , 2H, $J_{\text{AB}} = 12.38$ Hz, $\Delta\nu_{\text{AB}} = 9.12$ Hz), 4.92 (p, 1H, $J = 7.07$ Hz), 4.41-4.34 (m, 1H), 4.17-4.06 (m, 1H), 3.86-3.65 (m, 2H), 1.75-1.65 (bm, 6H), 1.35 (d, 3H, $J = 6.75$ Hz).

$\text{C}_{16}\text{H}_{22}\text{N}_2\text{O}_2\text{S}$ (MW = 306.43); mass spectroscopy (MH^+) 306.2.

10 **Step B -- Synthesis of Methyl 2,3-Diamino-2-phenylmethylpropionate**

Following the procedures described in Gilbert, et al., *Tetrahedron*, 1995 51, 6315-6336 and using L-phenylalanine methyl ester hydrochloride (Aldrich), the title compound was prepared in three steps (14% overall yield). The final reaction was monitored by tlc ($R_f = 0.26$ in 9:1 DCM/MeOH) and the product was purified by flash column chromatography, followed by recrystallization from cyclohexane/ethyl acetate (20:1).

NMR data was as follows:

^1H -nmr (CDCl_3 , 250 MHz): $\delta = 7.32\text{--}7.17$ (m, 3H), 7.14-7.09 (m, 2H), 3.70 (s, 3H), 2.96 (AB_q , 2H, $J_{\text{AB}} = 13.13$ Hz, $\Delta\nu_{\text{AB}} = 114.63$ Hz), 2.90 (AB_q , 2H, $J_{\text{AB}} = 13.38$ Hz, $\Delta\nu_{\text{AB}} = 86.35$ Hz), 1.55 (bs, 4H).

$\text{C}_{11}\text{H}_{16}\text{N}_2\text{O}_2$ (MW = 208.26); mass spectroscopy (MH^+) 209.1.

25 **Step C -- Synthesis of 2-[1-(*N*-Carbobenzyloxy)aminoethyl]-4-methoxycarbonyl-4-phenylmethyl-2-imidazoline**

The product from Step A above (1 equivalent) in iodomethane (35 equivalents) was heated to reflux under nitrogen for 8 hours. The dark yellow solution was concentrated *in vacuo* to a golden yellow foam, then azeotroped with methanol (2x) to remove any residual iodomethane. The residue was dissolved in methanol (0.2 M) and the product from Step B above (1 equivalent) was added. The resulting clear colorless solution was heated to reflux for 1 hour under nitrogen and then stirred at ambient temperature for 14 hours, and again heated to reflux for an additional 1 hour. The solution was allowed to

cool to ambient temperature and then concentrated *in vacuo*. The reaction was monitored by tlc ($R_f = 0.27$ in 95:5 DCM/MeOH) and the residue was purified by flash column chromatography to provide the title compound as a 1:1 mixture of diastereomers (75% yield).

5 NMR data was as follows:

^1H -nmr (CDCl_3 , 250 MHz): $\delta = 7.36\text{--}7.20$ (m, 8H), 7.14-7.08 (m, 2H), 5.84-5.74 (m, 1H), 5.15-5.02 (m, 2H), 4.96 (bs, 1H), 4.44-4.30 (m, 1H), 4.03-3.97 (m, 1H), 3.72-3.66 (m, 1H), 3.70 (s, 1.5H), 3.69 (s, 1.5H), 3.07 (AB_q , 1H, $J_{\text{AB}} = 13.38$ Hz, $\Delta\nu_{\text{AB}} = 54.25$ Hz), 3.06 (AB_q , 1H, $J_{\text{AB}} = 13.51$ Hz, $\Delta\nu_{\text{AB}} = 52.03$ Hz), 1.39 (d, 1.5H, $J = 7.00$ Hz), 1.35 (d, 1.5H, $J = 7.00$ Hz).

$\text{C}_{22}\text{H}_{25}\text{N}_3\text{O}_4$ (MW = 395.46); mass spectroscopy (MH^+) 396.1.

15 **Step D -- Synthesis of 1-*tert*-Butoxycarbonyl-2-[1-(*N*-carbobenzyloxy)aminoethyl]-4-methoxycarbonyl-4-phenylmethyl-2-imidazoline**

To a 1:1 mixture of the product from Step C above (1.815 g, 1 eq.) in THF (9 mL)/ H_2O (9 mL) at ambient temperature was added NaHCO_3 (0.377 g, 1.50 eq.) and di-*tert*-butyl dicarbonate (1.304 g, 2.00 eq.) (Aldrich) in THF (6 mL). The resulting pale yellow mixture was stirred at ambient temperature for 1 hour and then additional NaHCO_3 (0.188 g, 0.75 eq.) and di-*tert*-butyl dicarbonate (0.652 g, 1.00 eq.) in THF (3 mL) were added and the mixture was stirred for an additional hour. The mixture was then diluted with ethyl acetate, washed with brine (2x), dried over Na_2SO_4 , filtered, concentrated *in vacuo*, and purified by flash column chromatography using 3:2 hexanes/EtOAc as the eluent to provide the title compound in 77% yield as a viscous oil ($R_f = 0.31$ in 3:2 hexanes/EtOAc). The racemic product was isolated as a 1:1 mixture of diastereomers.

NMR data was as follows:

30 ^1H -nmr ($\text{DMSO}-d_6$, 250 MHz): $\delta = 7.38\text{--}7.09$ (m, 10H), 6.00 (bd, 1H, $J = 7.75$ Hz), 5.21-5.05 (m, 3H), 4.15 (d, 1H, $J = 11.76$ Hz), 4.08 (d, 1H, $J = 11.26$ Hz), 3.85-3.80 (m, 2H), 3.78 (s, 3H), 3.20-3.00 (m, 2H), 1.43 (s, 9H), 1.36 (d, 1.5H, $J = 6.75$ Hz), 1.24 (d, 1.5H, $J = 6.75$ Hz).

$C_{27}H_{33}N_3O_6$ (MW = 495.58); mass spectroscopy (MH^+) 496.4.

Step E -- Synthesis of 1-*tert*-Butoxycarbonyl-2-(1-aminoethyl)-4-methoxycarbonyl-4-phenylmethyl-2-imidazoline

5 A mixture of the racemic *N*-Cbz-protected amine from Step D above and 20% $Pd(OH)_2$ on carbon (20% weight eq.) in MeOH (0.010-0.015 M) under an atmosphere of hydrogen (35-40 psi) were shaken for 4 hours. The catalyst was removed by filtration through a plug of Celite and the filtrate was concentrated *in vacuo* to provide the title compound as a viscous oil (R_f = 0.26 in 95:5 DCM/MeOH).

NMR data was as follows:

^1H -nmr ($CDCl_3$, 250 MHz): δ = 7.32-7.15 (m, 5H), 4.19-4.05 (m, 2 H), 3.87-3.78 (m, 1H), 3.80 (s, 3H), 3.21-3.03 (m, 2H), 1.98 (bs, 2H), 1.43 (s, 9H), 1.33 (d, 1.5H, J = 7.00 Hz), 1.26 (d, 1.5H, J = 6.50 Hz).

15 $C_{19}H_{27}N_3O_4$ (MW = 361.44); mass spectroscopy (MH^+) 361.

Example K

Synthesis of 2-(1-Aminoethyl)-1-*tert*-butoxycarbonyl-4-methoxycarbonyl-4-phenyl-2-imidazoline

20 **Step A -- Synthesis of Methyl 2,3-Diamino-2-phenylpropionate**

Following the procedures described in Gilbert, et al., *Tetrahedron*, 1995 51, 6315-6336 and using (S)-(+)-2-phenylglycine methyl ester hydrochloride (Aldrich), the title compound was prepared in three steps (16% overall yield). The final reaction was monitored by tlc (R_f = 0.34 in 9:1 CH_2Cl_2 /MeOH) and

25 the product was purified by flash column chromatography.

NMR data was as follows:

^1H -nmr ($CDCl_3$, 250 MHz): δ = 7.52-7.47 (m, 2H), 7.39-7.25 (m, 3H), 3.74 (s, 3H), 3.42 (d, 1H, J = 13.26 Hz), 2.89 (d, 1H, J = 13.26 Hz), 1.88 (bs, 4H).

$C_{10}H_{14}N_2O_2$ (MW = 194.23); mass spectroscopy (MH^+) 195.

30

Step B -- Synthesis of 2-[1-(*N*-Carbobenzyloxy)aminoethyl]-4-methoxycarbonyl-4-phenyl-2-imidazoline

-- 118 --

The product from Example J -- Step A (5.206 g, 1.1 eq.) in iodomethane (36.5 mL, 38 eq.) was heated to reflux under nitrogen for 16 hours. The dark yellow solution was concentrated *in vacuo* to a golden yellow foam, then azeotroped once with methanol (30 mL) to remove any residual iodomethane.

- 5 The residue was dissolved in methanol (30 mL) and the product from Step A above (3.00 g, 1 eq.) was added. The resulting pale yellow solution was heated to reflux under nitrogen for 3.5 hours. The solution was then allowed to cool to ambient temperature, concentrated *in vacuo*, and purified by flash chromatography to yield (5.08 g, 86%) of the title compound as a
- 10 1:1 mixture of racemic diastereomers. The reaction was monitored by tlc (R_f = 0.32 in 95:5 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) and the product was purified by flash column chromatography.

NMR data was as follows:

- ^1H -nmr (CDCl_3 , 250 MHz): δ = 7.38-7.28 (m, 10H), 6.09-6.00 (m, 1H),
- 15 5.11-5.04 (m, 2H), 4.10 (bs, 1H), 3.84-3.68 (m, 4H), 1.53 (d, 3H, J = 7.00 Hz).
- $\text{C}_{20}\text{H}_{23}\text{N}_3\text{O}_4$ (MW = 381.43); mass spectroscopy (MH^+) 382.4

Step C -- Synthesis of 1-*tert*-Butoxycarbonyl-2-[1-(*N*-carbobenzyloxy)aminoethyl]-4-methoxycarbonyl-4-phenyl-2-imidazoline

- 20 To product from Step B above (4.94 g, 1 eq.) in THF (35 mL)/ H_2O (35 mL) at ambient temperature was added NaHCO_3 (2.00 g, 1.84 eq.) and di-*tert*-butyl dicarbonate (7.50 g, 2.65 eq.) (Aldrich). The resultant pale yellow mixture was stirred at ambient temperature for 1 hour and then additional NaHCO_3 (0.45 g, 0.41 eq.) and di-*tert*-butyl dicarbonate (0.98 g, 2.65 eq.) were added and the
- 25 mixture was stirred for an additional hour. The mixture was then diluted with ethyl acetate, washed with H_2O (1x), brine (2x), dried over Na_2SO_4 , filtered, concentrated *in vacuo*, and purified by flash chromatography. The racemic diastereomeric products [R_f = 0.38 (isomer A as a racemic mixture) and 0.28 (isomer B as a racemic mixture) eluting with 6:1 toluene/EtOAc] were separated
- 30 by flash chromatography using 6:1 toluene/EtOAc with a one step gradient to 5:1 toluene/EtOAc as the eluent to provide two sets of racemic enantiomer pairs

-- 119 --

in 73% yield, isomer A (1.122 g) as a viscous oil and isomer B (1.0868 g) as a white solid.

NMR data was as follows (isomer A):

¹H-nmr (CDCl₃, 250 MHz): δ = 7.39-7.27 (m, 10H), 6.20 (bd, 1H, J= 8.00 Hz), 5.40-5.30 (m, 1H), 5.13 (s, 2H), 4.84 (d, 1H, J= 11.26 Hz), 3.87 (d, 1H, J= 11.26 Hz), 3.70 (s, 3H), 1.52-1.50 (m, 12H).

C₂₆H₃₁N₃O₆ (MW = 481.55); mass spectroscopy (MH⁺) 482.3.

10 **Step D -- Synthesis of 1-tert-Butoxycarbonyl-2-(1-aminoethyl)-4-methoxycarbonyl-4-phenyl-2-imidazoline**

Isomer A of Step C above and 20% Pd(OH)₂ on carbon (20% weight eq.) in methanol (0.010-0.015 M) under an atmosphere of hydrogen (35-40 psi) were shaken for 4 hours. The catalyst was removed by filtration through a plug of Celite and the filtrate was concentrated *in vacuo* and purified by flash
15 chromatography to provide the title compound (88%) as a viscous oil (R_f = 0.28 in 95:5 DCM/MeOH).

NMR data was as follows:

¹H-nmr (CDCl₃, 250 MHz): δ = 7.43-7.27 (m, 5H), 4.80 (d, 1H, J= 11.26 Hz), 4.41 (q, 1H, J= 6.75 Hz), 3.87 (d, 1H, J= 11.51 Hz), 3.73 (s, 3H), 2.02 (s,
20 2H), 1.49 (s, 9H), 1.45 (d, 3H, J= 6.75 Hz).

C₁₈H₂₅N₃O₄ (MW = 347.42); mass spectroscopy (MH⁺) 348.2.

Example L

25 **Synthesis of (4R)-4-Carboxy-2-(3,5-difluorophenylmethyl)-4-methyl-2-thiazoline**

Step A -- Synthesis of Methyl 3,5-Difluorophenylacetimidate Hydrochloride

The title compound was prepared according to the procedures described in S. C. Zimmerman, et al., *J Org. Chem.* 1989, 54, 1256-1264, for the synthesis
30 of imidates. Specifically, a stream of anhydrous HCl gas was passed through a solution of 3,5-difluorophenylacetonitrile (5.045 g, 1 eq.) (Lancaster) and methanol (2.00 mL, 1.5 eq.) in diethyl ether (100 mL) at 0 °C for 20 minutes.

-- 120 --

The solution was then allowed to warm to ambient temperature under nitrogen with stirring for 23 hours, during which time a white precipitate formed. The white precipitate was collected by filtration and rinsed with diethyl ether to yield the title compound (6.6756 g, 91%) as a solid having a melting point of 156.5-157.5°C.

NMR data was as follows:

¹H-nmr (CDCl₃, 300 MHz): δ = 13.01 (bs, 1H), 11.93 (bs, 1H), 7.04-6.97 (m, 2H), 6.83-6.75 (m, 1H), 4.30 (s, 3H), 4.08 (s, 2H).

Step B -- Synthesis of Methyl (R)-2-Methylcysteine Hydrochloride

The title compound was prepared as a viscous oil in five steps (35% overall yield) from D-(S)-cysteine methyl ester hydrochloride as described in G.

Pattenden, et al., *Tetrahedron*, 1993, 49, 2131-2138 and references cited therein.

D-(S)-cysteine methyl ester hydrochloride was prepared in one step (98% yield)

from D-cysteine hydrochloride monohydrate (Aldrich) as described in J. E.

Baldwin, et al., *Tetrahedron*, 1989, 45, 4537-4550.

NMR data was as follows:

¹H-nmr (D₂O, 250 MHz): δ = 4.83 (bs, 4H), 3.92 (s, 3H), 3.27 (d, 1H, J= 15.26 Hz), 3.02 (d, 1H, J= 15.01 Hz), 1.69 (s, 3H).

Optical Rotation: [α]₂₀ = 2.44 (c 1.15, H₂O)

C₅H₁₂NO₂SCl (MW = 185.67); mass spectroscopy (MH⁺) 149.1.

Step C -- Synthesis of (4R)-2-(3,5-Difluorophenylmethyl)-4-methoxycarbonyl-4-methyl-2-thiazoline

The title compound was prepared according to the procedures described in G. Pattenden, et al., *Tetrahedron*, 1995, 51, 7313-7320, for the synthesis of thiazolines. Specifically, to a solution of methyl (R)-2-methylcysteine hydrochloride (1.7109 g, 1.00 eq.) from Step B above in CH₂Cl₂ (55 mL) at ambient temperature under nitrogen was added the imidate hydrochloride (2.042 g, 1.00 eq.) from Step A above followed by the dropwise addition of triethylamine (1.28 mL, 1.00 eq.) over a period of 20 minutes. The resulting opaque pale yellow solution was stirred at ambient temperature for 40 hours,

-- 121 --

during which time an off-white suspension formed. The mixture was diluted with CH_2Cl_2 , washed with 1N aqueous HCl (1x), H_2O (1x), and brine (1x); then the organic phase was dried over MgSO_4 , filtered, concentrated *in vacuo*, and the residue purified by flash chromatography using 20:1 DCM/EtOAc as the eluent to afford the title compound (1.6669 g, 63%) as a colorless oil ($R_f = 0.34$ in 20:1 DCM/EtOAc).

NMR data was as follows:

^1H -nmr (CDCl_3 , 300 MHz): $\delta = 6.85\text{--}6.79$ (m, 2H), $6.74\text{--}6.67$ (m, 1H), 3.81 (s, 2H), 3.80 (s, 3H), 3.79 (d, 1H, $J = 11.30$ Hz), 3.17 (d, 1H, $J = 11.30$ Hz), 1.56 (s, 3H).

Optical Rotation: $[\alpha]_{20} = 3.71$ (c 1.02, CHCl_3).

$\text{C}_{13}\text{H}_{13}\text{NO}_2\text{SF}_2$ (MW = 285.32); mass spectroscopy (MH^+) 285.2.

Step D -- Synthesis of (4R)-4-Carboxy-2-(3,5-difluorophenylmethyl)-4-methyl-2-thiazoline

To the product from Step C above (0.7265 g, 1.0 eq.) in 1,4-dioxane (15 mL) at ambient temperature was added LiOH (0.0671 g, 1.1 eq.) in water (1 mL) dropwise over a period of 2 minutes. Additional water (2 mL) was added and the resulting opaque colorless solution was stirred at ambient temperature for 1.25 hours, during which time the solution became clear and colorless. The solution was concentrated *in vacuo* to a volume of approximately 5 mL and the concentrate was diluted with ethyl acetate and washed with 1 N aqueous HCl (2x), and water (1x); then dried over Na_2SO_4 , filtered, and concentrated *in vacuo* to give the title compound (0.6111 g, 88% yield) as a white solid having a melting point of $119.5\text{--}122.0^\circ\text{C}$.

NMR data was as follows:

^1H -nmr (CDCl_3 , 300 MHz): $\delta = 10.88$ (bs, 1H), $6.86\text{--}6.78$ (m, 2H), $6.76\text{--}6.69$ (m, 1H), 3.89 (AB_q , 2H, $J_{\text{AB}} = 15.14$ Hz, $\Delta\nu_{\text{AB}} = 20.57$ Hz), 3.84 (d, 1H, $J = 11.48$ Hz), 3.21 (d, 1H, $J = 11.61$ Hz), 1.61 (s, 3H).

-- 122 --

The following General Procedures II-A to II-E and Examples II-A to II-S illustrate the synthesis of carboxylic acid intermediates which may be used to prepare the compounds of the present invention.

5

GENERAL PROCEDURE II-A

Ester Hydrolysis to Free Acid

Ester hydrolysis to the free acid was conducted by conventional methods. Below are two examples of such conventional de-esterification methods.

10

Method A: To a carboxylic ester compound in a 1:1 mixture of $\text{CH}_3\text{OH}/\text{H}_2\text{O}$ was added 2-5 equivalents of K_2CO_3 . The mixture was heated to 50°C for 0.5 to 1.5 hours until tlc showed complete reaction. The reaction was cooled to room temperature and the methanol was removed on a rotary evaporator. The pH of the remaining aqueous solution was adjusted to ~2, and ethyl acetate was added to extract the product. The organic phase was then washed with saturated aqueous NaCl and dried over MgSO_4 . The solution was stripped free of solvent on a rotary evaporator to yield the product.

15

20

Method B: The amino acid ester was dissolved in dioxane/water (4:1) to which was added LiOH (~2 eq.) that was dissolved in water such that the total solvent after addition was about 2:1 dioxane:water. The reaction mixture was stirred until reaction completion and the dioxane was removed under reduced pressure. The residue was dissolved in water and washed with ether. The layers were separated and the aqueous layer was acidified to pH 2. The aqueous layer was extracted with ethyl acetate. The ethyl acetate extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure after filtration. The residue was purified by conventional methods (e.g., recrystallization).

25

30

GENERAL PROCEDURE II-B

Acid Chloride Preparation

-- 123 --

3,5-Difluorophenylacetic acid (30 g, 0.174 mol) (Aldrich) was dissolved in dichloromethane and this solution was cooled to 0°C. DMF (0.5 mL, catalytic) was added followed by the dropwise addition of oxalyl chloride (18 mL, 0.20 mol) over a 5 minute period. The reaction was stirred for 3 h and then
5 rotoevaporated at reduced pressure to give an oil which was placed on a high vacuum pump for 1 h to afford 3,5-difluorophenylacetyl chloride as a thin yellow oil. Other acid chlorides can be prepared in a similar manner.

GENERAL PROCEDURE II-C

10

Schotten-Baumann Procedure

3,5-Difluorophenylacetyl chloride (from General Procedure II-B) was added dropwise to a 0°C solution of L-alanine (Aldrich) (16.7 g, 0.187 mol) in 2 N sodium hydroxide (215 mL, 0.43 mol). The reaction was stirred for 1 h at 0°C and then overnight at room temperature. The reaction was diluted with water
15 (100 mL), then extracted with ethyl acetate (3 x 150 mL). The organic layer was then washed with brine (200 mL), dried over MgSO₄, and rotoevaporated at reduced pressure to a residue. Recrystallization of the residue from ethyl acetate/hexanes afforded the desired product (34.5 g, 82% yield). Other acid chlorides may be used in this procedure to provide for intermediates useful in
20 this invention.

GENERAL PROCEDURE II-D

Reductive Amination

To a solution of the arylamine in ethanol in a hydrogenation flask was
25 added 1 equivalent of the 2-oxocarboxylic acid ester (e.g., pyruvate ester), followed by 10% palladium on carbon (25 weight percent based on the arylamine). The reaction was hydrogenated at 20 psi H₂ on a Parr shaker until complete reaction was indicated by tlc (30 minutes to 16 hours). The reaction mixture was then filtered through a pad of Celite 545 (available from Aldrich
30 Chemical Company, Inc.) and stripped free of solvent on a rotary evaporator. The crude product residue was then further purified via chromatography.

-- 124 --

GENERAL PROCEDURE II-E

EDC Coupling Procedure

To a 1:1 mixture of the corresponding carboxylic acid and the corresponding amino acid ester or amide in CH_2Cl_2 at 0°C was added 1.5 equivalents triethylamine, followed by 2.0 equivalents hydroxybenzotriazole monohydrate and then 1.25 equivalents of ethyl-3-(3-dimethylamino)propyl carbodiimide·HCl. The reaction mixture was stirred overnight at room temperature and then transferred to a separatory funnel. The mixture was washed with water, saturated aqueous NaHCO_3 , 1N HCl and saturated aqueous NaCl, and then dried over MgSO_4 . The resulting solution was stripped free of solvent on a rotary evaporator to yield the crude product.

Example II-A

Synthesis of N-(Phenylacetyl)-L-alanine

Using General Procedure II-C, the title compound was prepared from phenylacetyl chloride (Aldrich) and L-alanine (Aldrich) as a solid having a melting point of $102\text{--}104^\circ\text{C}$.

NMR data was as follows:

^1H -nmr (CDCl_3): δ = 9.14 (br s, 1H), 7.21-7.40 (m, 5H), 6.20 (d, J = 7.0 Hz, 1H), 4.55 (m, 1H), 3.61 (s, 2H), 1.37 (d, J = 7.1 Hz, 3H).

^{13}C -nmr (CDCl_3): δ = 176.0, 171.8, 134.0, 129.4, 127.5, 48.3, 43.2, 17.9.

Example II-B

Synthesis of N-(3,5-Difluorophenylacetyl)-L-alanine

Using General Procedure II-C, the title compound was prepared from 3,5-difluorophenylacetyl chloride (General Procedure II-B) and L-alanine (Aldrich).

NMR data was as follows:

^1H -nmr (CD_3OD): δ = 8.32 (br s, 0.3H), 6.71 (m, 2H), 6.60 (m, 1H), 4.74 (br s, 1.7H), 4.16 (m, 1H), 3.36 (s, 2H), 1.19 (d, J = 7.3 Hz, 3H).

^{13}C -nmr (CD_3OD): δ = 175.9, 172.4, 164.4 (dd, J = 13.0, 245.3 Hz), 141.1, 113.1 (dd, J = 7.8, 17.1 Hz), 102.9 (t, J = 25.7 Hz), 49.5, 42.7, 17.5.

Example II-C

Synthesis of N-(Cyclopentylacetyl)-L-phenylglycine

Step A - Preparation of N-(Cyclopentylacetyl)-L-phenylglycine Methyl Ester

Following General Procedure II-E above using cyclopentylacetic acid

- 5 (Aldrich) and L-phenylglycine methyl ester hydrochloride (Novabiochem), the title compound was prepared as a solid having a melting point of 83-86°C. The reaction was monitored by tlc on silica gel ($R_f = 0.28$ in 25% ethyl acetate/hexanes) and purification was by recrystallization from ethyl acetate/hexanes.

- 10 NMR data was as follows:

^1H -nmr (CDCl_3): $\delta = 7.35$ (s, 5H), 6.44 (bd, 1H), 5.6 (d, 1H), 3.72 (s, 3H), 2.24 (bs, 3H), 1.9-1.4 (m, 6H), 1.2-1.05 (m, 2H).

^{13}C -nmr (CDCl_3): $\delta = 172.3, 171.7, 136.7, 129.0, 128.6, 127.3, 56.2, 52.7, 42.5, 36.9, 32.40, 32.38, 24.8$.

- 15 $\text{C}_{16}\text{H}_{21}\text{NO}_3$ (MW = 275.35); mass spectroscopy (M+Na) 298.

Step B - Preparation of N-(Cyclopentylacetyl)-L-phenylglycine

Following General Procedure II-A above using N-(cyclopentylacetyl)-L-phenylglycine methyl ester (from Step A), the title compound was prepared as a solid having a melting point of 155-158°C. The reaction was monitored by tlc on silica gel ($R_f = 0.18$ in 10% methanol/dichloromethane).

- 20 NMR data was as follows:

^1H -nmr (CDCl_3): $\delta = 8.60$ (d, $J = 7.8$ Hz, 1H), 7.45 (m, 5H), 5.41 (d, $J = 7.2$ Hz, 1H), 2.20 (m, 3H), 1.8-1.1 (m, 8H)..

- 25 ^{13}C -nmr (CDCl_3): $\delta = 172.3, 172.0, 137.5, 128.7, 128.1, 127.8, 56.2, 40.9, 36.8, 31.8, 24.5$.

$\text{C}_{15}\text{H}_{19}\text{NO}_3$ (MW = 261.32); mass spectroscopy (M+Na) 284.

Example II-D

- 30 **Synthesis of N-(Cyclopentylacetyl)-L-alanine**

Step A - Preparation of N-(Cyclopentylacetyl)-L-alanine Methyl Ester

-- 126 --

Following General Procedure II-E above using cyclopentylacetic acid (Aldrich) and L-alanine methyl ester hydrochloride (Sigma), the title compound was prepared as a solid having a melting point of 43-46°C. Purification was by recrystallization from ethyl acetate/hexanes.

5 NMR data was as follows:

¹H-nmr (CDCl₃): δ = 6.38 (d, 1H), 4.50 (m, 1H), 3.65 (s, 3H), 2.13 (bs, 3H), 1.80-1.00 (m (includes d at 1.30, 3H), 11H).

¹³C-nmr (CDCl₃): δ = 173.7, 172.5, 52.1, 47.6, 42.3, 36.8, 32.15, 32.14, 18.0.

10 C₁₁H₁₉NO₃ (MW = 213.28); mass spectroscopy (MH⁺) 214.

Step B - Preparation of N-(Cyclopentylacetyl)-L-alanine

Following General Procedure II-A above using N-(cyclopentylacetyl)-L-alanine methyl ester (from Step A), the title compound was prepared. The reaction was monitored by tlc on silica gel (R_f = 0.18 in 10% methanol/dichloromethane).

NMR data was as follows:

15 ¹H-nmr (DMSO-d₆): δ = 12.45 (bs, 1H), 8.12 (d, J=7.2 Hz, 1H), 4.24 (quint, J = 7.2 Hz, 1H), 2.14 (m, 3H), 1.8-1.4 (m, 6H), 1.29 (d, J = 7.2 Hz, 3H), 1.2-1.0 (m, 3H).

¹³C-nmr (DMSO-d₆): δ = 174.6, 171.9, 47.3, 41.1, 36.7, 31.8, 24.5, 17.2.

C₁₀H₁₇NO₃ (MW = 199.25); mass spectroscopy (MH⁺) N/A.

Example II-E

25 Synthesis of N-(Cyclopropylacetyl)-L-alanine

Step A - Preparation of N-(Cyclopropylacetyl)-L-alanine Methyl Ester

Following General Procedure II-E above using cyclopropylacetic acid (Aldrich) and L-alanine methyl ester hydrochloride (Sigma), the title compound was prepared as an oil. The reaction was monitored by tlc on silica gel (R_f = 0.15 in 25% ethyl acetate/hexanes) and purification was by flash column chromatography using 25% ethyl acetate/hexanes as the eluant.

-- 127 --

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 6.60 (d, 1H), 4.55 (m, 1H), 3.69 (s, 3H), 2.10 (m, 2H), 1.34 (d, 3H), 0.95 (m, 1H), 0.58 (m, 2H), 0.15 (m, 2H).

¹³C-nmr (CDCl₃): δ = 173.7, 172.3, 52.3, 47.7, 41.0, 18.2, 6.7, 4.27, 4.22.

5 C₉H₁₅NO₃ (MW = 185.22); mass spectroscopy (MH⁺) N/A.

Step B - Preparation of N-(Cyclopentylacetyl)-L-alanine

Following General Procedure II-A above using N-(cyclopropylacetyl)-L-alanine methyl ester (from Step A), the title compound was prepared as an oil.

10 The reaction was monitored by tlc on silica gel (R_f = 0.27 in 10% methanol/dichloromethane).

NMR data was as follows:

¹H-nmr (DMSO-d₆): δ = 8.18 (d, 1H), 4.25 (m, 1H), 2.08 (m, 2H), 1.30 (d, 3H), 1.00 (m, 1H), 0.50 (m, 2H), 0.19 (m, 2H).

15 ¹³C-nmr (DMSO-d₆): δ = 174.6, 171.7, 47.4, 17.3, 7.6, 4.12, 4.06.

C₈H₁₃NO₃ (MW = 199.25); mass spectroscopy (MH⁺) N/A.

Example II-F

Synthesis of N-(Cyclopropylacetyl)-L-phenylglycine

20 Step A - Preparation of N-(Cyclopropylacetyl)-L-glycine Methyl Ester

Following General Procedure II-E above using cyclopropylacetic acid (Aldrich) and L-phenylglycine methyl ester, the title compound was prepared as a solid having a melting point of 74-76°C. The reaction was monitored by tlc on silica gel (R_f = 0.61 in 50% ethyl acetate/hexanes) and purification was by
25 recrystallization from ethyl acetate/hexanes.

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 7.35 (m, 5H), 6.97 (bd, J=7.2 Hz, 1H), 5.59 (d, J=7.8 Hz, 1H), 3.71 (s, 3H), 2.17 (m, 2H), 1.05-0.95 (m, 1H), 0.62 (m, 2H), 0.20 (m, 2H).

30 ¹³C-nmr (CDCl₃): δ = 171.9, 174.6, 136.6, 129.0, 128.5, 127.2, 56.1, 52.7, 41.0, 6.9, 4.37, 4.33.

-- 128 --

$C_{14}H_{17}NO_3$ (MW = 247.30); mass spectroscopy (MH⁺) N/A.

Step B - Preparation of N-(Cyclopentylacetyl)-L-phenylglycine

Following General Procedure II-A above using N-(cyclopropylacetyl)-L-phenylglycine methyl ester (from Step A), the title compound was prepared as a solid having melting point of 152-157°C. The reaction was monitored by tlc on silica gel (R_f = 0.23 in 10% methanol/dichloromethane) and purification was by recrystallization from ethyl acetate/hexanes.

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 8.47 (d, J = 7.69 Hz, 1H), 7.35 (m, 5H), 5.34 (d, J = 7.69 Hz, 1H), 2.10 (m, 2H), 0.90 (m, 1H), 0.40 (m, 2H), 0.10 (m, 2H).

¹³C-nmr (CDCl₃): δ = 172.3, 171.8, 137.6, 128.7, 56.2, 7.7, 4.0.

$C_{13}H_{15}NO_3$ (MW = 233.27); mass spectroscopy (MH⁺) N/A.

15

Example II-H

**Synthesis of
N-(2-Biphenyl)-D,L-alanine**

2-Aminobiphenyl (2 g, 11.8 mmol, Aldrich), triethylamine (1.2 eq.) and ethyl 2-bromopropionate (1.1 eq., Aldrich) were combined and heated to 85°C with stirring. After 7 days, the mixture was diluted with chloroform and washed with water. The organic portion was dried and concentrated to yield an oil which was purified by silica gel chromatography (1:1 CH₂Cl₂/hexanes). The resulting oil was dissolved in a 1:2 mixture of water/dioxane (200 mL) and LiOH (2 eq.) was added. After 2 hours, the mixture was concentrated to yield an oil which was dissolved in water. The aqueous solution was washed with ether then was adjusted to pH 3 with 5N HCl and extracted with ethyl acetate. The organic portion was dried and concentrated to yield an oil which was purified by silica gel chromatography (EtOAc) to yield the title compound.

30

Example II-I

**Synthesis of
N-(Phenyl-furazan-3-yl)-D,L-alanine**

4-Phenyl-furazan-3-ylamine (Maybridge) and ethyl pyruvate (Aldrich) were dissolved in dry ethanol. Platinum on sulfide carbon (5%) was added and the resulting mixture was hydrogenated (1000 psi, H₂) at 150°C for 8 hours. The reaction mixture was then filtered through Celite and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography using CHCl₃ as the eluent to provide the title compound as its ethyl ester. The ethyl ester was then hydrolyzed using General Procedure II-A, Method B (LiOH/H₂O/dioxane) to provide the title compound.

Example II-L

Synthesis of S-(+)-3,5-Difluoromandelic Acid

Step A - Preparation of Methyl S-(±)-3,5-difluoromandelate

To a solution of 3,5-difluorobenzaldehyde (Aldrich) in CH₂Cl₂ (100 mL) was added ZnCl₂ (6.7 g, 21.1 mmol) to form a slurry. Trimethylsilyl cyanide (21.0 g, 211.2 mmol) dissolved in CH₂Cl₂ (100 mL) was slowly added to the slurry at 0°C. The resulting solution was stirred at room temperature for 4 h. The reaction mixture was then diluted with water and the organic layer separated. The combined organic layers were concentrated to a residue. The residue was dissolved with MeOH (200 mL) at 0°C and anhydrous HCl gas bubbled into the solution for 10 min. After stirring at room temperature for 18 h, the solution was concentrated to a solid. The solid was dissolved in CH₂Cl₂ / H₂O and the aqueous portion extracted with CH₂Cl₂. The combined organics were washed with brine, dried over anhydrous MgSO₄ and concentrated to a solid (37.4 g, 87.6%), mp = 77-78°C.

¹H NMR (300 MHz, CDCl₃): δ = 6.97 (dd, J = 9.6 Hz, J = 1.79 Hz, 2H), 6.74 (dt, J = 8.82, J = 2.28 Hz, 1H), 5.14 (d, J = 4.64 Hz, 1H), 3.78 (s, 3H), 3.54 (d, J = 5.1 Hz, 1H).

Step B - Preparation of Methyl S-(+)-3,5-difluoromandelate

Methyl (±)-3,5-difluoromandelate was separated via preparative chiral HPLC to give a white solid having a melting point of 70-71°C.

-- 130 --

$C_9H_8F_2O_3$ (MW = 202.17); mass spectroscopy found ($M+NH_4^+$) 220.0:

Anal. calcd for $C_9H_8F_2O_3$: C, 53.47; H, 3.99. Found: C, 53.40; H, 3.89.

Step C - Preparation of S-(+)-3,5-Difluoromandelic acid

5 A solution of methyl S-(+)-3,5-difluoromandelate (1 eq.) in 74% aqueous THF was cooled to 0 °C and treated with lithium hydroxide. After 40 minutes at 0 °C the reaction was complete by TLC. The contents were transferred to a separatory funnel and partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$. The aqueous layer was acidified with 0.5 N $NaHSO_4$ and extracted
10 thrice with ethyl acetate. The combined extracts were washed with brine, dried over Na_2SO_4 , filtered, and concentrated to a white solid having a melting point of 119-122 °C. The ^1H NMR was consistent with known 3,5-difluoromandelic acid.

15

Example II-M

Synthesis of
2-Azido-(3,5-difluorophenyl)acetic Acid

Step A: To a three-necked flask equipped with a mechanical stirrer and a nitrogen inlet tube was added 3,5-difluorophenylacetic acid (Aldrich) and THF.
20 The reaction mixture was cooled to -78°C and 1.2 eq. of triethylamine was added, followed by dropwise addition of trimethylacetyl chloride (1.05 eq.) (Aldrich). During the addition, the temperature was maintained at -78°C. The cold bath was then removed and replaced with an ice bath. The temperature was allowed to warm to 0°C and stirring was continued for 1 hour. The
25 reaction mixture was then re-cooled to -78°C. To a second flask charged with THF, triphenylmethane (cat, 0.1 mole %) and (S)-(-)-4-benzyl-2-oxazolidione (1.1 eq.) (Aldrich) at -78°C was added an n-butyllithium solution dropwise until an orange color persisted. This reaction mixture was stirred at -78°C for 30
30 min. and then cannulated into the first reaction mixture. The resulting mixture was allowed to stir at -78°C for 1 hour and then quenched with 2.2 eq. of acetic acid. The solvent was removed under reduced pressure and the residue was redissolved in dichloromethane and this solution washed with water, followed by

1M potassium carbonate. The organic layer was then dried over sodium sulfate, filtered and concentrated. The residue was purified by LC 2000 chromatography, eluting with EtOAc/Hexane (15:85). The resulting oil was slurried in hexane to afford a white solid which was collected by filtration to give (S)-(-)-3-(3,5-difluorophenyl)-4-benzyl-2-oxazolidione.

Step B: To (S)-(-)-3-(3,5-difluorophenyl)-4-benzyl-2-oxazolidione (3.0 mM) in 20 mL of dry THF cooled to -78°C was added LiHMDS (1.05 eq.) dropwise while maintaining the temperature at -78°C. The reaction mixture was allowed to stir at -78°C for 15 min. and then a pre-cooled (-60°C) solution of trisyl azide (1.12 eq.) in 10 mL of THF was added. The reaction mixture was allowed to stir an additional 10 min. and then was quenched with 4.4 eq. of acetic acid. Using a warm water bath, the temperature was raised to 30-40°C for 6 hrs. The reaction mixture was then poured into a separatory funnel and extracted into dichloromethane. The organic layer was washed with bicarbonate solution, followed by brine, and then dried over sodium sulfate, filtered and solvent removed. The residue was purified by LC 2000 chromatography to afford methyl 2-azido-2-(3,5-difluorophenyl)acetate.

Step C: To a solution of methyl 2-azido-2-(3,5-difluorophenyl)acetate in THF/H₂O (2.6:1) cooled to 0°C was added 1.7 eq. of lithium hydroxide. The reaction mixture was stirred at room temperature for 3 hours and then poured into a separatory funnel. The mixture was extracted into water and washed with ether. The aqueous layer was acidified with 1N HCl and extracted with ethyl acetate. The organic layer was then washed with water and brine. The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure to give 2-azido-2-(3,5-difluorophenyl)acetic acid.

Example II-N

30

Synthesis of (R)-N,N'-Di-BOC-2-Hydrazinopropionic Acid

Step A: To (S)-(-)-4-benzyl-2-oxazolidanone (Aldrich) in THF cooled to

-- 132 --

-50°C was added *n*-butyllithium 1.1 eq. (1.6 M in hexane) dropwise. The reaction mixture was allowed to warm to -20°C and then was re-cooled to -78°C and propionyl chloride (1.1 eq) was added in one portion. The reaction mixture was allowed to stir an additional 15 min. at -78°C and then was allowed to warm to room temperature. The reaction was then quenched with a saturated solution of sodium bicarbonate and extracted with ethyl acetate. The organic extracts were washed with water, followed by brine and then dried over sodium sulfate, filtered and concentrated to give (S)-(-)-3-propionyl-4-benzyl-2-oxazolidanone.

Step B: To a solution of (S)-(-)-3-propionyl-4-benzyl-2-oxazolidanone in THF at -78°C was added KHMDS (1.05 eq.) (Aldrich) dropwise. The reaction mixture was allowed to stir at -78°C for 30 min. and then a precooled solution of di-*tert*-butyl-azodicarboxylate (Aldrich) was added via a cannula. After 5 min. 2.6 eq. of acetic acid was added. The reaction mixture was then extracted with dichloromethane and the organic layer was washed with 1M potassium phosphate. The organic layer was then dried over sodium sulfate, filtered and concentrated to give (S)-(-)-3-[(R)-N,N'-di-BOC-2-hydrazinopropionyl]-4-benzyl-2-oxazolidanone.

Step C: To (S)-(-)-3-[(R)-N,N'-di-BOC-2-hydrazinopropionyl]-4-benzyl-2-oxazolidanone (0.49 moles) at 0°C in 8 mL of THF and 3 mL of water was added LiOH (1.7 eq.) and H₂O₂ (3.0 eq.) and the reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was then poured into a separatory funnel and diluted with water. The aqueous mixture was extracted with ethyl acetate and then acidified to pH 2.0 with 1N HCl and extracted with ethyl acetate. The organic layer was then dried over sodium sulfate, filtered and solvent removed to give (R)-N,N'-di-BOC-2-hydrazinopropionic acid which was used without further purification.

Example II-O

**Synthesis of
3,5-Difluorophenyl- α -oxoacetic Acid**

Step A: Ethyl 3,5-difluorophenyl- α -oxoacetate was prepared from 1-bromo-3,5-difluorobenzene (Aldrich) according to the procedure described in *J. Org. Chem.*, 45 (14), 2883-2887 (1980).

Step B: Ethyl 3,5-difluorophenyl- α -oxoacetate was hydrolyzed using General Procedure II-A (Method B) to afford 3,5-difluorophenyl- α -oxoacetic acid.

Example II-P

**Synthesis of
Cyclopentyl- α -hydroxyacetic Acid**

The title compound (CAS No. 6053-71-0) was prepared in two steps from cyclopentylmethanal (CAS No. 872-53-7, Wiley) using the procedure described by Gibby, W. A.; Gubler, C. J. *Biochemical Medicine* 1982, 27, 15-25.

Example II-Q

Synthesis of N-(3,4-dichlorophenyl)alanine

Using the procedure set forth in U.S. Patent No. 3,598,859, the disclosure of which is incorporated herein by reference in its entirety, N-(3,4-dichlorophenyl)alanine was prepared. Specifically, to a solution of 3,4-dichloroaniline (1 equivalent) (Aldrich) in isopropanol (about 500 mL per mole of 3,4-dichloroaniline) is added water (about 0.06 mL per mL of isopropanol) and 2-chloropropionic acid (2 equivalents) (Aldrich). This mixture is warmed to 40°C and sodium bicarbonate (0.25 equivalents) is added in successive portions before heating under reflux for 4-5 days. After cooling, the reaction mixture is poured into water and the unreacted 3,4-dichloroaniline is removed by filtration. The filtrate is acidified to pH 3-4 with concentrated hydrochloric acid and the resultant precipitate is filtered, washed and dried to yield the title compound, m.p. = 148-149°C.

-- 134 --

Example II-R.

Synthesis of N-(3,5-difluorophenyl)alanine

Using the procedure set forth in U.S. Patent No. 3,598,859 and Example Q above, N-(3,5-difluorophenyl)alanine was prepared using 3,5-difluoroaniline (Aldrich) and 2-chloropropionic acid (Aldrich).

Example II-S

**Synthesis of
 α -Fluoro-3,5-difluorophenylacetic Acid**10 **Step A - Synthesis of Methyl 3,5-Difluoromandelate**

To a solution of 3,5-difluoromandelic acid (Fluorochem) in methanol was bubbled HCl gas for 10 minutes. The reaction was refluxed overnight. The mixture was then concentrated *in vacuo* and the residue was taken up in ethyl acetate and washed with saturated NaHCO₃ and brine. The organic layer was dried over Na₂SO₄, filtered, and concentrated to give the title intermediate as a white solid.

C₉H₈F₂O₃ (MW=202.17); mass spectroscopy 202.

¹H NMR (300 MHz, CDCl₃): δ = 7.00 (2H, d, J=6.58 Hz), 6.76 (1H, t, J=8.86 Hz), 5.16 (1H, d, J=5.29 Hz), 3.81 (3H, s), 3.54 (1H, d, J=5.39 Hz).

20

Step B - Synthesis of Methyl α -Fluoro-3,5-difluorophenylacetate

A solution of diethylaminosulfur trifluoride (DAST) (1.1 eq) in methylene chloride was cooled to 0°C and a pre-cooled solution of methyl 3,5-difluoromandelate (1 eq) in methylene chloride was added. The transfer flask was rinsed with a small portion of methylene chloride. After 15 minutes, the cooling bath was removed and the reaction mixture was stirred an additional 40 minutes at ambient temperature. The mixture was poured over ice and the layers separated. The organic phase was washed with saturated NaHCO₃ and brine. The organic layer was dried over Na₂SO₄, filtered, and concentrated. The residue was purified via HPLC eluting with 7% ethyl acetate/hexanes providing the title intermediate as a yellow oil.

30

C₉H₇F₃O₂ (MW=204.16); mass spectroscopy 204.

Anal. calcd for $C_9H_7F_3O_2$: C, 52.95; H, 3.46. Found: C, 52.80; H, 3.73.

Step C - Synthesis of α -Fluoro-3,5-difluorophenylacetic Acid

Following General Procedure II-A, Method B and using methyl α -fluoro-3,5-difluorophenylacetate, the title intermediate was prepared as a white solid having a melting point of 100-102°C.

$C_8H_5F_3O_2$ (MW = 190.13); mass spectroscopy 190.

Anal. calcd for $C_8H_5F_3O_2$: C, 50.54; H, 2.65. Found: C, 50.47; H, 2.79.

The following Examples 1-20 illustrate the synthesis of compounds of the present invention.

Example 1

Synthesis of

(S)-5-[1-*N*-(*N*-(3,5-Difluorophenylacetyl)-L-alaninyl)amino-2-phenylethyl]-3-methyl-1,2,4-oxadiazole

Following General Procedure A above and using *N*-(3,5-difluorophenylacetyl)-L-alanine (Example II-B) and (S)-5-(1-amino-2-phenylethyl)-3-methyl-1,2,4-oxadiazole hydrochloride (Example B), the title compound was prepared as a solid having a melting point of 159-162°C. The reaction was monitored by tlc (R_f = 0.6 in 10% MeOH/ $CHCl_3$) and the product was purified by silica gel chromatography using 7% MeOH/ $CHCl_3$ as the eluent, followed by recrystallization from 1-chlorobutane.

NMR data was as follows:

^1H -nmr (DMSO- d_6): δ = 4.30 (m, 1H), 5.26 (m, 1H).

$C_{21}H_{22}F_2N_4O_3$ (MW = 428.44); mass spectroscopy (MH^+) 428.

Example 2

Synthesis of

(S)-2-[1-(3,5-Difluorophenylacetamido)ethyl]-4-ethoxycarbonyl-2-thiazoline

Following General Procedure A above and using 3,5-difluorophenylacetic acid (Aldrich) and (S)-2-(1-aminoethyl)-4-ethoxycarbonyl-2-thiazoline

-- 136 --

hydrochloride (Example G), the title compound was prepared as a semisolid. The reaction was monitored by tlc ($R_f = 0.2$ in 1:1 EtOAc/hexanes) and the product was purified by silica gel chromatography using 1:1 EtOAc/hexanes as the eluent.

5 NMR data was as follows:

^1H -nmr (CDCl_3): $\delta = 1.33$ (t, 3H), 1.44 (t, 3H), 3.55 (s, 2H), 3.60 (m, 2H), 4.37 (m, 2H), 4.85 (m, 1H), 5.05 (m, 1H), 6.46 (t, 1H), 6.74 (t, 1H), 6.84 (d, 2H).

$\text{C}_{16}\text{H}_{18}\text{F}_2\text{N}_2\text{O}_3\text{S}$ (MW = 356.39); mass spectroscopy (MH^+) 356.

10

Example 3

Synthesis of

1-*tert*-Butoxycarbonyl-2-[1-(*N*-carbobenzyloxy)aminoethyl]- 4-methoxycarbonyl-4-phenylmethyl-2-imidazoline

15 To a 1:1 mixture of the product from Example J, Step C (1.815 g, 1 eq.) in THF (9 mL)/ H_2O (9 mL) at ambient temperature was added NaHCO_3 (0.377 g, 1.50 eq.) and di-*tert*-butyl dicarbonate (1.304 g, 2.00 eq.) (Aldrich) in THF (6 mL). The resulting pale yellow mixture was stirred at ambient temperature for 1 hour and then additional NaHCO_3 (0.188 g, 0.75 eq.) and di-*tert*-butyl
20 dicarbonate (0.652 g, 1.00 eq.) in THF (3 mL) were added and the mixture was stirred for an additional hour. The mixture was then diluted with ethyl acetate, washed with brine (2x), dried over Na_2SO_4 , filtered, concentrated *in vacuo*, and purified by flash column chromatography using 3:2 hexanes/EtOAc as the eluent to provide the title compound in 77% yield as a viscous oil ($R_f = 0.31$ in 3:2
25 hexanes/EtOAc). The racemic 1:1 mixture of diastereomers was inseparable by flash chromatography.

NMR data was as follows:

30 ^1H -nmr ($\text{DMSO}-d_6$, 250 MHz): $\delta = 7.38$ -7.09 (m, 10H), 6.00 (bd, 1H, $J = 7.75$ Hz), 5.21-5.05 (m, 3H), 4.15 (d, 1H, $J = 11.76$ Hz), 4.08 (d, 1H, $J = 11.26$ Hz), 3.85-3.80 (m, 2H), 3.78 (s, 3H), 3.20-3.00 (m, 2H), 1.43 (s, 9H), 1.36 (d, 1.5H, $J = 6.75$ Hz), 1.24 (d, 1.5H, $J = 6.75$ Hz).

$\text{C}_{27}\text{H}_{33}\text{N}_3\text{O}_6$ (MW = 495.58); mass spectroscopy (MH^+) 496.4.

-- 137 --

Example 4

Synthesis of

1-*tert*-Butoxycarbonyl-2-[1-(3,5-difluorophenylacetamido)ethyl]-4-methoxycarbonyl-4-phenylmethyl-2-imidazoline

5 Following General Procedure C above and using 3,5-difluorophenylacetic acid (Aldrich) and 1-*tert*-butoxycarbonyl-2-(1-aminoethyl)-4-methoxycarbonyl-4-phenylmethyl-2-imidazoline (Example J), the title compound was prepared as an amorphous solid. The reaction was monitored by tlc (R_f = 0.34 in 2:1 hexanes/EtOAc) and the product was purified by flash column chromatography.

10 NMR data was as follows:

^1H -nmr (CDCl_3 , 250 MHz): δ = 7.28-7.20 (m, 3H), 7.16-7.12 (m, 1 H), 7.07-7.03 (m, 1H), 6.91-6.80 (m, 3H), 6.77-6.67 (m, 1H), 5.35-5.21 (m, 1H), 4.17-4.05 (m, 1H), 3.86-3.79 (m, 1H), 3.79 (s, 3H), 3.55 (s, 1H), 3.52 (s, 1H), 3.18-2.99 (m, 2H), 1.43 (s, 4.5H), 1.41 (s, 4.5H), 1.33 (d, 1.5H, J = 6.75 Hz), 1.21 (d, 1.5H, J = 6.75 Hz).

$\text{C}_{27}\text{H}_{31}\text{F}_2\text{N}_3\text{O}_5$ (MW = 515.56); mass spectroscopy (MH^+) 516.2.

Example 5

Synthesis of

2-[1-(3,5-Difluorophenylacetamido)ethyl]-4-methoxycarbonyl-4-phenylmethyl-2-imidazoline

20 Following General Procedure D above and using the product from Example 4 above, the title compound was prepared as a white solid (93%) having a melting point of 158-160°C. The reaction was monitored by tlc (R_f = 0.31 in 95:5 DCM/MeOH).

25 NMR data was as follows:

^1H -nmr ($\text{DMSO}-d_6$ and CDCl_3 , 250 MHz): δ = 8.09 (bt, 1H, J = 7.75 Hz), 7.28-7.19 (m, 3H), 7.14-7.09 (m, 2H), 6.89 (bd, 2H, J = 7.25 Hz), 6.74 (bt, 1H, J = 9.13 Hz), 4.62-4.48 (m, 1H), 3.88 (bd, 1H, J = 12.51 Hz), 3.68 (s, 3H), 3.61-3.54 (m, 1H), 3.50 (s, 2H), 3.11-2.92 (m, 2H), 1.31 (d, 1.5H, J = 6.75 Hz), 1.30 (d, 1.5H, J = 7.00 Hz).

$\text{C}_{22}\text{H}_{20}\text{F}_2\text{N}_3\text{O}_3$ (MW = 415.44); mass spectroscopy (MH^+) 416.1.

Example 6

Synthesis of

**(S)-2-[1-(3,5-Difluorophenylacetamido)ethyl]-
5(R,S)-ethoxycarbonyl-2-oxazoline**

5 Following General Procedure A and using 3,5-difluorophenylacetic acid (Aldrich) and (S)-2-(1-aminoethyl)-5(R,S)-ethoxycarbonyl-2-oxazoline (Example F), the title compound was prepared as a semisolid. The reaction was monitored by tlc ($R_f = 0.3$ in 5% MeOH/ CHCl_3) and the product was purified by silica gel chromatography using 5% MeOH/ CHCl_3 as the eluent.

10 NMR data was as follows:

^1H -nmr ($\text{DMSO}-d_6$): $\delta = 1.20$ (t, 3H), 1.30 (d, 3H), 3.50 (s, 2H), 3.80 (m, 1H), 4.05 (m, 1H), 4.15 (q, 2H), 4.55 (m, 1H), 5.10 (m, 1H), 6.97 (d, 2H), 7.08 (m, 1H), 8.60 (d, 1H).

$\text{C}_{16}\text{H}_{18}\text{F}_2\text{N}_2\text{O}_4$ (MW = 340.33); mass spectroscopy (MH^+) 340.

15

Example 7

Synthesis of

**2-[1-(3,5-Difluorophenylacetamido)ethyl]-
4-methoxycarbonyl-4-phenyl-2-imidazoline**

20 **Step A -- Synthesis of 1-*tert*-Butoxycarbonyl-2-[1-(3,5-difluorophenylacetamido)ethyl]-4-methoxycarbonyl-4-phenyl-2-imidazoline**

25 Following General Procedure C above and using 3,5-difluorophenylacetic acid (Aldrich) and 1-*tert*-butoxycarbonyl-2-(1-aminoethyl)-4-methoxycarbonyl-4-phenyl-2-imidazoline (Example K), the title compound was prepared as a white foam (90%). The reaction was monitored by tlc ($R_f = 0.39$ in 3:2 hexanes/EtOAc) and the product was purified by flash column chromatography.

NMR data was as follows:

30 ^1H -nmr (CDCl_3 , 250 MHz): $\delta = 7.38$ -7.31 (m, 5H), 7.09 (d, 1H, $J = 7.50$ Hz), 6.90-6.82 (m, 2H), 6.76-6.66 (m, 1H), 5.57 (p, 1H, $J = 7.50$ Hz), 4.83 (d, 1H, $J = 11.26$ Hz), 3.87 (d, 1H, $J = 11.26$ Hz), 3.72 (s, 3H), 3.56 (s, 2H), 1.49 (s, 9H), 1.48 (d, 3H, $J = 7.00$ Hz).

$\text{C}_{26}\text{H}_{29}\text{F}_2\text{N}_3\text{O}_5$ (MW = 501.53); mass spectroscopy (MH^+) 502.

Step B -- Synthesis of 2-[1-(3,5-Difluorophenylacetamido)ethyl]-4-methoxycarbonyl-4-phenyl-2-imidazoline

Following General Procedure D above and using the product from Step A above, the title compound was prepared as a white foam (89%). The reaction was monitored by tlc ($R_f = 0.24$ in 95:5 DCM/MeOH) and the product was purified by flash column chromatography.

NMR data was as follows:

^1H -nmr (DMSO- d_6 , 300 MHz): $\delta = 8.47$ (d, 1H, $J = 7.89$ Hz), 7.34-7.27 (m, 5H), 7.12-7.06 (m, 1H), 7.03-7.00 (m, 2H), 4.55 (p, 1H, $J = 7.35$ Hz), 4.34 (bm, 1H), 3.62 (s, 2H), 3.53 (s, 2H), 1.31 (d, 3H, $J = 7.00$ Hz)..

$\text{C}_{21}\text{H}_{21}\text{F}_2\text{N}_3\text{O}_3$ (MW = 401.41); mass spectroscopy (MH^+) 402.

Example 8

Synthesis of 1-*tert*-Butoxycarbonyl-2-(3,5-difluorophenylmethyl)-4-ethoxycarbonyl-4-methyl-2-imidazoline

Step A -- Synthesis of Ethyl 2,3-Diamino-2-methylpropionate

Following the procedures described in Gilbert, et al., *Tetrahedron*, 1995 51, 6315-6336, the title compound was prepared as an oil. Purification was by Kugelrohr distillation.

NMR data was as follows:

^1H -nmr (DMSO- d_6): $\delta = 4.06$ (m, 2H), 2.70 (d, 1H), 2.46 (d, 1H), 2.18 (bs, 4H), 1.18 (t, 3H), 1.10 (s, 3H).

$\text{C}_6\text{H}_{14}\text{N}_2\text{O}_2$ (MW = 146.19); mass spectroscopy (MH^+) 147.

Step B -- Synthesis of 2-(3,5-Difluorophenylmethyl)-4-ethoxycarbonyl-4-methyl-2-imidazoline

In a round bottom flask fitted with an addition funnel was added 2.25 g (9.55 mmole) of the product from Example L -- Step A above and 20 mL of ethanol. The flask was cooled to 0° C and stirring was initiated under an atmosphere of nitrogen. The product from Step A above (1.40 g, 9.55 mmole) in 20 ml of ethanol was slowly added to the reaction via an addition funnel. The reaction was allowed to slowly warm to room temperature and stir

-- 140 --

overnight. The mixture was then filtered through a sintered glass funnel and the filtrate was concentrated on the rotary evaporator. The residue was partitioned between 50 mL of 1.0 N sodium hydroxide and 50 mL of dichloromethane. The organic phase was separated and the aqueous layer was washed twice with 50 mL of dichloromethane. The combined organic layers were washed with 50 mL of saturated brine and dried over sodium sulfate. Filtration followed by concentration on the rotary evaporator, yielded a yellow oil which was purified via flash chromatography on silica gel 60 (230-400 mesh) using 95:5 DCM/MeOH as the eluent. Concentration of the fractions gave 2.61 g (82% yield) of the title compound ($R_f = 0.17$ in 95:5 DCM/MeOH).

NMR data was as follows:

^1H -nmr (DMSO- d_6): $\delta = 7.05$ (m, 3H), 4.04 (m, 2H), 3.75 (d, $J = 11.71$ Hz, 1H), 3.49 (s, 2H), 3.27 (d, $J = 11.73$ Hz, 1H), 1.29 (s, 3H), 1.17 (t, 3H).

$\text{C}_{14}\text{H}_{16}\text{F}_2\text{N}_2\text{O}_2$ (MW = 282.29); mass spectroscopy (MH^+) 282.1.

Step C -- Synthesis of 1-*tert*-Butoxycarbonyl-2-(3,5-difluorophenylmethyl)-4-ethoxycarbonyl-4-methyl-2-imidazoline

In a round bottom flask fitted with an addition funnel was added the product from Step B above (2.00 g, 7.08 mmole), 0.743 g (8.85 mmole) of sodium bicarbonate, 30 mL of water, and 30 mL of THF. Stirring was initiated under an atmosphere of nitrogen and di-*tert*-butyl dicarbonate (3.47 g, 15.90 mmole) (Aldrich) in 15 mL of THF was added to the reaction via the addition funnel. After stirring for 1 hour, an additional 627 mg (7.05 mmole) of sodium bicarbonate and 1.17 g (5.40 mmole) of di-*tert*-butyl dicarbonate were added to the reaction. The reaction was monitored using thin layer chromatography, and when the reaction was complete, the reaction mixture was partitioned between 250 mL of ethyl acetate and 250 mL of saturated brine. The organic layer was washed twice with a 250 mL of saturated brine and then dried over sodium sulfate. Filtration followed by concentration on the rotary evaporator yielded a yellow oil which was purified by flash chromatography on silica gel 60 (230-400 mesh) using 15:85 ethyl acetate/dichloromethane as the eluent.

-- 141 --

Concentration of the fractions gave 2.10 g (78% yield) of the title compound (Rf = 0.15 in 15:85 EtOAc/hexanes).

NMR data was as follows:

¹H-nmr (DMSO-*d*₆): δ = 7.07 (m, 1H), 6.94 (m, 2H), 4.05 (m, 5H), 3.57 (d, 1H), 1.38 (d, 12H), 1.19 (t, 3H).

¹³C-nmr (DMSO-*d*₆): δ = 172.116, 163.599, 160.348, 157.624, 149.352, 140.855, 111.511, 101.584, 81.677, 69.950, 60.758, 55.442, 34.855, 27.423, 24.203, 13.581.

C₁₉H₂₄F₂N₂O₄ (MW = 382.41); mass spectroscopy (MH⁺) 382.1.

Example 9

Synthesis of 2-[1-*N*-[*N*-(3,5-Difluorophenylacetyl)- L-alaninyl]amino-1-phenyl]methyl-2-thiazoline

Following General Procedure F above and using *N*-(1-cyano-1-phenylmethyl)-*N'*-(3,5-difluorophenylacetyl)-L-alaninamide and 2-mercaptoethylamine, the title compound was prepared. The reaction was monitored by tlc (Rf = 0.3 in 5% MeOH/CHCl₃) and the product was purified by silica gel chromatography using 5% MeOH/CHCl₃ as the eluent.

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 1.31 (m, 3H), 3.31 (m, 2H), 3.50 (d, 2H), 4.24 (m, 2H), 4.55 (m, 1H), 4.64 (d, 1H), 6.30 (m, 1H), 6.76 (m, 2H), 7.33 (d, 5H), 7.52 (m, 1H).

C₂₁H₂₁F₂N₃O₂S (MW = 417.48); mass spectroscopy (MH⁺) 417.

Example 10

Synthesis of 2-[1-(3,5-Difluorophenylacetamido)-1-phenyl]methyl- 4-ethoxycarbonyl-2-thiazoline

Following General Procedure G above and using *N*-(3,5-difluorophenylacetyl)phenylglycinonitrile from Example I above and L-cysteine ethyl ester hydrochloride (Aldrich), the title compound was prepared as an amorphous solid. The reaction was monitored by tlc (Rf = 0.5 in 1:1

-- 142 --

EtOAc/hexanes) and the product was purified by silica gel chromatography using 40% EtOAc/hexanes as the eluent.

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 1.36 (t, 3H), 3.6 (m, 4H), 4.30 (m, 2H), 5.10 and
5 5.20 (t, 1H), 5.84 (d, 1H), 6.72 (m, 1H), 6.84 (m, 2H), 7.38 (m, 5H).

C₂₁H₂₀F₂N₂O₃S (MW = 418.47); mass spectroscopy (MH⁺) 418.

Example 11

Synthesis of

10 2-[(S)-1-(3,5-dichloroanilino)ethyl]-(S)-4-methoxycarbonyl-2-oxazolidine

Following General Procedure H above, the title compound was prepared as an oil. The reaction was monitored by tlc (R_f = 0.5 in 3:2 hexanes/EtOAc) and the product was purified by preparative tlc chromatography using 3:2 hexanes/EtOAc as the eluent.

15 NMR data was as follows:

¹H-nmr (CDCl₃): δ = 1.5 (d, J = 7 Hz, 3H), 3.79 (s, 3H), 4.15-4.3 (m, 1H), 4.3-4.65 (m, 3H), 4.7-4.85 (m, 1H), 6.45 (s, 2H), 6.7 (s, 1H).

¹³C-nmr (CDCl₃): δ = 14.2, 42.08, 42.15, 47.9, 62.9, 65.3, 106.67, 106.72, 113.0, 130.7, 143.3, 166.3.

20 C₁₃H₁₄Cl₂N₂O₃ (MW = 317); mass spectroscopy (MH⁺) N/A.

Example 12

Synthesis of

25 (S)-5-[1-N-[N-(3,5-Difluorophenylacetyl)-L-alaninyl]amino-1-phenyl]methyl-3-methyl-1,2,4-oxadiazole

Following General Procedure A above and using N-(3,5-difluorophenylacetyl)-L-alanine (Example II-B) and (S)-5-(1-amino-1-phenylmethyl)-3-methyl-1,2,4-oxadiazole hydrochloride (Example C), the title compound was prepared as a solid (3:2 mixture of diastereomers). The reaction
30 was monitored by tlc (R_f = 0.6 in 7% MeOH/CHCl₃) and the product was purified by silica gel chromatography using 7% MeOH/CHCl₃, followed by recrystallization from 1-chlorobutane/acetonitrile.

NMR data was as follows:

¹H-nmr (DMSO-*d*₆): δ = 1.21 (d, 3H), 2.32 (s, 3H), 3.53 (s, 2H), 4.43 (m, 1H), 6.35 (d, 1H), 6.97 (d, 2H), 7.07 (m, 1H), 7.38 (broad s, 5H), 8.38 (d, 1H), 9.27 (d, 1H).

5 C₂₀H₂₀F₂N₄O₃ (MW = 414.41); mass spectroscopy (MH⁺) 414.

Example 13

Synthesis of

10 **(S)-5-[1-*N*-[*N*-(3,5-Difluorophenylacetyl)-L-alaninyl]amino-1-phenyl]methyl-3-phenyl-1,2,4-oxadiazole**

Following General Procedure A above and using *N*-(3,5-difluorophenylacetyl)-L-alanine (Example II-B) and (S)-5-(1-amino-1-phenylmethyl)-3-phenyl-1,2,4-oxadiazole hydrochloride (Example D), the title compound was prepared. The reaction was monitored by tlc (R_f = 0.4 in 5% MeOH/CHCl₃) and the product was purified by silica gel chromatography using 5% MeOH/CHCl₃ as the eluent.

NMR data was as follows:

¹H-nmr (DMSO-*d*₆): δ = 1.31 (d, 3H), 3.51 (s, 2H), 4.47 (m, 1H), 6.42 (d, 1H), 6.97 (d, 2H), 7.07 (m, 1H), 7.35-7.60 (m, 8H), 7.97 (d, 2H), 8.40 (d, 1H), 9.27 (d, 1H).

20 C₂₆H₂₂F₂N₄O₃ (MW = 476.49); mass spectroscopy (MH⁺) 476.

Example 14

Synthesis of

25 **(S)-5-[1-*N*-[*N*-(3,5-Difluorophenylacetyl)-L-alaninyl]amino-1-phenyl]methyl-3-(4-methoxyphenylmethyl)-1,2,4-oxadiazole**

Following General Procedure A above and using *N*-(3,5-difluorophenylacetyl)-L-alanine (Example II-B) and (S)-5-(1-amino-1-phenylmethyl)-3-(4-methoxyphenylmethyl)-1,2,4-oxadiazole hydrochloride (Example E), the title compound was prepared (1:2 mixture of diastereomers). The reaction was monitored by tlc (R_f = 0.25 in 3.5% MeOH/CHCl₃) and the product was purified by silica gel chromatography using 3.5% MeOH/CHCl₃ as the eluent.

-- 144 --

NMR data was as follows:

¹H-nmr (DMSO-*d*₃): δ = 1.22 (d, 3H), 3.49 (s, 2H), 3.72 (s, 3H), 3.98 (s, 2H), 4.42 (m, 1H), 6.28 (d, 1H), 6.86 (d, 2H), 6.96 (d, 2H), 7.07 (m, 1H), 7.18 (d, 2H), 7.38 (broad s, 5H), 8.36 (d, 1H), 9.18 (d, 1H).

5 C₂₈H₂₆F₂N₄O₄ (MW = 520.54); mass spectroscopy (MH⁺) 520.

Example 15

Synthesis of

10 (4R)-4-[N-(1S)-(1-Methoxycarbonyl-1-phenyl)methyl]carbamoyl-2-(3,5-difluorophenylmethyl)-4-methyl-2-thiazoline

To a solution of (4R)-4-carboxy-2-(3,5-difluorophenylmethyl)-4-methyl-2-thiazoline (0.2509 g, 1.00 eq.) from Example L above in THF (20 mL) at 0°C under an atmosphere of nitrogen was added (S)-(+)-2-phenylglycine methyl ester hydrochloride (0.2052 g, 1.10 eq.) (Aldrich), 1-hydroxybenzotriazole hydrate
15 (0.1437 g, 1.15 eq.) (Aldrich), *N,N*-diisopropylethylamine (0.371 mL, 2.30 eq.), followed by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.2039 g, 1.15 eq.) (Aldrich). The cooling bath was removed and the mixture allowed to warm to ambient temperature with stirring for 19 hours. The solution was diluted with ethyl acetate, washed with 0.5 M aqueous HCl (2x),
20 dilute aqueous NaHCO₃ (1x), and brine (1x); then the organic phase was dried over Na₂SO₄, filtered, concentrated *in vacuo*, and the residue purified by flash column chromatography using 2:1 hexanes/EtOAc as the eluent to yield the title compound as a clear colorless viscous oil (0.3465 g, 90%).

NMR data was as follows:

25 ¹H-nmr (CDCl₃, 300 MHz): δ = 7.59 (d, 1H, J = 7.25 Hz), 7.36-7.27 (m, 5H), 6.80-6.78 (m, 2H), 6.75-6.68 (m, 1H), 5.51 (d, 1H, J = 7.37 Hz), 3.78 (s, 2H), 3.74 (s, 3H), 2.63 (d, 1H, J = 11.59 Hz), 2.22 (d, 1H, J = 11.60 Hz), 1.55 (s, 3H).

Optical Rotation: [α]₂₀ = 65.3 (c 1.0, CHCl₃).

30 C₂₁H₂₀F₂N₂O₃S (MW = 418.47); mass spectroscopy (MH⁺) 418.3.

Example 16

-- 145 --

Synthesis of
4-[N-(S)-(1-Methoxycarbonyl-1-phenyl)methyl]carbamoyl-
2-(3,5-difluorophenylmethyl)-2-thiazoline

Following General Procedure A above and using L-phenylglycine methyl ester and 2-(3,5-difluorophenylmethyl)-4-carboxy-2-thiazoline from Example H above, the title compound was prepared as two separate diastereomeric isomers. The reaction was monitored by tlc ($R_f = 0.6$ and 0.4 in 1:1 EtOAc/hexanes) and the products were purified by silica gel column chromatography using 40% EtOAc/hexanes as the eluent.

First Diastereomeric Isomer (amorphous solid):

NMR data was as follows:

^1H -nmr (CDCl_3): $\delta = 3.58\text{--}3.82$ (m, 5H), 3.94 (s, 2H), 5.10 (t, 1H), 5.57 (d, 1H), 6.75 (m, 1H), 6.90 (d, 2H), 7.35 (m, 5H), 7.84 (d, 1H).

$\text{C}_{19}\text{H}_{18}\text{F}_2\text{N}_2\text{O}_3\text{S}$ (MW = 404.44); mass spectroscopy (MH^+) N/A.

Second Diastereomeric Isomer (oil):

NMR data was as follows:

^1H -nmr (CDCl_3): $\delta = 3.61$ (d, 2H), 3.75 (s, 3H), 3.84 (s, 2H), 5.13 (t, 1H), 5.56 (d, 1H), 6.72 (m, 1H), 6.80 (d, 2H), 7.33 (m, 5H), 7.66 (d, 1H).

$\text{C}_{19}\text{H}_{18}\text{F}_2\text{N}_2\text{O}_3\text{S}$ (MW = 404.44); mass spectroscopy (MH^+) 404.

Example 17

Synthesis of
(S)-5-[1-N-[N-(3,5-Difluorophenylacetyl)-L-alaninyl]amino]ethyl-
3-ethyl-1,2,4-oxadiazole

Following General Procedure A and using N-(3,5-difluorophenylacetyl)-L-alanine (Example II-B) and (S)-5-(1-aminoethyl)-3-ethyl-1,2,4-oxadiazole hydrochloride (Example A), the title compound was prepared as a solid having a melting point of $181\text{--}183^\circ\text{C}$. The reaction was monitored by tlc ($R_f = 0.3$ in 7% MeOH/ CHCl_3) and the product was purified by silica gel column chromatography using 7% MeOH/ CHCl_3 as the eluent, followed by recrystallization from 1-chlorobutane.

NMR data was as follows:

¹H-nmr (DMSO-*d*₆): δ = 1.20 (m, 6H), 1.45 (d, 3H), 2.70 (q, 2H), 3.51 (s, 2H), 4.32 (m, 1H), 5.13 (m, 1H), 6.98 (d, 2H), 7.10 (m, 1H), 8.38 (d, 1H), 8.73 (d, 1H).

Optical Rotation: [α]₂₀ = +53.1 @ 589 nm (c 1.08, DMSO).

5 C₁₇H₂₀F₂N₄O₃ (MW = 366.37); mass spectroscopy (MH⁺) 367.

Example 18

Synthesis of

10 2-[1-(3,5-Difluorophenylacetamido)-1-phenyl]methyl-(4R)-4-methoxycarbonyl-2-thiazoline

Following General Procedure G above and using N-(3,5-difluorophenylacetyl)phenylglycinonitrile from Example I above and (R)-cysteine methyl ester hydrochloride (CAS No. 2485-62-3), the title compound was prepared. The product was purified by silica gel chromatography using 1:1
15 EtOAc/hexanes as the eluent, followed by crystallization from 1-chlorobutane.

First Diastereomeric Isomer (higher R_f):

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 5.08 (t, 1H), 5.18 (t, 1H), 5.47 (t, 1H), 5.82 (m, 1H).

20 C₂₀H₁₈F₂N₂O₃S (MW = 404.44); mass spectroscopy (M⁺) 404.

Second Diastereomeric Isomer (lower R_f):

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 5.12 (t, 1H), 5.21 (t, 1H), 5.47 (t, 1H), 5.83 (m, 1H).

25

C₂₀H₁₈F₂N₂O₃S (MW = 404.44); mass spectroscopy (M⁺) 404.

Example 19

Synthesis of

30 2-[1-(3,5-Difluorophenylacetamido)-1-phenyl]methyl-(4S)-4-methoxycarbonyl-2-thiazoline

Following General Procedure G above and using N-(3,5-difluorophenylacetyl)phenylglycinonitrile from Example I above and (S)-cysteine

methyl ester hydrochloride (Aldrich), the title compound was prepared. The product was purified by silica gel chromatography using 2:3 EtOAc/hexanes as the eluent, followed by crystallization from 1-chlorobutane/hexanes.

First Diastereomeric Isomer (higher R_f):

5

NMR data was as follows:

^1H -nmr (CD_3OD): $\delta = 3.76$ (s, 3H), 5.20 (t, 1H), 5.85 (s, 1H).

$\text{C}_{20}\text{H}_{18}\text{F}_2\text{N}_2\text{O}_3\text{S}$ (MW = 404.44); mass spectroscopy (M^+) 404.

Second Diastereomeric Isomer (lower R_f):

10

NMR data was as follows:

^1H -nmr (CD_3OD): $\delta = 3.78$ (s, 3H), 5.22 (t, 1H), 5.83 (s, 1H).

$\text{C}_{20}\text{H}_{18}\text{F}_2\text{N}_2\text{O}_3\text{S}$ (MW = 404.44); mass spectroscopy (M^+) 404.

Example 20

15

Synthesis of

N-[2-(3,5-Difluorophenylmethyl)-4-methyl-2-imidazoline-4-carboxamido]-L-phenylglycine Methyl Ester

20

Step A -- Synthesis of 1-*tert*-Butoxycarbonyl-2-(3,5-difluorophenylmethyl)-4-carboxy-4-methyl-2-imidazoline

25

A round bottom flask containing a magnetic stir bar was charged with 150 mL of THF, 50 mL of a 0.1N aqueous solution of lithium hydroxide, and 1-*tert*-butoxycarbonyl-2-(3,5-difluorophenylmethyl)-4-ethoxycarbonyl-4-methyl-2-imidazoline (Example 8, Step C) (2.58 g, 6.75 mmole). The reaction mixture was stirred for 1 hour and then an additional 75 mL of a 0.1N aqueous solution of lithium hydroxide was added and stirring was continued for 3.5 hours. The reaction mixture was then concentrated *in vacuo* and the resulting residue was partitioned between ethyl acetate and a 0.5N aqueous solution of hydrochloric acid. The organic phase was separated and washed with an additional 0.5N aqueous solution of hydrochloric acid. The organic phase was then dried over Na_2SO_4 . The drying agent was removed by filtration and the filtrate was partially concentrated *in vacuo*. The resulting solid was isolated via vacuum

30

-- 148 --

filtration through a sintered glass funnel, followed by drying under *vacuo* at 80°C.

Mass spectroscopy data was as follows:

$C_{17}H_{20}N_2O_4$ (MW = 354.36); mass spectroscopy (MH^+) 255.2.

5

Step B -- Synthesis of *N*-[1-*tert*-Butoxycarbonyl-2-(3,5-difluorophenylmethyl)-4-methyl-2-imidazoline-4-carboxamido]-*L*-phenylglycine Methyl Ester

Following General Procedure A above and using (S)-(+)-2-phenylglycine methyl ester hydrochloride and the product of Step A, the title compound was prepared. The product was purified by flash silica gel chromatography (230-400 mesh) using 95:5 DCM/MeOH as the eluent.

First Diastereomeric Isomer (viscous oil):

NMR data was as follows:

^1H -nmr ($CDCl_3$): δ = 7.60 (bs, 1H), 7.35 (s, 5H), 6.90 (m, 2H), 6.69 (m, 1H), 5.49 (d, 1H), 4.12 (m, 3H), 3.72 (s, 3H), 3.61 (d, 1H), 1.46 (s, 9H), 1.41 (s, 3H).

Second Diastereomeric Isomer (viscous oil):

NMR data was as follows:

^1H -nmr ($DMSO-d_6$): δ = 7.55 (bs, 1H), 7.31 (m, 5H), 6.84 (m, 2H), 6.67 (m, 1H), 5.49 (d, 1H), 4.08 (m, 3H), 3.72 (s, 3H), 3.56 (m, 1H), 1.50 (s, 1H), 1.43 (s, 9H).

Step C -- Synthesis of *N*-[2-(3,5-Difluorophenylmethyl)-4-methyl-2-imidazoline-4-carboxamido]-*L*-phenylglycine Methyl Ester

Following General Procedure D above and using the individual isomers from Step B, the title compound was prepared as two separate isomers. These products were purified by flash silica gel chromatography (230-400 mesh) using 97.5:2.5 DCM/MeOH as the eluent.

First Diastereomeric Isomer:

Mass spectroscopy data was as follows:

30

$C_{21}H_{21}F_2N_2O_3S$ (MW = 401.42); mass spectroscopy (MH^+) 402.0.

Second Diastereomeric Isomer:

Mass spectroscopy data was as follows:

5 $C_{21}H_{21}F_2N_2O_3S$ (MW = 401.42); mass spectroscopy (MH^+) 402.0.

Additionally, the following General Procedures and Examples provide various carboxylic acids (and carboxylic acid esters which can be hydrolyzed using General Procedures AC or BD below to afford the corresponding
10 carboxylic acids) which can be used to prepare additional compounds within the scope of this invention.

GENERAL PROCEDURE AA

Reductive Amination

15 To a solution of the arylamine in ethanol in a hydrogenation flask was added 1 equivalent of the 2-oxocarboxylic acid ester (e.g., pyruvate ester), followed by 10% palladium on carbon (25 weight percent based on the arylamine). The reaction was hydrogenated at 20 psi H_2 on a Parr shaker until complete reaction was indicated by tlc (30 minutes to 16 hours). The reaction
20 mixture was then filtered through a pad of Celite 545 (available from Aldrich Chemical Company, Inc.) and stripped free of solvent on a rotary evaporator. The crude product residue was then further purified via chromatography.

GENERAL PROCEDURE AB

25 First Transesterification Technique

A solution of 1-5 equivalents of the desired alcohol was added to 1 equivalent of sodium hydride in toluene. After off-gassing had ceased, the compound to be transesterified, dissolved in toluene, was added. After 0.5 hours, the reaction was either heated to 40°C and placed under house vacuum
30 (~20 mmHg), or nitrogen was bubbled through the solution while it was heated at 90°C. The reaction was followed by tlc, and when the reaction was complete

-- 150 --

the solution was cooled and quenched with water or 1M HCl, and in smaller scale reactions diluted with ethyl acetate. The organic phase was extracted with saturated aqueous NaHCO₃, then washed with saturated aqueous NaCl and dried over MgSO₄. The solution was stripped free of solvent on a rotary evaporator, and the crude product residue was then further purified by chromatography. Alternatively, the reaction mixture was worked-up by evaporation of the solvents and direct chromatography of the crude mixture.

This procedure is particularly useful in the case of costly and/or high boiling alcohols.

GENERAL PROCEDURE AC

Second Transesterification Technique

The compound to be transesterified was placed in a large excess of the desired alcohol. A catalytic amount of dry NaH was added, and the reaction was followed by tlc until the presence of starting material was no longer detected. The reaction was quenched with a few milliliters of 1N HCl, and after a few minutes of stirring saturated aqueous NaHCO₃ was added. The organic phase was washed with saturated aqueous NaCl and dried over MgSO₄. The solution was stripped free of solvent on a rotary evaporator, and the crude product residue was then further purified by chromatography.

GENERAL PROCEDURE AD

Third Transesterification Technique

The compound to be transesterified was placed in a large excess of the desired alcohol. A catalytic amount of dry NaH was added, and the reaction was followed by tlc until the presence of starting material was no longer detected. The reaction was quenched with a few milliliters of 1N HCl, and after a few minutes of stirring saturated aqueous NaHCO₃ was added. The volume of the reaction mixture was reduced on a rotary evaporator until the excess alcohol was removed and then the remaining residue was taken up in

ethyl acetate and additional water was added. The organic phase was washed with saturated aqueous NaCl and dried over MgSO_4 . The solution was stripped free of solvent on a rotary evaporator, and the crude product residue was then further purified by chromatography.

5

This procedure is particularly employed in the case of low boiling, inexpensive alcohols, miscible with water.

GENERAL PROCEDURE AE

10

O-Alkylation Technique

To a carboxylic acid compound (prepared, for example, by reductive amination via General Procedure AA to provide for the *N*-aryl amino acid ester, followed by hydrolysis via Procedure AF) in DMF was added 1.5 equivalents K_2CO_3 , followed by 1 equivalent of alkylating agent (e.g., *tert*-butyl bromoacetate). The reaction was stirred at room temperature for 2 hours, then was quenched with water and extracted into ethyl acetate. The organic phase was washed with saturated aqueous NaHCO_3 , water, and saturated aqueous NaCl, and was then dried over MgSO_4 . The solution was stripped free of solvent on a rotary evaporator to yield the crude product.

20

GENERAL PROCEDURE AF

Ester Hydrolysis to Free Acid

To a carboxylic ester compound (prepared, for example, by reductive amination via General Procedure AA to provide for the *N*-aryl amino acid ester) in a 1:1 mixture of $\text{CH}_3\text{OH}/\text{H}_2\text{O}$ was added 2-5 equivalents of K_2CO_3 . The mixture was heated to 50°C for 0.5 to 1.5 hours until tlc showed complete reaction. The reaction was cooled to room temperature and the methanol was removed on a rotary evaporator. The pH of the remaining aqueous solution was adjusted to ~ 2 , and ethyl acetate was added to extract the product. The organic phase was then washed with saturated aqueous NaCl and dried over MgSO_4 .

30

-- 152 --

The solution was stripped free of solvent on a rotary evaporator to yield the crude product.

GENERAL PROCEDURE AG

5

N-Heteroarylation of Alanine

A solution of 1.1 equivalents of L-alanine and 2 equivalents NaOH in DMSO was stirred at room temperature for 1 hour, then 1 equivalent of 2-chlorobenzothiazole was added. The mixture was heated to 100°C for 4 hours, then cooled to room temperature and poured onto ice. The pH of the resulting aqueous solution was adjusted to ~2, and the precipitated solid was removed by filtration. This solid was then dissolved in 1N NaOH and the resulting solution was filtered through a pad of Celite 545. The pH of the filtrate was adjusted to ~2, and the white precipitate was removed by filtration and washed with water to yield the crude product.

15

GENERAL PROCEDURE AH

EDC Coupling

To a 1:1 mixture of the desired acid and alcohol in CH_2Cl_2 at 0°C was added 1.5 equivalents triethylamine, followed by 2.0 equivalents hydroxybenzotriazole monohydrate, then 1.25 equivalents of ethyl-3-(3-dimethylamino)-propyl carbodiimide·HCl (EDC). The reaction was stirred overnight at room temperature, then transferred to a separatory funnel and washed with water, saturated aqueous NaHCO_3 , 1N HCl, and saturated aqueous NaCl, and was then dried over MgSO_4 . The solution was stripped free of solvent on a rotary evaporator to yield the crude product.

25

GENERAL PROCEDURE AI

Oxime or Amine Coupling Technique

The trichlorophenyl ester (1 eq) of a carboxylic acid was stirred in DMF or THF. The oxime or amine (1.2 eq) was added and the mixture was stirred at ambient temperature for 1-4 hours. In cases where the hydrochloride salt form

30

of an amine was used, a suitable base such as *N,N*-diisopropylethylamine (1.2 eq) was also added. The resulting mixture was concentrated under reduced pressure to yield a crude product which was used without purification or was purified by silica gel chromatography and/or crystallization.

5

GENERAL PROCEDURE AJ

Alkylation Technique

The amine (1 eq), the α -bromo ester (1.1 eq) and a suitable base (such as triethylamine) (2 eq) were stirred in chloroform. The resulting solution was heated at reflux for 4-12 hours. After cooling, the mixture was diluted with chloroform and washed with water. The organic portion was dried (sodium sulfate) and concentrated under reduced pressure. The crude product was purified by silica gel chromatography.

15

GENERAL PROCEDURE AK

Oxime or Alcohol Coupling Technique

The carboxylic acid (1 eq) was stirred in a suitable solvent (such as THF, dioxane or DMF). An alcohol or oxime (1-5 eq) was added. EDC hydrochloride (1.2 eq) and hydroxybenzotriazole hydrate (1 eq) were added. A suitable base (such as 4-methylmorpholine or triethylamine) (0-1 eq) was added. A catalytic amount (0.1 eq) of 4-dimethylaminopyridine was added. The mixture was stirred at ambient temperature and under a dry atmosphere of nitrogen. After 20 hours, the mixture was concentrated under reduced pressure. The resulting concentrate was partitioned between ethyl acetate and water. The organic portion was separated and washed with aqueous sodium bicarbonate and brine. The organic portion was dried (sodium sulfate) and concentrated under reduced pressure. The crude product was used without purification or was purified by silica gel chromatography and/or crystallization.

25
30

GENERAL PROCEDURE AL

EDC Coupling

-- 154 --

The carboxylic acid was dissolved in methylene chloride. The amino acid (1 eq.), N-methylmorpholine (5 eq.) and hydroxybenzotriazole monohydrate (1.2 eq.) were added in sequence. A cooling bath was applied to the round bottomed flask until the solution reached 0°C. At that time, 1.2 eq. of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) was added. The solution was allowed to stir overnight and come to room temperature under nitrogen pressure. The reaction mixture was worked up by washing the organic phase with saturated aqueous sodium carbonate, 0.1M citric acid, and brine before drying with sodium sulfate. The solvents were then removed to yield crude product. Pure products were obtained by flash chromatography in an appropriate solvent.

GENERAL PROCEDURE AM

Triflate Displacement

To a 0°C solution of *iso*-butyl R-(+)-lactate in CH₂Cl₂ was added 1.1 equivalents of trifluoromethanesulfonic anhydride. After stirring at room temperature for 20 min, 1.1 equivalents of 2,6-lutidine was added and stirring was continued for 10 min. This solution was then transferred to a flask containing 1 equivalent the arylamine and 1 equivalent *N,N*-diisopropylethylamine in CH₂Cl₂ or CH₃NO₂ at 0°C. The reaction was held overnight at room temperature and then stripped free of solvent on a rotary evaporator. The residue was dissolved in ethyl acetate, washed with 5% citric acid, followed by saturated aqueous NaCl, dried over magnesium sulfate or sodium sulfate and then the solution was stripped free of solvent on a rotary evaporator to yield the crude product, which was then purified by chromatography.

GENERAL PROCEDURE AN

BOC Removal

The BOC-protected compound was added to a 1:1 mixture of CH₂Cl₂ and trifluoroacetic acid, and was stirred until tlc indicated complete conversion,

typically 2h. The solution was then stripped to dryness and the residue was taken up in ethyl acetate and extracted with dilute HCl. The acid reaction was neutralized and extracted with ethyl acetate. The organic phase was washed with saturated aqueous NaCl and dried over MgSO₄. The solution was stripped
5 free of solvent on a rotary evaporator to yield the product.

GENERAL PROCEDURE AO

Synthesis of Pyruvate Esters

To a mixture of pyruvic acid (8.8 g, 0.1 mol) (Aldrich) in 100 mL of
10 benzene was added *iso*-butanol (14.82 g, 0.2 mol) and a catalytic amount of *p*-toluenesulfonic acid. The mixture was then refluxed using a Dean Stark apparatus. After 4 hours, the reaction appeared to be complete with the isolation of 1.8 g (0.1 mol) of water. The benzene and *iso*-butanol were removed on a rotary evaporator. The residue (14 g, 0.1 mol), which was primarily the
15 pyruvate *iso*-butyl ester by nmr [¹H-Nmr (CDCl₃): δ = 4.0 (d, 2H), 2.5 (s, 3H), 2.0 (m, 1H), 1.0 (d, 6H)], was used without further purification. By substituting other alcohols in place of *iso*-butanol (e.g., ethanol, isopropanol, *n*-butanol, benzyl alcohol and the like), other esters of pyruvic acid can be prepared in a similar manner.

20

GENERAL PROCEDURE AP

Aromatic Nucleophilic Substitution of Fluorobenzenes

A mixture of 1.82 g (10 mmol) of D,L-alanine *iso*-butyl ester hydrochloride, the fluorobenzene (10 mmol) and 3 g of anhydrous potassium
25 carbonate in 10 mL of DMSO was stirred at 120°C for 2-5 hours. The reaction mixture was then cooled to room temperature and diluted with 100 mL of ethyl acetate. The ethyl acetate extract was washed with water (3x), dried over MgSO₄ and evaporated to dryness to afford the crude product, which was further purified by column chromatography.

30

GENERAL PROCEDURE AQ

-- 156 --

Fourth Transesterification Technique

The ester to be transesterified was dissolved in a large excess of the alcohol and 0.3 equivalents of titanium(IV) isopropoxide (Aldrich) was added. The reaction was followed by tlc until complete and then the volatiles were removed at reduced pressure. The resulting crude material was then chromatographed to obtain the desired product.

GENERAL PROCEDURE AR

Synthesis of *N*-BOC Anilines

To a solution of the aniline in THF was added dropwise 1 equivalent of di-*tert*-butyl dicarbonate (Aldrich) in THF and then 1.5 equivalents of 10N aqueous sodium hydroxide at 0°C. After stirring at room temperature for 16 hours, or heating at 80°C for 3 hours, if needed, the reaction mixture was diluted with ether and washed with NaHCO₃, brine, dried over sodium sulfate and potassium carbonate, concentrated at reduced pressure and chromatographed to afford the *N*-BOC aniline.

GENERAL PROCEDURE AS

Oxime Ester Formation

The trichlorophenyl ester (1 eq.) was stirred in DMF or THF. The oxime (1.2 eq.) was added and the mixture was stirred at ambient temperature for 1 to 4 hours. The resulting mixture was concentrated under reduced pressure and the residue was purified by silica gel chromatography and/or crystallization.

Example AA

Synthesis of D,L-alanine *iso*-butyl ester hydrochloride

A mixture of 35.64 g (0.4 mol) of D,L-alanine (Aldrich), 44 mL (0.6 mol) of thionyl chloride (Aldrich) and 200 mL of *iso*-butanol was refluxed for 1.5 hours. The volatiles were removed at reduced pressure at 90°C under reduced pressure to give the title compound as an oil, which was used without further purification.

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 8.72 (br s, 3H), 4.27 (q, J = 7.4 Hz, 1H), 3.95 (m, 2H), 1.96 (s, 1H), 1.73 (d, J = 7.2 Hz, 3H), 0.92 (d, J = 6.7 Hz, 6H).

¹³C-nmr (CDCl₃): δ = 170.0, 72.2, 49.2, 27.5, 18.9, 16.1.

5

Example AB

Synthesis of N-(3,4-dichlorophenyl)alanine

Using the procedure set forth in U.S. Patent No. 3,598,859, the disclosure of which is incorporated herein by reference in its entirety, N-(3,4-dichlorophenyl)alanine was prepared. Specifically, to a solution of 3,4-dichloroaniline (1 equivalent) (Aldrich) in isopropanol (about 500 mL per mole of 3,4-dichloroaniline) is added water (about 0.06 mL per mL of isopropanol) and 2-chloropropionic acid (2 equivalents) (Aldrich). This mixture is warmed to 40°C and sodium bicarbonate (0.25 equivalents) is added in successive portions before heating under reflux for 4-5 days. After cooling, the reaction mixture is poured into water and the unreacted 3,4-dichloroaniline is removed by filtration. The filtrate is acidified to pH 3-4 with concentrated hydrochloric acid and the resultant precipitate is filtered, washed and dried to yield the title compound, m.p. = 148-149°C.

20

Alternatively, following General Procedure AF above and using N-(3,4-dichlorophenyl)alanine ethyl ester (from Example A1 below), the title compound was prepared.

25

Example AC

Synthesis of N-(3,5-difluorophenyl)alanine

Using the procedure set forth in U.S. Patent No. 3,598,859, N-(3,5-difluorophenyl)alanine was prepared using 3,5-difluoroaniline (Aldrich) and 2-chloropropionic acid (Aldrich).

30

Example AD

Synthesis of *Iso*-butyl 2-bromopropionate

To a mixture of *iso*-butanol and 1.0 equivalent of pyridine in dry diethyl ether was added dropwise 1.3 equivalents of 2-bromopropionyl bromide at 0°C. After stirring at room temperature for 16 hours, the reaction was diluted with
5 diethyl ether, washed with 1N HCl, water, aqueous NaHCO₃, brine and dried over magnesium sulfate or sodium sulfate. Removal of the solvents at reduced pressure gave the title compound as a clear oil.

Example AE

10 Synthesis of N-(2-naphthyl)alanine 2,4,5-trichlorophenyl ester

N-(2-Naphthyl)alanine methyl ester (5.0 g, 20.6 mmol) (from Example A44 below) was dissolved in dioxane (100 mL). NaOH (30 mL, 1N) was added and the resulting solution was stirred for 1 hour. The reaction mixture was concentrated under reduced pressure. The resulting solid was dissolved in water
15 and the aqueous mixture was washed with ether. The aqueous portion was adjusted to pH 3 with 1N HCl and extracted with ethyl acetate. The organic extracts were dried over magnesium sulfate or sodium sulfate and concentrated under reduced pressure to yield a white solid (4.35 g, 98%).

20 The resulting solid (4.35 g, 20 mmol) was dissolved in dichloromethane (300 mL). 2,4,5-Trichlorophenol (4.9 g, 25 mmol) (Aldrich) was added followed by dicyclohexylcarbodiimide (25 mL, 1M in dichloromethane) (Aldrich). After stirring for 18 hours, the mixture was filtered and concentrated to provide an oil which was purified by chromatography on silica gel using
25 chloroform as the eluant ($R_f = 0.6$). The title compound was obtained as a thick oil which slowly crystallized.

Example A1

Synthesis of N-(3,4-dichlorophenyl)alanine ethyl ester

30 Following General Procedure AA above and using 3,4-dichloroaniline (Aldrich) and ethyl pyruvate (Aldrich), the title compound was prepared as an

oil. The reaction was monitored by tlc on silica gel ($R_f = 0.4$ in 25% EtOAc/hexanes) and purification was by preparative plate chromatography (silica gel using 25% EtOAc/hexanes as the eluant).

NMR data was as follows:

5 ^1H -nmr (CDCl_3): $\delta = 7.2$ (d, 1H); 6.7 (d, 1H); 6.4 (dd, 1H); 4.30 (bs, 1H); 4.2 (q, 2H); 4.1 (q, 1H); 1.5 (d, 3H); 1.3 (t, 3H).

^{13}C -nmr (CDCl_3): $\delta = 175$; 146.7; 133; 131; 121; 114.9; 112.6; 72.0; 52.4; 28.3; 19.5.

$\text{C}_{11}\text{H}_{13}\text{Cl}_2\text{NO}_2$ (MW = 262.14).

10

Example A2

Synthesis of N-(3-trifluoromethyl-4-chlorophenyl)alanine ethyl ester

Following General Procedure AA above and using 4-chloro-3-(trifluoromethyl)aniline (Aldrich) and ethyl pyruvate (Aldrich), the title
15 compound was prepared.

Analysis: Calc.: C, 48.74; H, 4.43; N, 4.74. Found: C, 48.48; H, 4.54; N, 4.94.

$\text{C}_{12}\text{H}_{13}\text{F}_3\text{ClNO}_2$ (MW = 295.69); mass spectroscopy (MH^+) 295.

20

Example A3

Synthesis of N-(3,5-dichlorophenyl)alanine ethyl ester

Following General Procedure AA above and using 3,5-dichloroaniline (Aldrich) and ethyl pyruvate (Aldrich), the title compound was prepared.

Analysis: Calc.: C, 50.40; H, 5.00; N, 5.34. Found: C, 50.50; H, 5.06;
25 N, 5.25.

$\text{C}_{11}\text{H}_{13}\text{Cl}_2\text{NO}_2$ (MW = 262.14); mass spectroscopy (MH^+) NA.

Example A4

Synthesis of N-(3,4-difluorophenyl)alanine ethyl ester

30 Following General Procedure AA above and using 3,4-difluoroaniline (Aldrich) and ethyl pyruvate (Aldrich), the title compound was prepared. The

-- 160 --

reaction was monitored by tlc on silica gel ($R_f = 0.4$ in 25% EtOAc/hexanes) and purification was by preparative plate chromatography (silica gel using 25% EtOAc/hexanes as the eluant).

NMR data was as follows:

5 ^1H -nmr (CDCl_3): $\delta = 7.4$ (m, 1H), 6.8 (d, 1H), 6.5 (m, 1H), 4.30 (bs, 1H), 4.2 (q, 2H), 4.1 (q, 1H), 1.5 (d, 3H), 1.3 (t, 3H).

^{13}C -nmr (CDCl_3): $\delta = 175$, 146.7, 135, 132, 125, 116, 113, 72, 52, 28, 19.

$\text{C}_{11}\text{H}_{13}\text{F}_2\text{NO}_2$ (MW = 229.23); mass spectroscopy (MH^+) 230.

10

Example A5

Synthesis of N-(3,4-dichlorophenyl)alanine benzyl ester

Following General Procedure AA above and using 3,4-dichloroaniline (Aldrich) and benzyl pyruvate (prepared by following General Procedure AO above using benzyl alcohol in place of *iso*-butanol), the title compound was prepared as an oil. The reaction was monitored by tlc on silica gel ($R_f = 0.4$ in 25% EtOAc/hexanes) and purification was by preparative plate chromatography (silica gel using 25% EtOAc/hexanes as the eluant).

NMR data was as follows:

20 ^1H -nmr (CDCl_3): $\delta = 7.18$ (d, 1H); 7.0 (m, 5H); 6.6 (d, 1H); 6.4 (dd, 1H); 5.1 (s, 2H); 4.30 (bs, 1H); 4.08 (q, 1H); 1.94 (m, 1H); 1.47 (d, 3H); 0.91 (d, 6H).

^{13}C -nmr (CDCl_3): $\delta = 174.5$; 146.7; 133.5; 131.3; 121.3; 120.1; 114.9; 113.6; 72.0; 60.1; 52.4; 28.3; 19.5; 19.3.

25 $\text{C}_{16}\text{H}_{15}\text{Cl}_2\text{NO}_2$ (MW = 324.31); mass spectroscopy (MH^+) 325.

Example A6

Synthesis of N-(3,4-dichlorophenyl)alanine *iso*-butyl ester

30 Following General Procedure AA above and using 3,4-dichloroaniline (Aldrich) and *iso*-butyl pyruvate (prepared by following General Procedure AO above), the title compound was prepared as an oil. The reaction was monitored

-- 161 --

by tlc on silica gel ($R_f = 0.55$ in 25% EtOAc/hexanes) and purification was by preparative plate chromatography (silica gel using 25% EtOAc/hexanes as the eluant).

NMR data was as follows:

5 ^1H -nmr (CDCl_3): $\delta = 7.18$ (d, 1H, $J=8.7$ Hz), 6.66 (d, 1H, $J=2.7$ Hz), 6.43 (dd, 1H, $J = 8.7$ Hz, $J = 2.7$ Hz), 4.30 (bs, 1H), 4.08 (q, 1H, $J = 6.9$ Hz), 1.94 (sept, 1H, $J = 6.7$ Hz), 1.47 (d, 3H, $J = 6.9$ Hz), 0.91 (d, 6H, $J = 6.6$ Hz).

10 ^{13}C -nmr (CDCl_3) $\delta = 174.5, 146.7, 133.5, 131.3, 121.3, 114.9, 113.6, 72.0, 52.4, 28.3, 19.5, 19.3$.

$\text{C}_{13}\text{H}_{17}\text{Cl}_2\text{NO}_2$ (MW = 290.19); mass spectroscopy (MH^+) 290.

Example A7

Synthesis of N-(3,4-dichlorophenyl)alanine *iso*-propyl ester

15 Following General Procedure AA above and using 3,4-dichloroaniline (Aldrich) and isopropyl pyruvate (prepared by following General Procedure AO above using isopropanol in place of *iso*-butanol), the title compound was prepared as an oil. The reaction was monitored by tlc on silica gel ($R_f = 0.4$ in 25% EtOAc/hexanes) and purification was by preparative plate chromatography (silica gel using 25% EtOAc/hexanes as the eluant).

NMR data was as follows:

^1H -nmr (CDCl_3): $\delta = 7.18$ (d, 1H); 6.66 (d, 1H); 6.43 (dd, 1H); 4.30 (bs, 1H); 4.08 (m, 1H); 1.94 (m, 1H); 1.47 (d, 3H); 0.91 (d, 6H).

25 ^{13}C -nmr (CDCl_3): $\delta = 174.5; 146.7; 133.5; 131.3; 121.3; 114.9; 113.6; 72.0; 52.4; 19.5$.

$\text{C}_{12}\text{H}_{15}\text{Cl}_2\text{NO}_2$ (MW = 276.16); mass spectroscopy (MH^+) 277.

Example A8

Synthesis of N-(3,4-dichlorophenyl)alanine *n*-butyl ester

30 Following General Procedure AA above and using 3,4-dichloroaniline (Aldrich) and *n*-butyl pyruvate (prepared by following General Procedure AO

-- 162 --

above using *n*-butanol in place of *iso*-butanol), the title compound was prepared. The reaction was monitored by tlc on silica gel ($R_f = 0.7$ in 25% EtOAc/hexanes) and purification was by preparative plate chromatography (silica gel using 25% EtOAc/hexanes as the eluant).

5 NMR data was as follows:

^1H -nmr (CDCl_3): $\delta = 7.18$ (d, 1H); 6.66 (d, 1H); 6.43 (dd, 1H); 4.30 (bs, 1H); 4.2 (m, 2H); 4.08 (q, 1H); 1.94 (m, 1H); 1.47 (m, 4H); 0.91 (t, 3H).

^{13}C -nmr (CDCl_3): $\delta = 174.5$; 146.7; 133.5; 131.3; 121.3; 114.9; 113.6; 72.0; 52.4; 28.3; 20.2; 19.5.

10 $\text{C}_{13}\text{H}_{17}\text{Cl}_2\text{NO}_2$ (MW = 290.19); mass spectroscopy (MH^+) 291.

Example A9

15 Synthesis of N-(3,4-dichlorophenyl)alanine methyl ester (R,S isomers)

Following General Procedure AA above and using 3,4-dichloroaniline (Aldrich) and methyl pyruvate (Aldrich), the title compound was prepared as an oil. The reaction was monitored by tlc on silica gel ($R_f = 0.55$ in 25% EtOAc/hexanes) and purification was by flash chromatography (silica gel using 25% EtOAc/hexanes as the eluant).

NMR data was as follows:

25 ^1H -nmr (CDCl_3): $\delta = 7.19$ (d, $J = 8.73$ Hz, 1H), 6.66 (d, $J = 2.75$ Hz, 1H), 6.43 (dd, $J = 8.73$ Hz, 2.80 Hz, 1H), 4.25 (bd, $J = 8.25$ Hz, 1H), 4.08 (m, 1H), 3.76 (s, 3H), 1.47 (d, $J = 6.90$ Hz).

^{13}C -nmr (CDCl_3) $\delta = 174.35$, 145.96, 132.87, 130.70, 120.76, 114.38, 112.90, 52.43, 51.70, 18.67.

$\text{C}_{10}\text{H}_{11}\text{Cl}_2\text{NO}_2$ (MW = 248.11); mass spectroscopy (MH^+) 247.

30

Example A10

Synthesis of N-(3,4-dichlorophenyl)alanine cyclopentyl ester

35 Following transesterification General Procedure AB above and using N-(3,4-dichlorophenyl)alanine methyl ester (from Example A9 above) and

-- 163 --

cyclopentanol (Aldrich), the title compound was prepared as an oil. The reaction was monitored by silica gel tlc ($R_f = 0.66$ in 25% EtOAc/hexanes). Purification was by preparative plate chromatography (silica gel using 25% EtOAc/hexanes as the eluant).

5 NMR data was as follows:

^1H -nmr (CDCl_3): $\delta = 7.19$ (d, 1H, $J = 8.7$ Hz), 6.66 (d, 1H, $J = 2.7$ Hz), 6.43 (dd, 1H, $J = 8.7$ Hz, $J = 2.7$ Hz), 5.22 (m, 1H), 4.27 (d, 1H, $J = 8.1$ Hz), 4.02 (quint, 1H, $J = 7.5$ Hz), 1.74 (m, 8H), 1.43 (d, 3H, $J = 6.9$ Hz).

10 ^{13}C -nmr (CDCl_3): $\delta = 174.3, 146.7, 133.4, 131.2, 121.2, 114.9, 113.7, 78.9, 52.5, 33.2, 24.2, 24.1, 19.1$.

$\text{C}_{14}\text{H}_{17}\text{Cl}_2\text{NO}_2$ (MW = 302.20); mass spectroscopy (MH^+) 301.

Example A11

15 Synthesis of N-(3,4-dichlorophenyl)alanine *n*-propyl ester

Following General Procedure AA above and using 3,4-dichloroaniline (Aldrich) and *n*-propyl pyruvate (prepared by following General Procedure AO above using *n*-propanol in place of *iso*-butanol), the title compound was prepared as an oil. The reaction was monitored by tlc on silica gel ($R_f = 0.5$ in 25% EtOAc/hexanes) and purification was by preparative plate chromatography (silica gel using 25% EtOAc/hexanes as the eluant).

NMR data was as follows:

^1H -nmr (CDCl_3): $\delta = 7.2$ (d, 1H); 6.6 (d, 1H); 6.4 (dd, 1H); 4.30 (bs, 1H); 4.2 (q, 2H); 4.08 (q, 1H); 1.94 (m, 2H); 1.5 (d, 3H); 0.95 (t, 3H).

25 ^{13}C -nmr (CDCl_3): $\delta = 178; 144.7; 130.2; 120.62; 115.11; 71.82; 52.90$.

$\text{C}_{12}\text{H}_{15}\text{Cl}_2\text{NO}_2$ (MW = 276.16); mass spectroscopy (MH^+) 277.

Example A12

30

Synthesis of N-(3,4-dichlorophenyl)alanine allyl ester

-- 164 --

Following transesterification General Procedure AB above and using N-(3,4-dichlorophenyl)alanine methyl ester (from Example A9 above) and allyl alcohol (Aldrich), the title compound was prepared as an oil. The reaction was monitored by silica gel tlc ($R_f = 0.62$ in 25% EtOAc/hexanes). Purification was by preparative plate chromatography (silica gel using 25% EtOAc/hexanes as the eluant).

NMR data was as follows:

^1H -nmr (CDCl_3): $\delta = 7.19$ (d, 1H, $J = 8.7$ Hz), 6.67 (d, 1H, $J = 2.8$ Hz), 6.44 (dd, 1H, $J = 8.7$ Hz, $J = 2.8$ Hz), 5.90 (m, 1H), 5.30 (m, 2H), 4.64 (m, 2H), 4.26 (m, 1H), 4.10 (m, 1H), 1.48 (d, 3H, $J = 6.9$ Hz).

^{13}C -nmr (CDCl_3): $\delta = 174.1, 146.6, 133.5, 132.1, 131.3, 121.4, 119.6, 115.0, 113.6, 66.5, 52.4, 19.3$.

$\text{C}_{12}\text{H}_{13}\text{Cl}_2\text{NO}_2$ (MW = 274.15); mass spectroscopy (MH^+) 273.

15

Example A13

Synthesis of N-(3,4-dichlorophenyl)alanine 4-methylpentyl ester

Following transesterification General Procedure AB above and using N-(3,4-dichlorophenyl)alanine methyl ester (from Example A9 above) and 4-methylpentanol (Aldrich), the title compound was prepared as an oil. The reaction was monitored by silica gel tlc ($R_f = 0.70$ in 25% EtOAc/hexanes). Purification was by preparative plate chromatography (silica gel using 25% EtOAc/hexanes as the eluant).

25

NMR data was as follows:

^1H -nmr (CDCl_3): $\delta = 7.18$ (d, 1H, $J = 8.7$ Hz), 6.66 (d, 1H, $J = 2.7$ Hz), 6.43 (dd, 1H, $J = 8.7$ Hz, $J = 2.7$ Hz), 4.28 (m, 1H), 4.10 (m, 3H), 1.55 (m, 6H), 1.19 (m, 2H), 0.87 (d, 3H, $J = 6.6$ Hz).

^{13}C -nmr (CDCl_3): $\delta = 174.6, 146.7, 133.4, 131.3, 121.3, 115.0, 113.6, 66.4, 52.4, 35.4, 28.2, 27.0, 23.0, 19.3$.

30

$\text{C}_{15}\text{H}_{21}\text{Cl}_2\text{NO}_2$ (MW = 318.25); mass spectroscopy (MH^+) 317.

Example A14

Synthesis of N-(3,4-dichlorophenyl)alanine 2,2-dimethyl-1,3-dioxolane-4-methyl ester

Following transesterification General Procedure AB above and using N-(3,4-dichlorophenyl)alanine methyl ester (from Example A9 above) and 2,2-dimethyl-1,3-dioxolane-4-methanol (solketal) (Aldrich), the title compound was prepared as a mixture of diastereomers. The reaction was monitored by silica gel tlc ($R_f = 0.32$ in 25% EtOAc/hexanes). Purification was by preparative plate chromatography (silica gel using 25% EtOAc/hexanes as the eluant).

NMR data was as follows:

^1H -nmr (CDCl_3): $\delta = 7.19$ (d, 1H, $J = 8.7$ Hz), 6.66 (d, 1H, 2.7 Hz), 6.43 (dd, 1H, $J = 8.7$ Hz, $J = 2.7$ Hz), 4.22 (m, 6H), 3.70 (m, 1H), 1.43 (m, 9H).

^{13}C -nmr (CDCl_3): $\delta = 174.34, 174.32, 146.5, 133.5, 131.3, 121.5, 115.0, 113.6, 110.52, 110.51, 73.97, 73.89, 66.6, 66.01, 65.95, 52.42, 52.37, 27.3, 25.8, 19.3$.

$\text{C}_{15}\text{H}_{19}\text{Cl}_2\text{NO}_4$ (MW = 348.23); mass spectroscopy (MH^+) 347.

Example A15

Synthesis of N-(3,4-dichlorophenyl)alanine cyclohexylmethyl ester

Following transesterification General Procedure AB above and using N-(3,4-dichlorophenyl)alanine methyl ester (from Example A9 above) and cyclohexylmethanol (Aldrich), the title compound was prepared.

NMR data was as follows:

^1H -nmr (CDCl_3): $\delta = 7.19$ (d, 1H), 6.68 (d, 1H), 6.45 (dd, 1H), 4.26 (bd, 1H), 4.10 (m, 1H), 3.95 (d, 2H), 1.70-1.55 (m, 6H), 1.50 (d, 3H), 1.35-0.85 (m, 5H).

^{13}C -nmr (CDCl_3): $\delta = 174.58, 146.72, 133.48, 131.27, 121.34, 114.98, 113.72, 71.06, 52.52, 37.68, 30.10, 26.83, 26.17, 19.32$.

$\text{C}_{15}\text{H}_{21}\text{Cl}_2\text{NO}_2$ (MW = 318.25); mass spectroscopy (MH^+) 317.

Example A16

Synthesis of N-(3,4-dichlorophenyl)alanine *tert*-butyloxycarbonylmethyl ester

Following General Procedure AE above and using N-(3,4-dichlorophenyl)alanine (from Example AB above) and *tert*-butyl bromoacetate (Aldrich), the title compound was prepared as a solid. The reaction was monitored by silica gel tlc ($R_f = 0.57$ in 25% EtOAc/hexanes). Purification was by recrystallization from ethanol.

NMR data was as follows:

¹H-nmr (CDCl₃): $\delta = 7.19$ (d, 1H), 6.68 (d, 1H), 6.45 (dd, 1H), 4.55 (m, 2H), 4.20 (m, 2H), 1.55 (d, 3H), 1.45 (s, 9H).

¹³C-nmr (CDCl₃): $\delta = 173.9, 166.9, 146.5, 133.5, 131.3, 115.1, 113.6, 83.4, 62.2, 52.2, 28.6, 19.3$.

C₁₅H₁₉Cl₂NO₄ (MW = 348.23); mass spectroscopy (MH⁺) 347.

15

Example A17

Synthesis of N-(3,4-dichlorophenyl)leucine *iso*-butyl ester

Following General Procedure AA above and using 3,4-dichloroaniline (Aldrich) and *iso*-butyl 4-methyl-2-oxopentanoate (prepared by following General Procedure AO above using 4-methyl-2-oxovaleric acid (Fluka) and *iso*-butanol), the title compound was prepared as an oil. The reaction was monitored by tlc on silica gel ($R_f = 0.6$ in 25% EtOAc/hexanes) and purification was by preparative plate chromatography (silica gel using 25% EtOAc/hexanes as the eluant).

25 NMR data was as follows:

¹H-nmr (CDCl₃): $\delta = 7.2$ (d, 1H); 6.5 (d, 1H); 6.4 (dd, 1H); 4.30 (bs, 1H); 4.08 (q, 1H); 3.8(m, 2H); 1.8 (m, 3H); 0.91 (m, 12H).

¹³C-nmr (CDCl₃): $\delta = 174.5; 146.7; 133.5; 131.3; 121.3; 114.9; 113.6; 72.0; 52; 28.3; 20.1; 19.5$.

30 C₁₆H₂₃Cl₂NO₂ (MW = 332.27); mass spectroscopy (MH⁺) 333.

Example A18

Synthesis of 2-[N-(3,4-dichlorophenyl)amino]pentanoic acid *iso*-butyl ester

Following General Procedure AA above and using 3,4-dichloroaniline (Aldrich) and *iso*-butyl 2-oxopentanoate (prepared by following General Procedure AO above using 2-oxovaleric acid (Fluka) and *iso*-butanol), the title compound was prepared as an oil. The reaction was monitored by tlc on silica gel ($R_f = 0.5$ in 25% EtOAc/hexanes) and purification was by preparative plate chromatography (silica gel using 25% EtOAc/hexanes as the eluant).

NMR data was as follows:

^1H -nmr (CDCl_3): $\delta = 7.2$ (d, 1H); 6.6 (d, 1H); 6.4 (dd, 1H); 4.3 (d, 1H); 3.8 (m, 3H); 1.9 (m, 6H); 1.0 (t, 3H), 0.9 (m, 6H).

^{13}C -nmr (CDCl_3): $\delta = 178$; 144.7; 130.2; 120.62; 115.11; 71.82; 52.90; 28.30; 19.53.

$\text{C}_{15}\text{H}_{21}\text{Cl}_2\text{NO}_2$ (MW = 318.3); mass spectroscopy (MH^+) 319.

Example A19**Synthesis of N-(4-cyanophenyl)alanine *iso*-butyl ester**

Following General Procedure AP above and using 4-fluorobenzonitrile (Aldrich) and D,L-alanine *iso*-butyl ester hydrochloride (from Example AA above), the title compound was prepared as an oil. The product was recovered by column chromatography on silica gel using 1:5 EtOAc/hexanes as the eluant.

NMR data was as follows:

^1H -nmr (CDCl_3): $\delta = 7.44$ (d, $J = 8.8$ Hz, 2H), 6.57 (d, $J = 8.8$ Hz, 2H), 4.74 (d, $J = 8.1$ Hz, 1H), 4.18 (t, $J = 7.4$ Hz, 1H), 3.95 (m, 2H), 1.94 (m, 1H), 1.51 (d, $J = 6.9$ Hz, 3H), 0.91 (d, $J = 6.7$ Hz, 6H).

^{13}C -nmr (CDCl_3): $\delta = 173.4$, 149.7, 133.8, 120.1, 112.7, 99.8, 71.6, 51.2, 27.7, 18.9, 18.6.

$\text{C}_{14}\text{H}_{18}\text{N}_2\text{O}_2$ MW = 246.31; mass spectroscopy (MH^+) 247.

Example A20**Synthesis of N-(3-chloro-4-cyanophenyl)alanine *iso*-butyl ester**

-- 168 --

Following General Procedure AP above and using 2-chloro-4-fluorobenzonitrile (Aldrich) and D,L-alanine *iso*-butyl ester hydrochloride (from Example AA above), the title compound was prepared. The product was recovered by column chromatography on silica gel using 1:5 EtOAc/hexanes as the eluant.

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 7.40 (d, J = 8.5 Hz, 1H), 6.62 (d, J = 2.3 Hz, 1H), 6.48 (dd, J = 2.4, 8.6 Hz, 1H), 4.90 (d, J = 7.6 Hz, 1H), 4.16 (quintet, J = 7.1 Hz, 1H), 3.96 (dd, J = 2.2, 6.7 Hz, 2H), 1.97 (m, 1H), 1.51 (d, J = 7.0 Hz, 3H), 0.93 (d, J = 6.7 Hz, 6H).

¹³C-nmr (CDCl₃): δ = 173.0, 150.4, 138.3, 134.9, 117.3, 112.8, 111.3, 100.6, 71.7, 51.1, 27.7, 18.9, 18.4.

C₁₄H₁₇N₂O₂Cl MW = 280.76; mass spectroscopy (MH⁺) 281.

Example A21

Synthesis of N-(3,4-dichloro)alanine *iso*-butyl ester (S isomer)

Following General Procedure AM above and using 3,4-dichloroaniline (Aldrich) and *iso*-butyl R-(+)-lactate (Aldrich), the title compound was prepared as an oil. The reaction was monitored by silica gel tlc (R_f = 0.55 in 25% EtOAc/hexanes). Purification was column chromatography.

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 7.19 (d, J = 8.73, 1H), 6.67 (d, J = 2.75, 1H), 6.45 (dd, J = 8.73, J = 2.75, 1H), 4.28 (bd, J = 8.36, 1H), 4.09 (quint, 1H), 3.94 (d, J = 6.66, 2H), 1.95 (hept, J = 6.71, 1H), 1.49 (d, J = 6.90, 3H), 0.92 (d, J = 6.04, 6H).

¹³C-nmr (CDCl₃): δ = 174.57, 146.67, 133.47, 131.28, 121.29, 114.93, 113.63, 71.01, 52.43, 28.30, 19.55, 19.33.

C₁₃H₁₇Cl₂NO₂ (MW = 290.19); mass spectroscopy (MH⁺) 290.

Example A22

Synthesis of N-(3,4-dichloro)alanine tetrahydrofuran-3-yl-methyl ester

Following transesterification General Procedure AB above and using N-(3,4-dichlorophenyl)alanine methyl ester (from Example A9 above) and
5 tetrahydro-3-furanmethanol (Aldrich), the title compound was prepared as an oil. The reaction was monitored by silica gel tlc ($R_f = 0.33$ in 25% EtOAc/hexanes). Purification was by preparative plate chromatography (silica gel using 25% EtOAc/hexanes as the eluant).

NMR data was as follows:

10 $^1\text{H-nmr}$ (CDCl_3): $\delta = 7.18$ (d, 1H, $J = 8.7$ Hz), 6.65 (d, 1H, $J = 2.7$ Hz), 6.42 (dd, 1H, $J = 8.7$ Hz, $J = 2.7$ Hz), 4.30 (m, 1H), 4.09 (m, 3H), 3.78 (m, 3H), 3.53 (m, 1H), 2.56 (m, 1H), 1.94 (m, 1H), 1.58 (m, 1H), 1.46 (d, 3H, $J = 6.9$ Hz).

15 $^{13}\text{C-nmr}$ (CDCl_3): $\delta = 174.5, 146.6, 133.5, 131.3, 121.4, 114.9, 113.6, 70.86, 70.83, 68.2, 67.31, 67.29, 52.4, 38.7, 29.36, 29.33, 19.2$.

$\text{C}_{14}\text{H}_{17}\text{Cl}_2\text{NO}_3$ (MW = 318.20); mass spectroscopy (MH^+) 318.

Example A23**Synthesis of N-(3,5-dichlorophenyl)alanine *n*-propyl ester**

20 Following General Procedure AA above and using 3,5-dichloroaniline (Aldrich) and *n*-propyl pyruvate (which can be prepared by following General Procedure AO above using *n*-propanol in place of *iso*-butanol), the title compound could be prepared.

Example A24**Synthesis of 2-[N-(3,4-dichlorophenyl)amino]butanoic acid *iso*-butyl ester**

25 Following General Procedure AA above and using 3,4-dichloroaniline (Aldrich) and *iso*-butyl 2-oxobutanoate (prepared by following General Procedure AO above using 2-oxobutyric acid (Aldrich) and *iso*-butanol), the title
30 compound was prepared as an oil. The reaction was monitored by tlc on silica gel ($R_f = 0.3$ in 25% EtOAc/hexanes) and purification was by preparative plate chromatography (silica gel using 25% EtOAc/hexanes as the eluant).

-- 170 --

NMR data was as follows:

^1H -nmr (CDCl_3): δ = 7.2 (d, 1H); 6.6 (d, 1H); 6.4 (dd, 1H); 4.3 (d, 1H); 3.8 (m, 3H); 1.9 (m, 3H); 1.0 (t, 3H); 0.9(m, 6H).

^{13}C -nmr (CDCl_3): δ = 178; 144.7; 130.2; 120.62; 115.11; 71.82; 52.90; 28.30; 20.5; 19.53.

$\text{C}_{14}\text{H}_{19}\text{Cl}_2\text{NO}_2$ (MW = 304.22); mass spectroscopy (MH^+) 305.

Example A25

Synthesis of N-(4-chlorophenyl)alanine *iso*-butyl ester

10 Following General Procedure AA above and using 4-chloroaniline (Aldrich) and *iso*-butyl pyruvate (prepared by following General Procedure AO above), the title compound was prepared as an oil. The reaction was monitored by tlc on silica gel (R_f = 0.6 in 25% EtOAc/hexanes) and purification was by preparative plate chromatography (silica gel using 25% EtOAc/hexanes as the
15 eluant).

NMR data was as follows:

^1H -nmr (CDCl_3): δ = 7.18 (d, 2H), 6.66 (d, 2H), 4.30 (bs, 1H), 4.08 (q, 1H), 1.94 (sept, 1H), 1.47 (d, 3H), 0.91 (d, 6H).

^{13}C -nmr (CDCl_3): δ = 174.5, 146.7, 133.5, 131.3, 121.3, 114.9, 113.6, 20 72.0, 52.4, 28.3, 19.5, 19.3.

$\text{C}_{13}\text{H}_{18}\text{ClNO}_2$ (MW = 255.75); mass spectroscopy (MH^+) 256.

Example A26

Synthesis of N-(3,5-dichlorophenyl)alanine *iso*-butyl ester

25 Following General Procedure AA above and using 3,5-dichloroaniline (Aldrich) and *iso*-butyl pyruvate (prepared by following General Procedure AO above), the title compound was prepared as an oil. The reaction was monitored by tlc on silica gel (R_f = 0.4 in 25% EtOAc/hexanes) and purification was by preparative plate chromatography (silica gel using 25% EtOAc/hexanes as the
30 eluant).

NMR data was as follows:

-- 171 --

^1H -nmr (CDCl_3): δ = 7.18 (d, 2H), 6.66 (m, 1H), 4.30 (bs, 1H), 4.08 (q, 1H), 1.94 (m, 1H), 1.47 (d, 3H), 0.91 (d, 6H).

^{13}C -nmr (CDCl_3): δ = 175; 146.7; 133; 131; 121; 114.9; 112.6; 72.0; 52.4; 28.3; 19.5.

5 $\text{C}_{13}\text{H}_{17}\text{Cl}_2\text{NO}_2$ (MW = 290.2); mass spectroscopy (MH^+) 291.

Example A27

Synthesis of N-(4-ethylphenyl)alanine methyl ester

A solution of 0.68 g (5 mmol) of 4'-aminoacetophenone (Aldrich), 0.60 mL of 90% methyl pyruvate (Aldrich) and 0.05 g (0.25 mmol) of *p*-toluenesulfonic acid in ethanol was hydrogenated in the presence of a catalytic amount of 10% Pd/C at from 30 to 15 psi of hydrogen for 16 hours. The catalyst was removed by filtering the reaction mixture through Celite and the solvent was evaporated to provide the crude product. The product was purified by column chromatography (silica gel using 1:9 EtOAc/hexanes as the eluant) to provide the title compound.

NMR data was as follows:

^1H -nmr (CDCl_3): δ = 1.19 (t, J = 7.6 Hz, 3H), 1.47 (d, J = 6.8 Hz, 3H), 2.54 (q, J = 7.6 Hz, 2H), 3.74 (s, 3H), 4.04 (bs, 1H), 4.13 (m, 1H), 6.57 (d, J = 8.5 Hz, 2H), 7.03 (d, J = 8.4 Hz, 2H).

^{13}C -nmr (CDCl_3): δ = 15.8, 18.0, 27.9, 52.17, 52.19, 113.5, 128.6, 134.1, 144.4, 175.3.

$\text{C}_{12}\text{H}_{17}\text{NO}_2$ MW = 207.27; mass spectroscopy (MH^+) 208.

25

Example A28

Synthesis of N-(4-(1-ethoxy)ethylphenyl)alanine methyl ester

Following the procedure for Example A27 above, the title compound was isolated as another reaction product by column chromatography (silica gel using 1:9 EtOAc/hexanes as the eluant).

30

NMR data was as follows:

-- 172 --

¹H-nmr (CDCl₃): δ = 1.15 (t, J = 7.0 Hz, 3H), 1.40 (d, J = 6.5 Hz, 3H), 1.47 (d, J = 6.1 Hz, 3H), 3.31 (q, J = 5.1 Hz, 2H), 3.74 (s, 3H), 4.14 (m, 2H), 4.29 (q, J = 6.4 Hz, 1H), 6.57 (d, J = 8.5 Hz, 2H), 7.12 (d, J = 8.4 Hz, 2H).

¹³C-nmr (CDCl₃): δ = 15.4, 19.0, 23.9, 51.9, 52.2, 63.4, 77.3, 113.1, 127.3, 133.6, 145.8, 175.1.

C₁₄H₂₁NO₃ MW = 251.33; mass spectroscopy (MH⁺) 251.

Example A29

10 Synthesis of N-(3,4-dichloro)alanine 2,2-dimethylpropyl ester (R,S isomers)

Following transesterification General Procedure AQ above and using N-(3,4-dichlorophenyl)alanine methyl ester (from Example A9 above) and neopentyl alcohol (Aldrich), the title compound was prepared. The reaction was
15 monitored by silica gel tlc (R_f = 0.72 in 25% EtOAc/hexanes). Purification was by flash chromatography (silica gel using 25% EtOAc/hexanes as the eluant).

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 7.19 (d, 1H, J = 8.7 Hz), 6.68 (d, 1H, J = 2.7 Hz), 6.45 (dd, 1H, J = 8.7 Hz, J = 2.7 Hz), 4.29 (m, 1H), 4.11 (m, 1H), 3.85 (m,
20 2H), 1.49 (d, 3H, J = 6.9 Hz), 0.93 (s, 9H).

¹³C-nmr (CDCl₃): δ = 174.6, 146.7, 133.5, 131.3, 121.3, 114.9, 113.7, 75.2, 52.4, 32.0, 26.9, 19.4.

C₁₄H₁₉Cl₂NO₂ (MW = 304.22); mass spectroscopy (MH⁺) 303.

25 Example A30

Synthesis of N-(3,4-dichlorophenyl)glycine *iso*-butyl ester

3,4-Dichloroaniline (Aldrich) was treated with di-*tert*-butyl dicarbonate (Aldrich) using conventional procedures to produce the N-BOC aniline. The N-BOC aniline was treated with sodium hydride in THF and then with *iso*-butyl 2-bromoacetate (from Example AD above) to produce the N-BOC N-(3,4-dichlorophenyl)glycine *iso*-butyl ester. The BOC group was then removed using
30 General Procedure AN above to afford the title compound. The reaction was

monitored by tlc on silica gel ($R_f = 0.78$ in 50% EtOAc/hexanes) and purification was by preparative plate chromatography (silica gel using 50% EtOAc/hexanes as the eluant).

NMR data was as follows:

5 ^1H -nmr (CDCl_3): $\delta = 7.19$ (dd, $J=4.1, 4.7, 3.4$, 1H); 6.65 (d, $J=2.7$, 1H); 6.44 (dd, $J=2.7, 4.5, 4.2$, 1H); 4.4 (m, 1H); 3.97 (dd, $J=3.6, 3.0, 2.3$, 2H); 3.87 (s, 2H); 1.9 (m, 1H); 0.93 (d, $J=6.7$, 6H).

^{13}C -nmr (CDCl_3): $\delta = 171.2, 147.0, 133.5, 131.3, 121.2, 114.5, 113.3, 72.2, 46.0, 28.2, 19.6$.

10 $\text{C}_{12}\text{H}_{15}\text{Cl}_2\text{NO}_2$ (MW = 276); mass spectroscopy (MH^+) 277.

Example A31

Synthesis of N-(3,4-dichlorophenyl)alanine 2-ethylbutyl ester

Following General Procedure AA above and using 3,4-dichloroaniline (Aldrich) and 2-ethylbutyl pyruvate (prepared by following General Procedure AO above using 2-ethylbutanol (Aldrich) in place of *iso*-butanol), the title compound was prepared as an oil. The reaction was monitored by tlc on silica gel ($R_f = 0.6$ in 25% EtOAc/hexanes) and purification was by preparative plate chromatography (silica gel using 25% EtOAc/hexanes as the eluant).

20 NMR data was as follows:

^1H -nmr (CDCl_3): $\delta = 7.2$ (d, 1H); 6.6 (d, 1H); 6.4 (dd, 1H); 4.2 (t, 2H); 4.1 (q, 1H); 1.5 (d, 3H); 1.4 (m, 4H); 1.0 (m, 6H).

^{13}C -nmr (CDCl_3): $\delta = 178; 144.7; 130.2; 120.62; 115.11; 70.7; 51.90; 26.3; 19.53, 18.5$.

25 $\text{C}_{15}\text{H}_{21}\text{Cl}_2\text{NO}_2$ (MW = 318.25); mass spectroscopy (MH^+) 319.

Example A32

Synthesis of N-(3-chloro-4-iodophenyl)alanine *iso*-butyl ester

Following General Procedure AR above and using 3-chloro-4-iodoaniline (Aldrich), *N*-BOC-3-chloro-4-iodoaniline was prepared. To a stirred slurry of 30 5.0 equivalents of sodium hydride in DMF was added 1.0 equivalent of *N*-BOC-

-- 174 --

3-chloro-4-iodoaniline and then 1.1 equivalents of *iso*-butyl 2-bromopropionate (from Example AD above) were slowly added. The reaction was heated to 100°C for 10 hours, cooled, diluted with dichloromethane and washed with cold 1N HCl, water and brine. The solvents were removed at reduced pressure and the residue was chromatographed to provide *N*-BOC-*N*-(3-chloro-4-iodophenyl)alanine *iso*-butyl ester as a clear oil. Following General Procedure AN above, the BOC group was removed from *N*-BOC-*N*-(3-chloro-4-iodophenyl)alanine *iso*-butyl ester to provide the title compound. The BOC-removal reaction was monitored by tlc on silica gel ($R_f = 0.58$ in 30% EtOAc/hexanes) and purification was by preparative plate chromatography (silica gel using 30% EtOAc/hexanes as the eluant). The compound was further purified by chromatography on an HPLC chiral column (Chiralcel OD).

NMR data was as follows:

^1H -nmr (CDCl_3): $\delta = 7.52$ (d, $J=8.7$, 1H); 6.72 (d, $J=2.7$, 1H); 6.25 (dd, $J=2.7, 5.9, 2.7$, 1H); 4.35 (d, $J=6.6$, 1H); 4.08 (quintex, $J=7.2, 6.7$, 1H); 3.93 (d, $J=6.7$, 2H); 1.94 (m, 1H); 1.47 (d, $J=6.9$, 3H); 0.92 (d, $J=6.9$, 6H).

^{13}C -nmr (CDCl_3): $\delta = 174.5, 148.3, 140.7, 139.5, 114.4, 114.3, 82.6, 72.0, 52.2, 28.3, 19.6, 19.3$.

$\text{C}_{13}\text{H}_{17}\text{ClINO}_2$ (MW = 381.5); mass spectroscopy (MH^+) 382.

Example A33

Synthesis of *N*-(4-azidophenyl)alanine *iso*-butyl ester

Following General Procedure AA above and using 4-azidoaniline (Aldrich) and *iso*-butyl pyruvate (prepared by following General Procedure AO above), the title compound was prepared as an oil. The reaction was monitored by tlc on silica gel ($R_f = 0.3$ in 25% EtOAc/hexanes) and purification was by preparative plate chromatography (silica gel using 25% EtOAc/hexanes as the eluant).

NMR data was as follows:

^1H -nmr (CDCl_3): $\delta = 7.3$ (d, 2H), 6.8 (d, 2H), 4.30 (bs, 1H), 4.08 (q, 1H), 1.94 (sept, 1H), 1.47 (d, 3H), 0.91 (d, 6H).

^{13}C -nmr (CDCl_3): $\delta = 174.5, 148.7, 131.5, 130.3, 121.3, 114.9, 113.6, 72.0, 52.4, 28.3, 19.5, 19.3$.

$\text{C}_{13}\text{H}_{18}\text{N}_4\text{O}_2$ (MW = 262.31); mass spectroscopy (MH^+) 263.

5

Example A34

Synthesis of

N-[(4-phenylcarbonyl)phenyl]alanine *iso*-butyl ester

Following General Procedure AA above and using 4'-

aminobenzophenone (Aldrich) and *iso*-butyl pyruvate (prepared by following
General Procedure AO above), the title compound was prepared as an oil. The
reaction was monitored by tlc on silica gel ($R_f = 0.4$ in 25% EtOAc/hexanes)
and purification was by preparative plate chromatography (silica gel using 25%
EtOAc/hexanes as the eluant).

NMR data was as follows:

15

^1H -nmr (CDCl_3): $\delta = 7.7$ (d, 2H), 7.1 (m, 5H), 6.9 (d, 2H), 4.30 (bs, 1H), 4.08 (q, 1H), 1.94 (sept, 1H), 1.47 (d, 3H), 0.91 (d, 6H).

^{13}C -nmr (CDCl_3): $\delta = 199, 178.5, 149.7, 131.5, 130.3, 126, 121.3, 114.9, 113.6, 72.0, 52.4, 28.3, 19.5, 19.3$.

$\text{C}_{20}\text{H}_{23}\text{NO}_3$ (MW = 325.41); mass spectroscopy (MH^+) 326.

20

Example A35

Synthesis of N-(3,5-difluorophenyl)alanine *iso*-butyl ester

Following General Procedure AH above and using N-(3,5-

difluorophenyl)alanine (from Example AC above) and *iso*-butanol, the title
compound was prepared as an oil. The reaction was monitored by tlc on silica
gel ($R_f = 0.9$ in 3% methanol/methylene chloride) and purification was by
preparative plate chromatography (silica gel using 3% methanol/methylene
chloride as the eluant).

NMR data was as follows:

30

^1H -nmr (CDCl_3): $\delta = 6.1$ (m, 3H), 4.5 (bs, 1H), 4.1 (d, 1H), 3.95 (m, 2H), 2.0 (m, 1H), 1.5 (d, $J = 7$ Hz, 3H), 0.95 (d, $J = 6$ Hz, 6H).

^{13}C -nmr (CDCl_3): $\delta = 174.44, 166.40, 166.19, 163.16, 162.95, 149.43, 96.73, 96.60, 96.48, 96.35, 94.06, 93.72, 93.37, 72.03, 52.30, 28.29, 19.47, 19.23.$

$\text{C}_{13}\text{H}_{17}\text{F}_2\text{NO}_2$ (MW = 290.2); mass spectroscopy (MH^+) 291.

5

Example A36

Synthesis of N-(3,4-dichlorophenyl)alanine O-acylacetamidoxime ester

Following General Procedure AK above and using N-(3,4-dichlorophenyl)alanine (from Example AB above) and acetamide oxime (prepared according to the procedures described in *J. Org. Chem.*, 46, 3953 (1981)), the title compound was prepared as a semisolid. The reaction was monitored by tlc on silica gel ($R_f = 0.4$ in ethyl acetate) and purification was by preparative plate chromatography (silica gel using ethyl acetate as the eluant).

NMR data was as follows:

^1H -nmr ($\text{DMSO}-d_6$): $\delta = 7.27$ (d, 1H), 6.81 (s, 1H) 6.4 (broad s, 2H), 6.62 (d, 1H), 6.45 (d, 1H), 4.22 (m, 1H), 1.74 (s, 3H), 1.40 (d, 3H).

$\text{C}_{11}\text{H}_{13}\text{Cl}_2\text{N}_3\text{O}_2$ (MW = 290.15); mass spectroscopy (MH^+) 291.

Example A37

Synthesis of N-(3,4-dichlorophenyl)alanine pyrrolyl amide

Following General Procedure AL above and using N-(3,4-dichlorophenyl)alanine (from Example AB above) and pyrrole (Aldrich), the title compound was prepared as an oil. The reaction was monitored by tlc on silica gel ($R_f = 0.28$ in 10% ethyl acetate/hexanes) and purification was by preparative plate chromatography (silica gel using 10% ethyl acetate/hexanes as the eluant).

NMR data was as follows:

^1H -nmr (CDCl_3): $\delta = 7.36$ (d, $J=2.2$, 2H); 7.20 (d, $J=8.7$, 1H); 6.71 (d, $J=2.7$, 1H); 6.5 (m, 1H); 6.38 (t, $J=2.4$, 2H); 4.8 (m, 1H); 4.57 (d, $J=8.7$, 1H); 1.59 (d, $J=6.8$, 3H).

30

^{13}C -nmr (CDCl_3): $\delta = 171.9, 146.1, 133.6, 131.5, 121.9, 119.6, 115.4, 114.7, 113.8, 51.8, 20.2$.

$\text{C}_{13}\text{H}_{12}\text{Cl}_2\text{N}_2\text{O}$ (MW = 283); mass spectroscopy (MH^+) 284.

5

Example A38

Synthesis of N-(3,4-dichlorophenyl)alanine O-acylbutyramidoxime ester

Following General Procedure AI above and using N-(3,4-dichlorophenyl)alanine 2,4,6-trichlorophenyl ester (prepared from N-(3,4-dichlorophenyl)alanine methyl ester (from Example A9) using essentially the same procedure as described in Example AE above) and butyramide oxime (prepared according to the procedures described in *J. Org. Chem.*, 46, 3953 (1981)), the title compound was prepared as a semisolid. The reaction was monitored by tlc on silica gel ($R_f = 0.25$ in 50% ethyl acetate/hexanes) and purification was by preparative plate chromatography (silica gel using 50% ethyl acetate/hexanes as the eluant).

15

NMR data was as follows:

^1H -nmr (d_6 -DMSO): $\delta = 7.27$ (d, 1H), 6.83 (s, 1H) 6.38 (broad s, 2H), 6.61 (d, 1H), 6.46 (d, 1H), 4.25 (m, 1H), 2.02 (t, 2H), 1.55 (m, 2H), 1.40 (d, 3H), 0.88 (t, 3H).

20

$\text{C}_{13}\text{H}_{17}\text{Cl}_2\text{N}_3\text{O}_2$ (MW = 318.20); mass spectroscopy (MH^+) 319.

Example A39

Synthesis of 2-[N-(naphth-2-yl)amino]butanoic acid ethyl ester

Following General Procedure AJ above and using 2-aminonaphthalene (Aldrich) and ethyl 2-bromobutyrate (Aldrich), the title compound was prepared as a solid, m.p. 81-83°C. The reaction was monitored by silica gel tlc ($R_f = 0.5$ in CHCl_3). Purification was by chromatography (silica gel using chloroform as the eluant).

25

NMR data was as follows: ^1H -nmr (d_6 -DMSO): $\delta = 7.63$ (m, 2H), 7.54 (d, 1H), 7.31 (t, 1H), 7.12 (t, 1H), 7.03 (d, 1H), 6.62 (s, 1H), 6.32 (d, 1H), 4.15 (m, 3H), 1.42 (d, 3H), 1.19 (t, 3H).

30

$C_{16}H_{19}NO_2$ (MW = 257.34); mass spectroscopy (MH^+) 258.

Example A40

Synthesis of N-(2-naphthyl)alanine *iso*-butyl ester

5 Following General Procedure AA above and using 2-aminonaphthalene (Aldrich) and *iso*-butyl pyruvate (prepared by following General Procedure AO above), the title compound was prepared as an oil. Purification was by preparative plate chromatography (silica gel using 25% EtOAc/hexanes as the eluant).

10 NMR data was as follows:

^1H -nmr ($CDCl_3$): δ = 7.65 (m, 3H), 7.38 (t, 1H, J = 6.9 Hz), 7.23 (t, 1H, J = 6.9 Hz), 6.93 (m, 1H), 6.81 (d, 1H, J = 2.3 Hz), 4.31 (q, 1H, J = 6.9 Hz), 3.95 (dd, 1H, J = 6.7 Hz, J = 1.6 Hz), 1.96 (sept, 1H, J = 6.7 Hz), 1.57 (d, 3H, J = 6.9 Hz), 0.93 (dd, 6H, J = 6.7 Hz, J = 1.6 Hz).

15 ^{13}C -nmr ($CDCl_3$) δ = 174.6, 144.2, 134.9, 129.1, 127.8, 127.6, 126.3, 126.0, 122.3, 118.1, 105.3, 71.2, 52.0, 27.7, 18.9, 18.8.

Example A41

20 Synthesis of N-(2-methylquinolin-6-yl)alanine *iso*-butyl ester

 Following General Procedure AA above and using 6-amino-2-methylquinoline (Lancaster) and *iso*-butyl pyruvate (prepared by following General Procedure AO above), the title compound was prepared. The reaction
25 was monitored by silica gel tlc (R_f = 0.44 in 50% EtOAc/hexanes). Purification was by flash chromatography (silica gel using 50% EtOAc/hexanes as the eluant).

 NMR data was as follows:

30 ^1H -nmr ($CDCl_3$): δ = 7.90 (m, 2H), 7.10 (m, 2H), 6.66 (d, 1H, J = 2.6), 4.50 (bd, 1H), 4.24 (m, 1H), 3.91 (d, 2H, J = 6.6 Hz), 2.64 (s, 3H), 1.91 (sept, 1H, J = 6.7 Hz), 1.52 (d, 3H, J = 6.9 Hz), 0.87 (d, 6H, J = 6.7 Hz).

^{13}C -nmr ($CDCl_3$) δ = 175.0, 155.4, 144.6, 143.4, 134.9, 130.2, 128.4, 122.8, 121.8, 104.9, 71.8, 52.7, 28.3, 25.4, 19.5, 19.4.

$C_{17}H_{22}Cl_2N_2O_2$ (MW = 286.38); mass spectroscopy (MH^+) 287.

Example A42

Synthesis of N-(3,4-methylenedioxyphenyl)alanine *iso*-butyl ester

5

Following reductive amination General Procedure AA above and using 3,4-methylenedioxyaniline (Aldrich) and methyl pyruvate (Aldrich), N-(3,4-methylenedioxyphenyl)alanine methyl ester was prepared. The methyl ester was then transesterified following General Procedure AQ above and using *iso*-butanol to provide the title compound as an oil. The reaction was monitored by silica gel tlc (R_f = 0.61 in 25% EtOAc/hexanes). Purification was by preparative plate chromatography with silica gel using 25% EtOAc/hexanes as the eluant.

10

NMR data was as follows:

15

^1H -nmr ($CDCl_3$): δ = 6.63 (d, 1H, 8.3 Hz), 6.25 (d, 1H, J = 2.3 Hz), 6.04 (dd, 1H, J = 8.3 Hz, J = 2.3 Hz), 5.83 (s, 2H), 3.96 (m, 4H), 1.92 (sept, 1H, J = 6.7 Hz), 1.44 (d, 3H, J = 6.9 Hz), 0.90 (d, 6H, J = 6.6 Hz).

^{13}C -nmr ($CDCl_3$): δ = 175.4, 148.9, 142.9, 140.8, 109.2, 105.8, 101.2, 97.4, 71.6, 53.6, 28.3, 19.6, 19.5.

20

$C_{14}H_{19}NO_4$ (MW = 265.31); mass spectroscopy (MH^+) 265.

Example A43

Synthesis of N-(3,4-ethylenedioxyphenyl)alanine *iso*-butyl ester

Following reductive amination General Procedure AA above and using 1,4-benzodioxo-6-amine (Aldrich) and methyl pyruvate (Aldrich), N-(3,4-ethylenedioxyphenyl)alanine methyl ester was prepared. The methyl ester was then transesterified following General Procedure AQ above using *iso*-butanol to provide the title compound. Purification was by preparative plate chromatography.

25

30

NMR data was as follows:

-- 180 --

^1H -nmr (CDCl_3): δ = 0.91 (d, J = 7Hz, 6H), 1.42 (d, J = 7Hz, 3H), 1.8-2.0 (m, 1H), 3.8-3.95 (m, 3H), 4.0-4.1 (m, 1H), 4.15-4.25 (m, 4H), 6.12-6.2 (m, 2H), 6.65-6.75 (m, 1H).

^{13}C -nmr (CDCl_3): δ = 19.55, 19.56, 19.67, 28.3, 53.4, 64.7, 65.3, 71.7,
5 103.1, 108.0, 118.3, 142.1, 144.6, 175.4.

$\text{C}_{15}\text{H}_{21}\text{NO}_4$ (MW = 279.34); mass spectroscopy (MH^+) 280.

Example A44

Synthesis of N-(2-naphthyl)alanine methyl ester

10

Following reductive amination General Procedure AA above and using 2-aminonaphthalene (Aldrich) and methyl pyruvate (Aldrich), the title compound was prepared. The reaction was monitored by silica gel tlc (R_f = 0.50 in 25% EtOAc/hexanes). Purification was by flash chromatography with silica gel using
15 25% EtOAc/hexanes as the eluant.

NMR data was as follows:

^1H -nmr (CDCl_3): δ = 7.65 (m, 3H), 7.48 (m, 1H), 7.25 (m, 1H), 6.91 (m, 1H), 6.79 (m, 1H), 4.31 (m, 2H), 3.76 (s, 3H), 1.55 (d, 3H).

^{13}C -nmr (CDCl_3): δ = 175.66, 144.78, 135.55, 129.78, 128.47, 128.22,
20 126.96, 126.67, 123.01, 118.66, 105.88, 52.95, 52.51, 19.45.

$\text{C}_{14}\text{H}_{15}\text{NO}_2$ (MW = 229.28); mass spectroscopy (MH^+) 229.

Example A45

Synthesis of N-(benzothiazol-6-yl)alanine ethyl ester

25

To a solution of 6-aminobenzothiazole (Lancaster) in dichloromethane was added 1.2 equivalents of pyridine, followed by 1.5 equivalents of trifluoroacetic anhydride. The reaction was stirred at room temperature for 3 hours and then washed with 5% citric acid, dried over MgSO_4 , and stripped free
30 of solvent on a rotary evaporator to yield 6-trifluoroacetamidobenzothiazole. This material was dissolved in THF and then added to a suspension of KH in THF at 0°C . A catalytic amount of 18-crown-6 was added, followed by ethyl 2-bromopropionate (Aldrich). The reaction was held at room temperature for 1

-- 181 --

hour, and then heated to reflux for 24 hours, and then cooled to room temperature. The reaction mixture was stripped free of solvent on a rotary evaporator and the resulting residue was dissolved in ether. This solution was washed with water, saturated aqueous NaCl, and dried over MgSO₄. The solution was stripped free of solvent on a rotary evaporator and the title compound was obtained by chromatography of the residue using 5% methanol/dichloromethane (R_f = 0.59) as the eluant.

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 8.69 (s, 1H), 7.90 (d, 1H, J = 8.8 Hz), 7.04 (d, 1H, J = 2.3 Hz), 6.84 (dd, 1H, J = 8.8 Hz, J = 2.4 Hz), 4.41 (bd, 1H, J = 7.5 Hz), 4.20 (m, 3H), 1.53 (d, 3H, J = 6.9 Hz), 1.27 (t, 3H, J = 7.1 Hz).

¹³C-nmr (CDCl₃): δ = 174.9, 150.2, 147.1, 145.6, 136.3, 124.6, 115.7, 103.5, 61.9, 52.9, 19.4, 14.8.

C₁₂H₁₄N₂O₂S (MW = 250.32); mass spectroscopy (MH⁺) 251.

Example A46

Synthesis of N-(indol-5-yl)alanine *iso*-butyl ester (S isomer)

Following General Procedure AM and using 5-aminoindole (Aldrich) and *iso*-butyl R-(+)-lactate (Aldrich), the title compound was prepared as an oil. The reaction was monitored by silica gel tlc (R_f = 0.46 in 33% EtOAc/hexanes). Purification was by preparative plate chromatography with silica gel using 33% EtOAc/hexanes as the eluant.

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 8.11 (bs, 1H), 7.07 (d, J=8.8 Hz, 1H), 6.98 (d, J=2.8 Hz, 1H), 6.83 (d, J=2.2 Hz, 1H), 6.61 (m, 1H), 6.32 (m, 1H), 4.18 (q, J=6.9 Hz, 1H), 3.95 (bs, 1H), 3.87 (d, J=6.7 Hz, 2H), 1.89 (hept, J=6.7 Hz, 1H), 1.48 (d, J=6.96 Hz, 3H), 0.86 (dd, J=6.7 Hz, J=1.6 Hz, 6H).

¹³C-nmr (CDCl₃): δ = 176.15, 141.06, 131.28, 129.24, 125.34, 113.34, 112.53, 104.21, 102.17, 71.65, 54.28, 28.36, 19.87, 19.62.

C₁₅H₂₀N₂O₂ (MW = 260.34); mass spectroscopy (MH⁺) 261.

-- 182 --

Example A47

Synthesis of N-(naphth-2-yl)alanine O-acetylacetamidoxime ester

Following General Procedure AI above using N-(naphth-2-yl)alanine 2,4,6-trichlorophenyl ester (from Example AE above) and acetamide oxime (prepared according to the procedures described in *J. Org. Chem.*, 46, 3953 (1981)), the title compound was prepared as a semisolid. The reaction was monitored by tlc on silica gel ($R_f = 0.4$ in ethyl acetate) and purification was by preparative plate chromatography (silica gel using ethyl acetate as the eluant).

NMR data was as follows:

¹H-nmr (d^6 -DMSO): $\delta = 7.64$ (t, 2H), 7.54 (d, 1H), 7.32 (t, 1H), 7.13 (t, 1H), 7.04 (d, 1H), 6.78 (s, 1H), 6.42 (broad s, 2H), 6.32 (d, 1H), 4.33 (m, 1H), 1.72 (s, 3H), 1.46 (d, 3H).

$C_{15}H_{17}N_3O_2$ (MW = 271.32); mass spectroscopy: 271.

Example A48

Synthesis of N-(2-naphthyl)alanine ethyl ester

Following reductive amination General Procedure AA above and using 2-aminonaphthalene (Aldrich) and ethyl pyruvate (Aldrich), the title compound was prepared as a solid having a melting point of 52-56°C. The reaction was monitored by silica gel tlc ($R_f = 0.50$ in 25% EtOAc/hexanes). Purification was by flash chromatography with silica gel using 25% EtOAc/hexanes as the eluant.

NMR data was as follows:

¹H-nmr ($CDCl_3$): $\delta = 7.65$ (m, 3H), 7.48 (m, 1H), 7.25 (m, 1H), 6.91 (m, 1H), 6.79 (m, 1H), 4.31 (m, 2H), 3.76 (s, 3H), 1.55 (d, 3H).

¹³C-nmr ($CDCl_3$): $\delta = 175.66, 144.78, 135.55, 129.78, 128.47, 128.22, 126.96, 126.67, 123.01, 118.66, 105.88, 52.95, 52.51, 19.45$.

$C_{14}H_{15}NO_2$ (MW = 229.28); mass spectroscopy (MH^+) 229.

Example A49

Synthesis of N-(3,4-dichlorophenyl)alanine O-acylpropionamidoxime ester

Following General Procedure AI above using N-(3,4-dichlorophenyl)alanine 2,4,6-trichlorophenyl ester (prepared from N-(3,4-dichlorophenyl)alanine methyl ester (from Example A9) using essentially the same procedure as described in Example AE above) and propionamide oxime (prepared according to the procedures described in *J. Org. Chem.*, 46, 3953 (1981)), the title compound was prepared as a semisolid. The reaction was monitored by tlc on silica gel ($R_f = 0.2$ in 50% ethyl acetate/hexane) and purification was by preparative plate chromatography (silica gel using 50% ethyl acetate/hexane as the eluant).

NMR data was as follows:

^1H -nmr (d_6 -DMSO): $\delta = 7.27$ (d, 1H), 6.83 (s, 1H), 6.64 (d, 1H), 6.47 (d, 1H), 6.38 (broad s, 2H), 4.24 (m, 1H), 2.07 (q, 2H), 1.41 (d, 3H).

$\text{C}_{12}\text{H}_{15}\text{Cl}_2\text{N}_3\text{O}_2$ (MW = 304.17); mass spectroscopy (MH^+) 305.

15

Example A50

Synthesis of N-(4-ethoxycarbonylphenyl)alanine *iso*-butyl ester (S isomer)

Following General Procedure AM and using ethyl 4-aminobenzoate (Aldrich) and *iso*-butyl R-(+)-lactate (Aldrich), the title compound was prepared as an oil. The reaction was monitored by silica gel tlc ($R_f = 0.21$ in 10% EtOAc/hexanes). Purification was by preparative plate thin layer chromatography using 25% EtOAc/hexanes as the eluant.

NMR data was as follows:

^1H -nmr (CDCl_3): $\delta = 7.82$ (d, $J = 8.73$ Hz, 2H), 6.51 (d, $J = 8.79$ Hz, 2H), 4.81 (d, $J = 7.82$ Hz, 1H), 4.25 (q, $J = 7.14$ Hz, 2H), 4.15 (quint, $J = 7.40$ Hz, 1H), 3.87 (m, 2H), 1.87 (sept, $J = 6.70$ Hz, 1H), 1.43 (d, $J = 6.95$ Hz, 3H), 1.30 (t, $J = 7.14$ Hz, 3H), 0.84 (d, $J = 6.71$ Hz, 6H).

^{13}C -nmr (CDCl_3): $\delta = 174.5, 167.3, 151.0, 132.0, 119.9, 112.5, 71.9, 60.8, 51.9, 28.2, 19.5, 19.2, 15.0$.

$\text{C}_{16}\text{H}_{23}\text{NO}_4$ (MW = 293.37); mass spectroscopy (MH^+) 294.

Example A51

-- 184 --

Synthesis of N-[3,5-di(trifluoromethyl)phenyl]alanine *iso*-butyl ester (S isomer)

Following General Procedure AM and using 3,5-

- 5 di(trifluoromethyl)aniline (Aldrich) and *iso*-butyl R-(+)-lactate (Aldrich), the title compound was prepared as an oil. The reaction was monitored by silica gel tlc ($R_f = 0.38$ in 10% EtOAc/hexanes). Purification was by preparative plate thin layer chromatography using 10% EtOAc/hexanes as the eluant.

NMR data was as follows:

- 10 ^1H -nmr (CDCl_3): $\delta = 7.13$ (s, 1H), 6.91 (s, 2H), 4.97 (d, $J = 8.24$ Hz, 1H), 4.18 (m, 1H), 3.93 (d, $J = 6.59$ Hz, 2H), 1.93 (sept, $J = 6.71$ Hz, 1H), 1.49 (d, $J = 7.02$ Hz, 3H), 0.89 (d, $J = 6.59$ Hz, 6H).

- ^{13}C -nmr (CDCl_3): $\delta = 174.4, 147.9, 133.6, 133.2, 132.7, 132.3, 129.4, 125.8, 122.2, 118.6, 112.81, 112.76, 111.42, 111.37, 111.32, 111.27, 111.22,$
15 $72.2, 52.0, 32.1, 28.24, 28.17, 23.2, 19.5, 19.3, 19.2, 18.9, 14.6$.

$\text{C}_{15}\text{H}_{17}\text{F}_6\text{NO}_2$ (MW = 357.30); mass spectroscopy (MH^+) 358.

Example A52

20 **Synthesis of N-(3,5-dimethoxyphenyl)alanine *iso*-butyl ester**

- N-(3,5-dimethoxyphenyl)alanine (crude, 454 mg) (prepared according to the procedure described in U.S. Patent No. 3,598,859 using 3,5-dimethoxyaniline (Aldrich) and 2-chloropropionic acid (Aldrich)) was treated in dry *iso*-butanol
25 (10 mL) with 0.1 mL of chlorotrimethylsilane and the reaction mixture refluxed overnight. The excess alcohol was removed at reduced pressure and the residue dissolved in ethyl acetate. The ethyl acetate solution was washed with saturated aqueous NaHCO_3 , dried with Na_2SO_4 and the solvent removed to provide the
30 title compound. The reaction was monitored by silica gel tlc ($R_f = 0.3$ in 20% EtOAc/hexanes). Purification was by preparative thin layer chromatography using 20% EtOAc/hexanes as the eluant.

NMR data was as follows:

-- 185 --

¹H-nmr (CDCl₃): δ = 0.9 (d, J = 7, 6H), 1.47 (d, J = 7, 3H); 1.9-2.0 (m, 1H), 3.7 (s, 6H), 3.85-4.0 (m, 2H), 4.1-4.2 (m, 1H), 4.3 (brs, 1H), 5.8 (s, 2H), 5.9 (s, 1H).

¹³C-nmr (CDCl₃): δ = 19.49, 19.52, 19.54, 28.3, 52.5, 55.6, 71.7, 91.1, 92.7, 149.2, 162.3, 175.2.

C₁₅H₂₃NO₄ (MW = 281.35).

Example A53

Synthesis of N-(2-naphthyl)alanine O-acylpropionamidoxime ester

10

Following General Procedure AS and using N-(2-naphthyl)alanine 2,4,5-trichlorophenyl ester (from Example AE above) and propionamide oxime (prepared according to the procedures described in *J. Org. Chem.*, 46, 3953 (1981)), the title compound was prepared. The reaction was monitored by silica gel tlc (R_f = 0.5 in EtOAc). Purification was by silica gel chromatography using 1:1 EtOAc/hexanes as the eluant.

15

NMR data was as follows:

¹H-nmr (DMSO-*d*₆): δ = 1.03 (t, 3H), 1.45 (d, 3H).

C₁₆H₁₉N₃O₂ (MW = 285.35); mass spectroscopy (M⁺) 285.

20

Example A54

Synthesis of N-(2-naphthyl)alanine O-acylbutyramidoxime ester

Following General Procedure AS and using N-(2-naphthyl)alanine 2,4,5-trichlorophenyl ester (from Example AE above) and butyramide oxime (prepared according to the procedures described in *J. Org. Chem.*, 46, 3953 (1981)), the title compound was prepared as an oil. The reaction was monitored by silica gel tlc (R_f = 0.6 in EtOAc). Purification was by silica gel chromatography using 1:1 EtOAc/hexanes as the eluant.

25

30

NMR data was as follows:

¹H-nmr (DMSO-*d*₆): δ = 0.86 (t, 3H), 1.46 (d, 3H).

C₁₇H₂₁N₃O₂ (MW = 299.37); mass spectroscopy (M⁺) 299.

-- 186 --

Example A55:

Synthesis of N-(2-naphthyl)alanine O-acylisovaleramidoxime ester

Following General Procedure AS and using N-(2-naphthyl)alanine 2,4,5-trichlorophenyl ester (from Example AE above) and isovaleramide oxime (prepared according to the procedures described in *J. Org. Chem.*, 46, 3953 (1981)), the title compound was prepared as an oil. The reaction was monitored by silica gel tlc ($R_f = 0.3$ in 1:1 EtOAc/hexanes). Purification was by silica gel chromatography using 1:1 EtOAc/hexanes as the eluant.

NMR data was as follows:

^1H -nmr (DMSO- d_6): $\delta = 0.86$ (t, 3H), 1.45 (d, 3H).

$\text{C}_{18}\text{H}_{23}\text{N}_3\text{O}_2$ (MW = 313.40); mass spectroscopy (MH^+) 313.

Example A56

Synthesis of N-(2-naphthyl)alanine O-acylbenzamidoxime ester

Following General Procedure AS and using N-(2-naphthyl)alanine 2,4,5-trichlorophenyl ester (from Example AE above) and benzamide oxime (prepared according to the procedures described in *J. Org. Chem.*, 46, 3953 (1981)), the title compound was prepared as an oil. The reaction was monitored by silica gel tlc ($R_f = 0.3$ in 1:1 EtOAc/hexanes). Purification was by silica gel chromatography using 1:1 EtOAc/hexanes as the eluant.

NMR data was as follows:

^1H -nmr (DMSO- d_6): $\delta = 4.42$ (m, 1H), 1.53 (d, 3H).

$\text{C}_{20}\text{H}_{19}\text{N}_3\text{O}_2$ (MW = 333.39); mass spectroscopy (MH^+) 333.

Example A57

Synthesis of N-(2-naphthyl)alanine O-acylcyclopropanecarboxamidoxime ester

Following General Procedure AS and using N-(2-naphthyl)alanine 2,4,5-trichlorophenyl ester (from Example AE above) and cyclopropanecarboxamide oxime (prepared according to the procedures described in *J. Org. Chem.*, 46, 3953 (1981)), the title compound was prepared as an oil. The reaction was

monitored by silica gel tlc ($R_f = 0.3$ in 1:1 EtOAc/hexanes). Purification was by silica gel chromatography using 1:1 EtOAc/hexanes as the eluant.

NMR data was as follows:

^1H -nmr (DMSO- d_6): $\delta = 0.85$ (m, 4H), 1.43 (d, 3H).

5 $\text{C}_{17}\text{H}_{19}\text{N}_3\text{O}_2$ (MW = 297.36); mass spectroscopy (MH^+) 297.

Example A58

Synthesis of N-(2-naphthyl)alanine O-acylcyclopropylacetamidoxime ester

10 Following General Procedure AS and using N-(2-naphthyl)alanine 2,4,5-trichlorophenyl ester (from Example AE above) and cyclopropylacetamide oxime (prepared according to the procedures described in *J. Org. Chem.*, 46, 3953 (1981)), the title compound was prepared as an oil. The reaction was monitored by silica gel tlc ($R_f = 0.3$ in 1:1 EtOAc/hexanes). Purification was by silica gel
15 chromatography using 1:1 EtOAc/hexanes as the eluant.

NMR data was as follows:

^1H -nmr (DMSO- d_6): $\delta = 1.43$ (d, 3H), 1.91 (d, 2H).

$\text{C}_{18}\text{H}_{21}\text{N}_3\text{O}_2$ (MW = 311.39); mass spectroscopy (MH^+) 311.

20

Example A59

Synthesis of N-(2-naphthyl)alanine O-acylcyclopentanecarboxamidoxime ester

25 Following General Procedure AS and using N-(2-naphthyl)alanine 2,4,5-trichlorophenyl ester (from Example AE above) and cyclopentanecarboxamide oxime (prepared according to the procedures described in *J. Org. Chem.*, 46, 3953 (1981)), the title compound was prepared as an oil. The reaction was monitored by silica gel tlc ($R_f = 0.3$ in 1:1 EtOAc/hexanes). Purification was by silica gel chromatography using 1:1 EtOAc/hexanes as the eluant.

30

NMR data was as follows:

^1H -nmr (DMSO- d_6): $\delta = 1.43$ (d, 3H), 2.43 (m, 1H).

$\text{C}_{17}\text{H}_{19}\text{N}_3\text{O}_2$ (MW = 297.36).

GENERAL PROCEDURE BA

Coupling of $R^1C(X')(X'')C(O)Cl$ with $H_2NCH(R^2)C(O)XR^3$

To a stirred solution of (D,L)-alanine *iso*-butyl ester hydrochloride (from Example BB below) (4.6 mmol) in 5 mL of pyridine was added 4.6 mmol of an acid chloride. Precipitation occurred immediately. The mixture was stirred for 3.5 h, diluted with 100 mL of diethyl ether, washed with 10% HCl three times, brine once, 20% potassium carbonate once and brine once. The solution was dried over magnesium sulfate, filtered, and evaporated at reduced pressure to yield the product. Other amino acid esters may also be employed in this procedure.

GENERAL PROCEDURE BB

Coupling of $R^1C(X')(X'')C(O)OH$ with $H_2NCH(R^2)C(O)XR^3$

A solution of the acid (3.3 mmol) and CDI in 20 mL THF was stirred for 2 h. L-alanine *iso*-butyl ester hydrochloride (from Example BB below) (3.6 mmol) was added, followed by 1.5 mL (10.8 mmol) of triethylamine. The reaction mixture was stirred overnight. The reaction mixture was diluted with 100 mL of diethyl ether, washed with 10% HCl three times, brine once, 20% potassium carbonate once and brine once. The solution was dried over magnesium sulfate, filtered, and evaporated at reduced pressure to yield the product. Other amino acid esters may also be employed in this procedure.

GENERAL PROCEDURE BC

Esterification of $R^1C(X')(X'')C(O)NHCH(R^2)C(O)OH$ With HOR^3

To a stirred solution of phenylacetylvaline (1.6470 g, 7.0 mmol) in 20 mL THF was added CDI (1.05 g, 6.5 mmol) and the mixture was stirred for 1.5 h. 2-Methylbutanol (0.53 g, 6 mmol) was added the mixture, followed by addition of NaH (0.16 g, 6.5 mmol). Bubbling occurred immediately. The reaction mixture was stirred overnight. The reaction mixture was diluted with 100 mL of diethyl ether, washed with 10% HCl three times, brine once, 20% potassium carbonate once and brine once. The solution was dried over

magnesium sulfate, filtered, and evaporated at reduced pressure to yield the product. Other N-acyl amino acids and alcohols may also be employed in this procedure.

5

GENERAL PROCEDURE BD

Ester Hydrolysis to the Free Acid

Ester hydrolysis to the free acid was conducted by conventional methods. Below are two examples of such conventional de-esterification methods.

10

To the ester in a 1:1 mixture of $\text{CH}_3\text{OH}/\text{H}_2\text{O}$ was added 2-5 equivalents of K_2CO_3 . The mixture was heated to about 50°C for about 0.5 to 1.5 hours until tlc showed complete reaction. The reaction was cooled to room temperature and the methanol was removed at reduced pressure. The pH of the remaining aqueous solution was adjusted to about 2, and ethyl acetate was added to extract the product. The organic phase was then washed with saturated aqueous NaCl and dried over MgSO_4 . The solution was stripped free of solvent at reduced pressure to yield the product.

15

20

The amino acid ester was dissolved in dioxane/water (4:1) to which was added LiOH (~2 eq.) that was dissolved in water such that the total solvent after addition was about 2:1 dioxane:water. The reaction mixture was stirred until reaction completion and the dioxane was removed under reduced pressure. The residue was diluted with EtOAc , the layers were separated and the aqueous layer acidified to pH 2. The aqueous layer was back extracted with EtOAc , the combined organics were dried over Na_2SO_4 and the solvent was removed under reduced pressure after filtration. The residue was purified by conventional methods (e.g., recrystallization).

25

30

The following exemplifies this later example. The methyl ester of 3- NO_2 phenylacetyl alanine 9.27 g (0.0348 mols) was dissolved in 60 mL dioxane and 15 mL of H_2O and adding LiOH (3.06 g, 0.0731 mol) that has been dissolved in

-- 190 --

15 mL of H₂O. After stirring for 4 hours, the dioxane was removed under reduced pressure and the residue diluted with EtOAc, the layers were separated and the aqueous layer acidified to pH 2. The aqueous layer was back extracted with EtOAc (4 X 100 mL), the combined organics were dried over Na₂SO₄ and the solvent was removed under reduced pressure after filtration. The residue was recrystallized from EtOAc/isooctane giving 7.5 g (85%) of 3-nitrophenylacetyl alanine. C₁₁H₁₂N₂O₅ requires C = 52.38, H = 4.80, and N = 11.11. Analysis found C = 52.54, H = 4.85, and N = 11.08. [α]_D²⁵ = - 29.9 @ 589 nm.

10

GENERAL PROCEDURE BE

Low Temperature BOP Coupling of Acid and Alcohol

A solution of methylene chloride containing the carboxylic acid (100M%) and N-methyl morpholine (150 M%) was cooled to -20°C under nitrogen. BOP (105 M%) was added in one portion and the reaction mixture was maintained at -20°C for 15 minutes. The corresponding alcohol (120 M%) was added and the reaction mixture was allowed to warm to room temperature and stirred for 12 hours. The reaction mixture was then poured into water and extracted with ethyl acetate (3x). The combined ethyl acetate portions were backwashed with saturated aqueous citric acid (2x), saturated aqueous sodium bicarbonate (2x), brine (1x), dried over anhydrous magnesium sulfate or sodium sulfate and the solvent removed under reduced pressure to yield the crude product.

15

20

25

GENERAL PROCEDURE BF

EDC Coupling of Acid and Amine

The acid derivative was dissolved in methylene chloride. The amine (1 eq.), N-methylmorpholine (5 eq.), and hydroxybenzotriazole monohydrate (1.2 eq.) were added in sequence. The reaction was cooled to about 0°C and then 1.2 eq. of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride was added. The solution was allowed to stir overnight and come to room

30

-- 191 --

temperature under N₂ pressure. The reaction mix was worked up by washing the solution with saturated, aqueous Na₂CO₃, 0.1M citric acid, and brine before drying with Na₂SO₄ and removal of solvents to yield crude product. Pure products were obtained by flash chromatography in an appropriate solvent.

5

GENERAL PROCEDURE BG

EDC Coupling of Acid and Amine

A round bottom flask was charged with carboxylic acid (1.0 eq.), hydroxy-benzotriazole hydrate (1.1 eq.) and amine (1.0 eq.) in THF under nitrogen atmosphere. An appropriate amount (1.1 eq. for free amines and 2.2 eq. for hydrochloride amine salts) of base, such as Hunig's base was added to the well stirred mixture followed by EDC (1.1 eq.). After stirring from 4 to 17 hours at room temperature the solvent was removed at reduced pressure, the residue taken up in EtOAc (or similar solvent)/water. The organic layer was washed with saturated aqueous sodium bicarbonate solution, 1N HCl, brine and dried over anhydrous sodium sulfate. In some cases, the isolated product was analytically pure at this stage while, in other cases, purification via chromatography and/or recrystallization was required prior to biological evaluation.

15
20

GENERAL PROCEDURE BH

Coupling of R¹C(X')(X'')C(O)Cl with H₂NCH(R²)C(O)XR³

An excess of oxalyl chloride in dichloromethane was added to the acid derivative together with one drop of DMF. The resulting mixture was stirred for about 2 hours or until bubbling ceases. The solvent was then removed under reduced pressure and rediluted with dry methylene chloride. To the resulting solution was added about 1.1 eq. of the appropriate amino acid ester and triethylamine (1.1 eq. in methylene chloride). The system was stirred at room temperature for 2 hours and then the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate, washed with 1N HCl followed by 1N NaOH. The organic layer was dried over anhydrous sodium

25
30

-- 192 --

sulfate, filtered and the solvent removed under reduced pressure to provide for the desired product.

GENERAL PROCEDURE BI

5

P-EPC coupling

P-EPC coupling employs an amino acid ester and a substituted acetic acid compound. The acetic acid derivative is well known in the art and is typically commercially available. The amino acid ester is prepared by conventional methods from the known and typically commercially available N-BOC amino acid as described in GENERAL PROCEDURE BJ below.

10

Specifically, the appropriate amino ester free base (0.0346 mmols) and substituted phenylacetic acid (0.069 mmols) were dissolved in 2.0 mL CHCl_3 (EtOH free), treated with 150 mg of P-EPC (0.87 meq./g) and the reaction was mixed for 4 days at 23°C. The reaction was filtered through a plug of cotton, rinsed with 2.0 mL of CHCl_3 and the filtrate evaporated under a stream of nitrogen. The purity of each sample was determined by ^1H NMR and ranged from 50% to >95%. Between 8.0 and 15.0 mg of final product was obtained from each reaction and was tested without additional purification.

15

20

GENERAL PROCEDURE BJ

Synthesis of Amino Acid Esters From the Corresponding N-BOC Amino Acid

A. Esterification of the Acid.

The N-BOC amino acid was dissolved in dioxane and treated with an excess of alcohol (~1.5 eq.) and catalytic DMAP (100 mg) at 0°C. Stirring was continued until reaction completion whereupon the product was recovered by conventional methods.

25

B. Removal of N-BOC Group.

30

The N-BOC protected amino acid was dissolved in methylene chloride (0.05M) and treated with 10 eq. of TFA at room temperature under a nitrogen

-- 193 --

atmosphere. The reaction was monitored by tlc until starting material was consumed usually within 1-5 hours. An additional 10 eq. of TFA was added to the reaction if the starting material was still present after 5 hours. The reaction was carefully neutralized with Na_2CO_3 , separated, the organic layer washed
5 with brine and dried over anhydrous Na_2SO_4 . The crude amine was then used without purification.

Specific exemplification of these procedures are as follows:

1. Racemic (+/-)-N-BOC- α -amino butyric acid (Aldrich) (9.29 g, 0.0457 mol) was dissolved in 100 mL of dioxane and treated with *iso*-butyl alcohol (6.26 mL, 0.0686 mol), EDC (8.72 g, 0.0457) and catalytic DMAP (100 mg) at 0°C. After stirring for 17 hours, the organics were evaporated at reduced pressure, the residue diluted with EtOAc washed with NaHCO_3 , brine and dried over Na_2SO_4 . Evaporation yields 8.42 g (71%) of an oil. $\text{C}_{13}\text{H}_{25}\text{NO}_4$
10 requires: C = 60.21, H = 9.72, and N = 5.40. Anal found: C = 59.91, H = 9.89, and N = 5.67.
15

The above N-BOC amino acid ester (8.00 g, 0.032 mol) was deprotected as above giving 3.12 g (61%) of the free base as a colorless oil which solidifies
20 upon standing.

2. L-N-BOC-alanine (Aldrich) (8.97 g, 0.047 mol) was dissolved in 100 mL of CH_2Cl_2 , *iso*-butyl alcohol (21.9 mL, 0.238 mol) and treated with DMAP (100 mg) and EDC (10.0 g, 0.52 mol) at 0°C. The mixture was
25 stirred for 17 hours, diluted with H_2O , washed with 1.0 N HCl, NaHCO_3 , then brine and the organics were dried over Na_2SO_4 . Filtration and evaporation yields 11.8 g (quantitative) of L-N-BOC alanine *iso*-butyl ester which is contaminated with a small amount of solvent. A sample was vacuum dried for analytical analysis. $\text{C}_{12}\text{H}_{23}\text{NO}_4$ requires: C = 58.79, H = 9.38, and N =
30 5.71. Anal found: C = 58.73, H = 9.55, and N = 5.96.

-- 194 --

The above N-BOC amino acid ester (11.8 g, 0.0481 mol) was deprotected as above. The free base was converted to the corresponding HCl salt using saturated HCl (g)/EtOAc to give L-N-alanine *iso*-butyl ester hydrochloride. Obtained 4.2 g (48%) of a colorless solid. $C_7H_{15}NO_2 \cdot HCl$ requires:

C = 46.28, H = 8.88, and N = 7.71. Anal found: C = 46.01, H = 8.85, and N = 7.68.

GENERAL PROCEDURE BK

Methyl ester formation from amino acids

The amino acid (amino acid or amino acid hydrochloride) is suspended in methanol and chilled to 0°C. HCl gas is bubbled through this solution for 5 minutes. The reaction is allowed to warm to room temperature then stirred for 4 hours. The solvents are then removed at reduced pressure to afford the desired amino acid methyl ester hydrochloride. This product is usually used without further purification.

Example BA

Synthesis of free and polymer bound PEPC

N-ethyl-N'-3-(1-pyrrolidinyl)propylurea

To a solution of 27.7 g (0.39 mol) ethyl isocyanate in 250 mL chloroform was added 50 g (0.39 mol) 3-(1-pyrrolidinyl)propylamine dropwise with cooling. Once the addition was complete, the cooling bath was removed and the reaction mixture stirred at room temperature for 4 hours. The reaction mixture was then concentrated under reduced pressure to give 74.5 g (96.4%) of the desired urea as a clear oil.

1-(3-(1-pyrrolidinyl)propyl)-3-ethylcarbodiimide (P-EPC)

To a solution of 31.0 g (0.156 mol) N-ethyl-N'-3-(1-pyrrolidinyl)propylurea in 500 mL dichloromethane was added 62.6 g (0.62 mol) triethylamine and the solution was cooled to 0°C. To this solution were then added 59.17 g (0.31

mol) 4-toluenesulfonyl chloride in 400 mL dichloromethane dropwise at such a rate as to maintain the reaction at 0-5°C. After the addition was complete, the reaction mixture was warmed to room temperature and then heated to reflux for 4 hours. After cooling to room temperature, the reaction mixture was washed
5 with saturated aqueous potassium carbonate (3 x 150 mL). The aqueous phases were combined and extracted with dichloromethane. All organic phases were combined and concentrated under reduced pressure. The resultant orange slurry was suspended in 250 mL diethyl ether and the solution decanted off from the solid. The slurry/decantation process was repeated 3 more times. The ether
10 solutions were combined and concentrated under reduced pressure to give 18.9 g (67%) of the desired product as a crude orange oil. A portion of the oil was distilled under vacuum to give a colorless oil distilling at 78-82°C (0.4 mm Hg).

15 Preparation of a polymer supported form of 1-(3-(1-pyrrolidinyl)propyl)-3-ethylcarbodiimide (P-EPC)

A suspension of 8.75 g (48.3 mmol) 1-(3-(1-pyrrolidin-yl)propyl)-3-ethylcarbodiimide and 24.17 g (24.17 mmol) Merrifield's resin (2% cross-linked, 200-400 mesh, chloromethylated styrene/divinylbenzene copolymer, 1
20 meq. Cl/g) in dimethylformamide was heated at 100°C for 2 days. The reaction was cooled and filtered and the resulting resin washed sequentially with 1L DMF, 1L THF and 1L diethyl ether. The remaining resin was then dried under vacuum for 18 hours.

25

Example BB

Preparation of alanine *iso*-butyl ester hydrochloride

A mixture of 35.64 g (0.4 mol) of (D,L)-alanine (Aldrich) (or L-alanine (Aldrich)); 44 mL (0.6 mol) of thionyl chloride (Aldrich) and 200 mL of isobutanol was refluxed for 1.5 hours and the volatiles were removed
30 completely on a rotavapor of 90°C under reduced pressure to give (D,L)-

-- 196 --

alanine *iso*-butyl ester hydrochloride (or L-alanine *iso*-butyl ester hydrochloride), which was pure enough to be used for further transformations.

Example BC

5 Preparation of 3,5-dichlorophenylacetic acid

To a solution of 3.5 g of 3,5-dichlorobenzyl alcohol (Aldrich) in 75 mL of dichloromethane at 0°C was added 1.8 mL of methane sulfonylchloride followed by 3.5 mL of triethylamine added dropwise. After 2 hours the solution was diluted to 150 mL with dichloromethane, washed with 3N HCl,
10 saturated aqueous NaHCO₃ dried with Na₂SO₄ and the solvents removed to yield the desired 3,5-dichlorobenzyl methanesulfonate as a yellow oil that was used without purification.

The crude sulfonate was dissolved in 50 mL of DMF at 0°C and then 3 g of KCN was added. After 2 hours an additional 50 mL of DMF was added
15 and the solution was stirred for 16 hours. The red solution was diluted with 1 L of H₂O and acidified to pH 3 with 3N HCl. The aqueous solution was extracted with dichloromethane. The combined organics were washed with 3N HCl, dried with Na₂SO₄ and the solvents removed at reduced pressure to yield crude 3,5-dichlorophenylacetonitrile which was used without purification.

The nitrile was added to a mixture of 40 mL of concentrated sulfuric acid and 50 mL H₂O and heated to reflux for 48 hours, cooled to room temperature and stirred for 48 hours. The reaction was diluted into 1 L of crushed ice, warmed to room temperature and extracted with 2 x 200 mL of dichloromethane and 2 x 200 mL of ethylacetate. Both sets of organics were
25 combined and washed with saturated aqueous NaHCO₃. The NaHCO₃ fractions were combined and acidified to pH 1 with 3N HCl. The white solid was too fine to filter and was extracted out with 2 X 200 mL of dichloromethane. The combined organics were dried with Na₂SO₄ and the solvents removed at reduced pressure to yield crude 3,5-dichlorophenylacetic acid as a white solid. The solid
30 was slurried with hexane and filtered to get 1.75g of white solid.

NMR (CDCl₃): (in ppm) 3.61 (s, 2H), 7.19 (s, 1H), 7.30 (s, 1H)

-- 197 --

Example BD

Synthesis of N-(3-chlorophenylacetyl)alanine

The title compound was prepared using L-alanine (Nova Biochem) and 3-chlorophenyl acetic acid (Aldrich) by following General Procedures BF or BG, followed by hydrolysis using General Procedure BD.

Example B1

Synthesis of N-(phenylacetyl)-D,L-alanine *iso*-butyl ester

Following General Procedure BA above and using phenylacetyl chloride (Aldrich) and D,L-alanine *iso*-butyl ester hydrochloride (from Example BB above), the title compound was prepared. The reaction was monitored by tlc on silica gel and purification was by extraction with Et₂O followed by washes with aqueous K₂CO₃ and aqueous HCl.

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 7.23-7.36 (m, 5H), 6.18 (d, 1H), 4.58 (t, *J* = 7.3 Hz, 1H), 3.87 (m, 2H), 3.57 (s, 2H), 1.90 (m, 1H), 1.34 (d, *J* = 7.2 Hz, 3H), 0.89 (d, *J* = 6.8 Hz, 6H).

¹³C-nmr (CDCl₃): δ = 172.7, 170.3, 134.5, 129.2, 128.8, 127.2, 71.3, 48.1, 43.4, 27.5, 18.8, 18.3.

C₁₅H₂₁NO₃ (MW = 263.34; Mass Spectroscopy (MH⁺ = 264))

Example B2

Synthesis of N-(3-phenylpropionyl)-D,L-alanine *iso*-butyl ester

Following General Procedure BA above and using 3-phenylpropionyl chloride (Aldrich) and D,L-alanine *iso*-butyl ester hydrochloride (from Example BB above), the title compound was prepared as a solid having a melting point of from 51°-54°C. The reaction was monitored by tlc on silica gel and purification was by extraction with Et₂O followed by washes with aqueous K₂CO₃ and aqueous HCl.

NMR data was as follows:

-- 198 --

^1H -nmr (CDCl_3): δ = 7.25 (m, 2H), 7.19 (m, 3H), 6.28 (d, J = 7.2 Hz, 1H), 4.58 (quint., J = 7.2 Hz, 1H), 3.89 (m, 2H), 2.95 (t, J = 7.7 Hz, 2H), 2.50 (m, 2H), 1.92 (m, 1H), 1.33 (d, J = 7.1 Hz, 3H), 0.91 (d, J = 6.7 Hz, 6H).

^{13}C -nmr (CDCl_3): δ = 173.0, 171.5, 140.6, 128.3, 128.1, 126.0, 71.2,
5 47.8, 37.9, 31.4, 27.5, 18.79, 18.77, 18.3.

$\text{C}_{16}\text{H}_{23}\text{NO}_3$ (MW = 277.37, Mass Spectroscopy (MH^+ 278))

Example B3

Synthesis of *N*-(3-methylpentanoyl)-L-alanine *iso*-butyl ester

10 Following General Procedure BB and using 3-methylpentanoic acid (Aldrich) and L-alanine *iso*-butyl ester hydrochloride (from Example BB above), the title compound was prepared as an oil. The reaction was monitored by tlc on silica gel and purification was by extraction with Et_2O followed by washes with aqueous K_2CO_3 and aqueous HCl.

15 NMR data was as follows:

^1H -nmr (CDCl_3): δ = 6.08 (d, J = 5.9 Hz, 1H), 4.62 (quint., J = 7.3 Hz, 1H), 3.92 (m, 2H), 2.22 (m, 1H), 1.84-2.00 (m, 3H), 1.40 (d, J = 7.2 Hz, 3H), 1.35 (m, 1H), 1.20 (m, 1H), 0.85-0.96 (m, 12H).

^{13}C -nmr (CDCl_3): δ = 173.3, 172.1, 71.4, 47.9, 43.9, 32.3, 29.38, 29.35,
20 27.6, 19.10, 19.06, 18.93, 18.91, 18.72, 18.67, 11.3.

$\text{C}_{13}\text{H}_{25}\text{NO}_3$ (MW = 243.35, Mass Spectroscopy (MH^+ 244))

Example B4

Synthesis of *N*-[(4-chlorophenyl)acetyl]-L-alanine *iso*-butyl ester

25 Following General Procedure BB and using 4-chlorophenylacetic acid (Aldrich) and L-alanine *iso*-butyl ester hydrochloride (from Example BB above), the title compound was prepared as a solid having a melting point of 111°-113°C. The reaction was monitored by tlc on silica gel and purification was by extraction with Et_2O followed by washes with aqueous K_2CO_3 and aqueous HCl.

30 NMR data was as follows:

-- 199 --

¹H-nmr (CDCl₃): δ = 7.30 (d, *J* = 8.2 Hz, 2H), 7.21 (d, *J* = 8.3 Hz, 2H), 6.18 (d, *J* = 5.5 Hz, 1H), 4.57 (quint., *J* = 7.2 Hz, 1H), 3.88 (m, 2H), 3.53 (s, 2H), 1.91 (m, 1H), 1.36 (d, *J* = 7.1 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 6H).

¹³C-nmr (CDCl₃): δ = 172.8, 169.8, 133.1, 133.0, 130.6, 128.9, 71.4, 48.2, 42.6, 27.6, 18.85, 18.82, 18.4.

C₁₅H₂₀NO₃Cl (MW = 297.78, Mass Spectroscopy (MH⁺ 298))

Example B5

Synthesis of *N*-[(3,4-dichlorophenyl)acetyl]-L-alanine *iso*-butyl ester

Following General Procedure BB and using 3,4-dichlorophenylacetic acid (Aldrich) and L-alanine *iso*-butyl ester hydrochloride (from Example BB above), the title compound was prepared as a solid having a melting point of 81°-83°C. The reaction was monitored by tlc on silica gel and purification was by extraction with Et₂O followed by washes with aqueous K₂CO₃ and aqueous HCl.

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 0.90 (d, *J* = 6.8 Hz, 6H), 1.38 (d, *J* = 7.1 Hz, 3H), 1.91 (m, 1H), 3.50 (s, 2H), 3.90 (m, 2H), 4.57 (quint., *J* = 7.1 Hz, 1H), 6.31 (d, *J* = 4.9 Hz, 1H), 7.12 (m, 1H), 7.38 (m, 2H).

¹³C-nmr (CDCl₃): δ = 18.4, 18.8, 18.9, 27.6, 42.2, 48.3, 71.5, 128.6, 130.6, 131.2, 131.3, 132.6, 134.7, 169.2, 172.8.

C₁₅H₁₉NO₃Cl₂ (MW = 332.23, Mass Spectroscopy (MH⁺ 332))

Example B6

Synthesis of *N*-[(4-methylphenyl)acetyl]-D,L-alanine *iso*-butyl ester

Following General Procedure BB and using 4-methylphenylacetic acid (Aldrich) and D,L-alanine *iso*-butyl ester hydrochloride (from Example BB above), the title compound was prepared as a solid having a melting point of 102°-104°C. The reaction was monitored by tlc on silica gel (R_f = 0.6 in 33% ethyl acetate/hexanes) and purification was by extraction with Et₂O followed by washes with aqueous K₂CO₃ and aqueous HCl.

NMR data was as follows:

-- 200 --

^1H -nmr (CDCl_3): δ = 0.90 (d, J = 6.7 Hz, 6H), 1.35 (d, J = 7.2 Hz, 3H), 1.91 (m, 1H), 2.34 (s, 3H), 3.55 (s, 2H), 3.88 (m, 2H), 4.58 (m, 1H), 6.05 (bd, 1H), 7.16 (s, 4H).

^{13}C -nmr (CDCl_3): δ = 18.5, 18.85, 18.87, 21.0, 27.6, 43.1, 48.1, 71.3,
5 129.2, 129.6, 131.3, 136.9, 170.6, 172.8.

$\text{C}_{16}\text{H}_{23}\text{NO}_3$ (MW = 277.37, Mass Spectroscopy (MH^+ 278))

Example B7

Synthesis of *N*-[(3-pyridyl)acetyl]-D,L-alanine *iso*-butyl ester

10 Following General Procedure BF and using 3-pyridylacetic acid hydrochloride (Aldrich) and D,L-alanine *iso*-butyl ester hydrochloride (from Example BB above), the title compound was prepared as a solid having a melting point of 62°-64°C. The reaction was monitored by tlc on silica gel (R_f = 0.48 10% methanol/dichloromethane) and purification was by silica gel
15 chromatography.

NMR data was as follows:

^1H -nmr (CDCl_3): δ = 8.40 (d, J = 2.8, 2H); 7.6 (m, 1H); 7.16 (m, 2H); 4.5 (quint., J = 7.2, 7.2, 1H); 3.8 (m, 2H); 3.48 (s, 2H); 1.8 (m, 1H); 1.30 (d, J = 7.2, 3H); 0.81 (d, J = 6.7, 6H).

20 ^{13}C -nmr (CDCl_3): δ = 173.4, 170.1, 150.6, 148.8, 137.4, 131.4, 124.1, 71.9, 48.9, 40.6, 28.1, 19.5, 19.4, 18.6.

$\text{C}_{14}\text{H}_{20}\text{N}_2\text{O}_3$ (MW = 264, Mass Spectroscopy (MH^+ 265))

Example B8

Synthesis of *N*-[(1-naphthyl)acetyl]-L-alanine *iso*-butyl ester

25 Following General Procedure BB and using 1-naphthylacetic acid (Aldrich) and L-alanine *iso*-butyl ester hydrochloride (from Example BB above), the title compound was prepared as a solid having a melting point of 69°-73°C. The reaction was monitored by tlc on silica gel and purification was by
30 extraction with Et_2O followed by washes with aqueous K_2CO_3 and aqueous HCl.

NMR data was as follows:

-- 201 --

¹H-nmr (CDCl₃): δ = 0.83 (m, 6H), 1.25 (d, *J* = 7.1 Hz, 3H); 1.81 (m, 1H), 3.79 (m, 2H), 4.04 (2s, 2H), 4.57 (quint., *J* = 7.3 Hz, 1H), 5.99 (d, *J* = 7.1 Hz, 1H), 7.44 (m, 2H), 7.53 (m, 2H), 7.85 (m, 2H), 7.98 (m, 1H).

¹³C-nmr (CDCl₃): δ = 18.2, 18.81, 18.83, 27.5, 41.5, 48.2, 71.3, 123.7,
5 125.6, 126.1, 126.6, 128.2, 128.5, 128.7, 130.7, 132.0, 133.9, 170.3, 172.5.

C₁₉H₂₃NO₃ (MW = 313.40, Mass Spectroscopy (MH⁺ 314))

Example B9

Synthesis of *N*-[(2-naphthyl)acetyl]-L-alanine *iso*-butyl ester

10 Following General Procedure BB and using 2-naphthylacetic acid (Aldrich) and L-alanine *iso*-butyl ester hydrochloride (from Example BB above), the title compound was prepared as a solid having a melting point of 128°-129°C. The reaction was monitored by tlc on silica gel and purification was by extraction with Et₂O followed by washes with aqueous K₂CO₃ and aqueous HCl.

15 NMR data was as follows:

¹H-nmr (CDCl₃): δ = 0.86 (m, 6H), 1.35 (d, *J* = 7.1 Hz, 3H), 1.78 (m, 1H), 3.76 (s, 2H), 3.87 (m, 2H), 4.62 (quint., *J* = 7.2 Hz, 1H), 6.13 (d, *J* = 7.1 Hz, 1H), 7.41 (m, 1H), 7.48 (m, 2H), 7.74 (s, 1H), 7.83 (m, 3H).

¹³C-nmr (CDCl₃): δ = 18.4, 18.82, 18.85, 27.6, 43.7, 48.2, 71.4, 125.9,
20 126.3, 127.2, 127.6, 127.7, 128.2, 128.7, 132.0, 132.5, 133.5, 170.3, 172.8.

C₁₉H₂₃NO₃ (MW = 313.40, Mass Spectroscopy (MH⁺ 314)).

Example B10

Synthesis of *N*-(4-phenylbutanoyl)-L-alanine *iso*-butyl ester

25 Following General Procedure BB and using 4-phenylbutanoic acid (Aldrich) and L-alanine *iso*-butyl ester hydrochloride (from Example BB above), the title compound was prepared as an oil. The reaction was monitored by tlc on silica gel and purification was by extraction with Et₂O followed by washes with aqueous K₂CO₃ and aqueous HCl.

30 NMR data was as follows:

-- 202 --

¹H-nmr (CDCl₃): δ = 0.92 (d, *J* = 6.7 Hz, 6H), 1.38 (d, *J* = 7.1 Hz, 3H), 1.96 (m, 3H), 2.21 (t, *J* = 7.1 Hz, 2H), 2.64 (t, *J* = 7.3 Hz, 2H), 3.90 (m, 2H), 4.59 (quint., *J* = 7.2 Hz, 1H), 6.31 (d, 1H), 7.16 (m, 3H), 7.24 (m, 2H).

¹³C-nmr (CDCl₃): δ = 18.3, 18.75, 18.78, 26.8, 27.5, 34.9, 35.3, 47.8,
5 71.2, 125.7, 128.2, 128.3, 141.3, 172.1, 173.0.

C₁₇H₂₅NO₃ (MW = 291.39, Mass Spectroscopy (MH⁺ 292)).

Example B11

Synthesis of *N*-(5-phenylpentanoyl)-L-alanine *iso*-butyl ester

10 Following General Procedure BB and using 5-phenylpentanoic acid (Aldrich) and L-alanine *iso*-butyl ester hydrochloride (from Example BB above), the title compound was prepared as an oil. The reaction was monitored by tlc on silica gel and purification was by extraction with Et₂O followed by washes with aqueous K₂CO₃ and aqueous HCl.

15 NMR data was as follows:

¹H-nmr (CDCl₃): δ = 7.23 (m, 2H), 7.17 (m, 3H), 6.30 (d, 1H), 4.59 (quint., *J* = 7.3 Hz, 1H), 3.91 (m, 2H), 2.61 (t, *J* = 7.2 Hz, 2H), 2.22 (t, *J* = 7.2 Hz, 2H), 1.93 (m, 1H), 1.66 (m, 4H), 1.38 (d, *J* = 7.2 Hz, 3H), 0.92 (d, *J* = 6.7 Hz, 6H).

20 ¹³C-nmr (CDCl₃): δ = 173.1, 172.3, 142.0, 128.2, 128.1, 125.6, 71.2, 47.8, 36.1, 35.5, 30.8, 27.5, 25.0, 18.80, 18.77, 18.4.

C₁₈H₂₇NO₃ (MW = 305.39, Mass Spectroscopy (MH⁺ 306)).

Example B12

25 Synthesis of *N*-[(4-pyridyl)acetyl]-D,L-alanine *iso*-butyl ester

Following General Procedure BF and using 4-pyridylacetic acid hydrochloride (Aldrich) and (D,L)-alanine *iso*-butyl ester hydrochloride (from Example BB above), the title compound was prepared as a solid having a melting point of 64°-66°C. The reaction was monitored by tlc on silica gel (R_f = 0.43 10% methanol/dichloromethane) and purification was by silica gel
30 chromatography.

-- 203 --

NMR data was as follows:

^1H -nmr (CDCl_3): δ = 8.51 (dd, J = 1.6, 2.8, 1.6, 2H); 7.23 (dd, J = 4.3, 1.6, 4.4, 2H); 6.71 (d, J = 6.8, 1H); 4.56 (quint., J = 7.3, 7.2, 1H); 3.88 (m, 2H); 3.53 (s, 2H); 1.89 (m, 1H); 1.36 (d, J = 7.2, 3H); 0.88 (d, J = 6.7, 6H).

5 ^{13}C -nmr (CDCl_3): δ = 173.5, 169.3, 150.5, 144.4, 125.1, 72.1, 48.9, 43.0, 28.2, 19.5, 19.5, 18.9.

$\text{C}_{14}\text{H}_{20}\text{N}_2\text{O}_3$ (MW = 264, Mass Spectroscopy (MH^+ 265))

Example B13

10 Synthesis of N-(phenylacetyl)-L-alanine *iso*-butyl ester

Following General Procedure BB and using phenylacetyl chloride (Aldrich) and L-alanine *iso*-butyl ester hydrochloride (from Example BB above), the title compound was prepared as a solid having a melting point of 45°-47°C. The reaction was monitored by tlc on silica gel and purification was by
15 extraction with Et_2O followed by washes with aqueous K_2CO_3 and aqueous HCl.

NMR data was as follows:

^1H -nmr (CDCl_3): δ = 7.24-7.39 (m, 5H), 6.14 (d, 1H), 4.58 (t, J = 7.3 Hz, 1H), 3.88 (m, 2H), 3.58 (s, 2H), 1.90 (m, 1H), 1.35 (d, J = 7.2 Hz, 3H), 0.89 (d, J = 6.7 Hz, 6H).

20 ^{13}C -nmr (CDCl_3): δ = 172.8, 170.4, 134.5, 129.3, 128.9, 127.2, 71.3, 48.1, 43.5, 27.5, 18.9, 18.8, 18.4.

$\text{C}_{15}\text{H}_{21}\text{NO}_3$ (MW = 263.34, Mass Spectroscopy (MH^+ 264)).

Example B14

25 Synthesis of 2-[(3,4-dichlorophenyl)acetamido]butyric acid *iso*-butyl ester

Following General Procedure BI above and using 3,4-dichlorophenylacetic acid (Aldrich) and *iso*-butyl 2-aminobutyrate (prepared following General Procedure BJ above) the title compound was prepared. The reaction was monitored by tlc on silica gel and purification was by filtration as
30 described in the general procedure.

NMR data was as follows:

-- 204 --

¹H-nmr (CDCl₃): δ = 7.36 (m, 3H), 6.03 (bd, 1H), 4.54 (m, 1H), 3.87 (m, 2H), 3.49 (s, 2H), 1.93 (m, 2H), 1.72 (m, 1H), 0.88 (d, 6H), 0.80 (t, 3H).

Example B15

5 **Synthesis of 2-[(3-methoxyphenyl)acetamido]butyric acid *iso*-butyl ester**

Following General Procedure BI above and using 3-methoxyphenylacetic acid (Aldrich) and *iso*-butyl 2-aminobutyrate (prepared following General Procedure BJ above), the title compound was prepared. The reaction was monitored by tlc on silica gel and purification was by filtration as described in the general procedure.

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 6.75 (m, 4H), 5.93 (bd, 1H), 4.51 (m, 1H), 3.83 (m, 2H), 3.75 (s, 2H), 3.52 (s, 2H), 1.82 (m, 2H), 1.60 (m, 1H), 0.84 (d, 6H), 0.74 (t, 3H).

15 C₁₇H₂₅NO₄ (MW = 307.39, Mass Spectroscopy (MH⁺ 309)).

Example B16

20 **Synthesis of 2-[(4-nitrophenyl)acetamido]butyric acid *iso*-butyl ester**

Following General Procedure BI above and using 4-nitrophenylacetic acid (Aldrich) and *iso*-butyl 2-aminobutyrate (prepared following General Procedure BJ above), the title compound was prepared. The reaction was monitored by tlc on silica gel and purification was by filtration as described in the general procedure.

NMR data was as follows:

25 ¹H-nmr (CDCl₃): δ = 8.16 (d, 2H), 7.44 (d, 2H), 6.04 (bd, 1H), 4.55 (m, 1H), 3.86 (m, 2H), 3.66 (s, 2H), 1.86 (m, 2H), 1.67 (m, 1H), 0.85 (d, 6H), 0.81 (t, 3H).

C₁₆H₂₂N₂O₅ (MW = 322.36, Mass Spectroscopy (MH⁺ 323)).

30

Example B17

Synthesis of 2-[(3,4-methylenedioxyphenyl)acetamido]butyric acid *iso*-butyl ester

-- 205 --

Following General Procedure BI above and using 3,4-(methylenedioxy)-phenyl acetic acid (Aldrich) and *iso*-butyl 2-aminobutyrate (prepared following General Procedure BJ above), the title compound was prepared. The reaction was monitored by tlc on silica gel and purification was by filtration as described in the general procedure.

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 6.72 (m, 3H), 5.92 (bd, 1H), 4.54 (m, 1H), 3.86 (m, 2H), 3.66 (s, 2H), 1.86 (m, 2H), 1.66 (m, 1H), 0.89 (d, 6H), 0.79 (t, 3H).

Example B18

Synthesis of 2-[(thien-3-yl)acetamido]butyric acid *iso*-butyl ester

Following General Procedure BI above and using 3-thiopheneacetic acid (Aldrich) and *iso*-butyl 2-aminobutyrate (prepared following General Procedure BJ above), the title compound was prepared. The reaction was monitored by tlc on silica gel and purification was by filtration as described in the general procedure.

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 7.37 (m, 1H), 7.16 (m, 1H), 7.04 (m, 1H), 6.05 (bd, 1H), 4.57 (m, 1H), 3.66 (s, 2H), 1.93 (m, 2H), 1.67 (m, 1H), 0.91 (d, 6H), 0.86 (t, 3H).

Example B19

Synthesis of 2-[(4-chlorophenyl)acetamido]butyric acid *iso*-butyl ester

Following General Procedure BI above and using 4-chlorophenylacetic acid (Aldrich) and *iso*-butyl 2-aminobutyrate (prepared following General Procedure BJ above), the title compound was prepared. The reaction was monitored by tlc on silica gel and purification was by filtration as described in the general procedure.

NMR data was as follows:

-- 206 --

¹H-nmr (CDCl₃): δ = 7.22 (m, 2H), 7.11 (m, 2H), 5.80 (m, 1H), 4.44 (m, 1H), 3.78 (m, 2H), 3.43 (s, 2H), 1.77 (m, 2H), 1.56 (m, 1H), 0.83 (d, 6H) 0.71 (t, 3H).

5

Example B20**Synthesis of 2-[(3-nitrophenyl)acetamido]butyric acid *iso*-butyl ester**

Following General Procedure BI above and using 3-nitrophenylacetic acid (Aldrich) and *iso*-butyl 2-aminobutyrate (prepared following General Procedure BJ above), the title compound was prepared. The reaction was monitored by tlc on silica gel and purification was by filtration as described in the general procedure.

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 8.15 (m, 2H), 7.65 (m, 1H), 6.08 (m, 1H), 4.46 (m, 1H), 3.92 (m, 2H), 3.68 (s, 2H), 1.91 (m, 2H), 1.75 (m, 1H), 0.98 (d, 6H) 0.71 (t, 3H).

15

Example B21**Synthesis of 2-[(2-hydroxyphenyl)acetamido]butyric acid *iso*-butyl ester**

Following General Procedure BI above and using 2-hydroxyphenylacetic acid (Aldrich) and *iso*-butyl 2-aminobutyrate (prepared following General Procedure BJ above), the title compound was prepared. The reaction was monitored by tlc on silica gel and purification was by filtration as described in the general procedure.

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 7.14 (m, 1H), 7.01 (m, 1H), 6.93 (m, 1H), 6.79 (m, 1H), 6.46 (m, 1H), 4.51 (m, 1H), 3.87 (m, 2H), 3.57 (s, 2H), 2.01 (m, 2H), 1.75 (m, 1H), 0.89 (d, 6H), 0.85 (t, 3H).

25

Example B22**Synthesis of 2-[(2-naphthyl)acetamido]butyric acid *iso*-butyl ester**

30

-- 207 --

Following General Procedure BI above and using 2-naphthylacetic acid (Aldrich) and *iso*-butyl 2-aminobutyrate (prepared following General Procedure BJ above), the title compound was prepared. The reaction was monitored by tlc on silica gel and purification was by filtration as described in the general procedure.

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 7.83 (m, 7H), 5.95 (m, 1H), 4.58 (m, 1H), 3.84 (m, 2H), 3.75 (s, 2H), 1.89 (m, 2H), 1.63 (m, 1H), 0.91 (d, 6H), 0.81 (t, 3H).

C₂₀H₂₅NO₃ (MW = 327.42, Mass Spectroscopy (MH⁺ 328)).

Example B23

Synthesis of 2-[(2,4-dichlorophenyl)acetamido]butyric acid *iso*-butyl ester

Following General Procedure BI above and using 2,4-dichlorophenylacetic acid (Aldrich) and *iso*-butyl 2-aminobutyrate (prepared following General Procedure BJ above), the title compound was prepared. The reaction was monitored by tlc on silica gel and purification was by filtration as described in the general procedure.

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 7.49 (m, 1H), 7.22 (m, 2H) 5.98 (m, 1H), 4.52 (m, 1H), 3.86 (m, 2H), 3.61 (s, 2H), 1.84 (m, 2H), 1.62 (m, 1H) 0.87 (d, 6H), 0.80 (t, 3H).

Example B24

Synthesis of 2-[(4-bromophenyl)acetamido]butyric acid *iso*-butyl ester

Following General Procedure BI above and using 4-bromophenylacetic acid (Aldrich) and *iso*-butyl 2-aminobutyrate (prepared following General Procedure BJ above), the title compound was prepared. The reaction was monitored by tlc on silica gel and purification was by filtration as described in the general procedure.

NMR data was as follows:

-- 208 --

^1H -nmr (CDCl_3): δ = 7.43 (d, 2H), 7.19 (d, 2H), 5.85 (m, 1H), 4.51 (m, 1H), 3.81 (m, 2H), 3.47 (s, 2H), 1.84 (m, 2H), 1.61 (m, 1H), 0.84 (d, 6H), 0.76 (t, 3H).

$\text{C}_{16}\text{H}_{22}\text{NO}_3\text{Br}$ (MW = 356.26, Mass Spectroscopy (MH^+ 358)).

5

Example B25

Synthesis of 2-[(3-chlorophenyl)acetamido]butyric acid *iso*-butyl ester

Following General Procedure BI above and using 3-chlorophenylacetic acid (Aldrich) and *iso*-butyl 2-aminobutyrate (prepared following General Procedure BJ above), the title compound was prepared. The reaction was monitored by tlc on silica gel and purification was by filtration as described in the general procedure.

NMR data was as follows:

^1H -nmr (CDCl_3): δ = 7.25 (m, 3H), 7.12 (m, 1H), 5.80 (m, 1H), 4.52 (m, 1H), 3.86 (m, 2H), 3.50 (s, 2H), 1.87 (m, 2H), 1.67 (m, 1H), 0.88 (d, 6H), 0.77 (t, 3H).

$\text{C}_{16}\text{H}_{22}\text{NO}_3\text{Cl}$ (MW = 311.81 Mass Spectroscopy (MH^+ 313)).

Example B26

Synthesis of 2-[(3-fluorophenyl)acetamido]butyric acid *iso*-butyl ester

Following General Procedure BI above and using 3-fluorophenylacetic acid (Aldrich) and *iso*-butyl 2-aminobutyrate (prepared following General Procedure BJ above), the title compound was prepared. The reaction was monitored by tlc on silica gel and purification was by filtration as described in the general procedure.

NMR data was as follows:

^1H -nmr (CDCl_3): δ = 7.31 (m, 1H), 7.01 (m, 3H), 5.95 (m, 1H), 4.54 (m, 1H), 3.84 (m, 2H), 3.54 (s, 2H), 1.88 (m, 2H), 1.65 (m, 1H), 0.87 (d, 6H), 0.81 (t, 3H).

$\text{C}_{16}\text{H}_{22}\text{NO}_3\text{F}$ (MW = 295.35 Mass Spectroscopy (MH^+ 296)).

30

-- 209 --

Example B27

Synthesis of 2-[(benzothiazol-4-yl)acetamido]butyric acid *iso*-butyl ester

Following General Procedure BI above and using 4-benzothiazol-4-yl acetic acid (Chemservice) and *iso*-butyl 2-aminobutyrate (prepared following General Procedure BJ above), the title compound was prepared. The reaction was monitored by tlc on silica gel and purification was by filtration as described in the general procedure.

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 7.82 (m, 1H), 7.51-7.21 (m, 4H) 5.84 (m, 1H), 4.51 (m, 1H), 3.90 (s, 2H), 3.79 (m, 2H), 1.78 (m, 2H), 1.58 (m, 1H) 0.80 (d, 6H), 0.66 (t, 3H).

Example B28

Synthesis of 2-[(2-methylphenyl)acetamido]butyric acid *iso*-butyl ester

Following General Procedure BI above and using 2-methylphenylacetic acid (Aldrich) and *iso*-butyl 2-aminobutyrate (prepared following General Procedure BJ above), the title compound was prepared. The reaction was monitored by tlc on silica gel and purification was by filtration as described in the general procedure.

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 7.18 (m, 4H), 5.79 (m, 1H), 4.54 (m, 1H), 3.85 (m, 2H), 3.59 (s, 2H), 3.29 (s, 3H), 1.81 (m, 2H), 1.59 (m, 1H) 0.87 (d, 6H), 0.77 (t, 3H).

C₁₇H₂₅NO₃ (MW = 291.39 Mass Spectroscopy (M⁺ 291)).

Example B29

Synthesis of 2-[(2-fluorophenyl)acetamido]butyric acid *iso*-butyl ester

Following General Procedure BI above and using 2-fluorophenylacetic acid (Aldrich) and *iso*-butyl 2-aminobutyrate (prepared following General Procedure BJ above), the title compound was prepared. The reaction was

-- 210 --

monitored by tlc on silica gel and purification was by filtration as described in the general procedure.

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 7.28 (m, 1H), 7.09 (m, 3H) 6.03 (m, 1H), 4.54 (m, 1H), 3.87 (m, 2H), 3.57 (s, 2H), 1.89 (m, 2H), 1.64 (m, 1H) 0.88 (d, 6H), 0.80 (t, 3H).

Example B30

Synthesis of 2-[(4-fluorophenyl)acetamido]butyric acid *iso*-butyl ester

Following General Procedure BI above and using 4-fluorophenylacetic acid (Aldrich) and *iso*-butyl 2-aminobutyrate (prepared following General Procedure BJ above), the title compound was prepared. The reaction was monitored by tlc on silica gel and purification was by filtration as described in the general procedure.

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 7.20 (m, 2H), 6.97 (m, 2H) 5.87 (m, 1H), 4.492 (m, 1H), 3.83 (m, 2H), 3.48 (s, 2H), 1.86 (m, 2H), 1.60 (m, 1H) 0.87 (d, 6H), 0.78 (t, 3H).

C₁₆H₂₂NO₃F (MW = 295.35 Mass Spectroscopy (MH⁺ 296)).

Example B31

Synthesis of 2-[(3-bromophenyl)acetamido]butyric acid *iso*-butyl ester

Following General Procedure BI above and using 3-bromophenylacetic acid (Aldrich) and *iso*-butyl 2-aminobutyrate (prepared following General Procedure BJ above), the title compound was prepared. The reaction was monitored by tlc on silica gel and purification was by filtration as described in the general procedure.

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 7.45 (m, 2H), 7.23 (m, 2H) 5.95 (m, 1H), 4.55 (m, 1H) 3.84 (m, 2H) 3.55 (s, 2H), 1.89 (m, 2H), 1.68 (m, 1H) 0.91 (d, 6H), 0.81 (t, 3H).

-- 211 --

$C_{16}H_{22}NO_3Br$ (MW = 356.26 Mass Spectroscopy (M^+ 357)).

Example B32

Synthesis of 2-[(3-trifluoromethylphenyl)acetamido]butyric acid *iso*-butyl ester

5

Following General Procedure BI above and using 3-trifluoromethylphenylacetic acid (Aldrich) and *iso*-butyl 2-aminobutyrate (prepared following General Procedure BJ above), the title compound was prepared. The reaction was monitored by tlc on silica gel and purification was by filtration as described in the general procedure.

10

NMR data was as follows:

^1H -nmr ($CDCl_3$): δ = 7.52 (m, 1H), 7.47 (m, 2H) 6.01 (m, 1H), 4.56 (m, 1H), 3.86 (m, 2H), 3.61 (s, 2H), 1.84 (m, 2H), 1.62 (m, 1H) 0.87 (d, 6H), 0.80 (t, 3H).

15

$C_{17}H_{22}NO_3F_3$ (MW = 345.36 Mass Spectroscopy (MH^+ 345)).

Example B33

Synthesis of 2-[(2-thienyl)acetamido]butyric acid *iso*-butyl ester

Following General Procedure BI above and using 2-thiopheneacetic acid (Aldrich) and *iso*-butyl 2-aminobutyrate (prepared following General Procedure BJ above), the title compound was prepared. The reaction was monitored by tlc on silica gel and purification was by filtration as described in the general procedure.

20

NMR data was as follows:

^1H -nmr ($CDCl_3$): δ = 6.89 (m, 3H), 6.07 (bd, 1H), 4.50 (m, 1H), 3.82 (m, 2H), 3.71 (s, 2H), 1.85 (m, 2H), 1.62 (m, 1H), 0.81 (d, 6H), 0.75 (t, 3H).

25

$C_{14}H_{21}NO_3S$ (MW = 283.39, Mass Spectroscopy (MH^+ 284)).

Example B34

30

Synthesis of 2-(phenylacetamido)butyric acid *iso*-butyl ester

Following General Procedure BH above and using phenylacetic acid (Aldrich) and *iso*-butyl 2-aminobutyrate (prepared following General Procedure

-- 212 --

BJ above), the title compound was prepared. The reaction was monitored by tlc on silica gel and purification was by chromatography on silica gel using 9:1 toluene:EtOAc as the eluant.

NMR data was as follows:

5 ^1H -nmr (CDCl_3): δ = 7.17-7.28 (m, 5H), 6.23 (bd, 1H), 4.51 (m, 1H), 3.86 (m, 2H), 3.54 (s, 2H), 1.87 (m, 2H), 1.62 (m, 1H), 0.87 (d, 6H), 0.78 (t, 3H).

$\text{C}_{16}\text{H}_{23}\text{NO}_3$ (MW = 277.36, Mass Spectroscopy (MH^+ 277)).

10

Example B35

Synthesis of *N*-(phenylacetyl)valine 2-methylbutyl ester

Step A. Preparation of *N*-(phenylacetyl) valine

To a stirred solution of 5.15 g (44 mmol) of valine (Bachem) in 50 mL (100 mmol) of 2N NaOH cooled to 0°C was added dropwise 5.3 mL (40 mmol) of phenylacetyl chloride (Aldrich). A colorless oil precipitated. The reaction mixture was allowed to warm to room temperature and stirred for 18 hours, washed with 50 mL diethyl ether, acidified to pH 2-3 with aqueous HCl. The white precipitate formed was filtered off, washed thoroughly with water, followed by diethyl ether to give 7.1 g (30 mmol, 69% yield) of the title compound.

20

NMR data was as follows:

^1H -nmr ($\text{DMSO}-d_6$): δ = 12.63 (s, 1H), 8.25 (d, J = 8.6 Hz, 1H), 7.27 (m, 5H), 4.15 (m, 1H), 3.56 (d, J = 13.8 Hz, 1H), 3.47 (d, J = 13.8 Hz, 1H), 2.05 (m, 1H), 0.87 (d, J = 6.8 Hz, 3H), 0.84 (d, J = 6.8 Hz, 3)

25

^{13}C -nmr ($\text{DMSO}-d_6$): δ = 173.2, 170.4, 136.6, 129.0, 128.2, 126.3, 57.1, 41.9, 30.0, 19.2, 18.0

$\text{C}_{13}\text{H}_{17}\text{NO}_3$ (MW=235.29; Mass Spectroscopy (MH^+ = 236))

Step B. Synthesis of *N*-(phenylacetyl)valine 2-methylbutyl ester

30

Following General Procedure BC and using the *N*-(phenylacetyl) valine prepared in Step A above and 2-methylbutan-1-ol (Aldrich), the title compound

was prepared as a diastereomeric mixture. The reaction was monitored by tlc on silica gel and purification was by filtration as described in the general procedure.

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 7.25-7.40 (m, 5H), 5.95 (d, 1H), 4.56 (m, 1H),
5 3.84-4.00 (m, 2H), 3.61 (s, 2H), 2.10 (m, 1H), 1.68 (m, 1H), 1.38 (m, 1H), 1.15
(m 1H), 0.82-0.94 (m, 9H), 0.76 (d, 3H).

¹³C-nmr (CDCl₃): δ = 171.84, 171.81, 170.7, 134.6, 129.31, 129.27,
128.9, 127.3, 69.8, 57.0, 43.7, 33.9, 31.3, 25.9, 25.8,, 18.9, 17.4, 16.34, 16.27,
11.12, 11.07.

10 C₁₈H₂₇NO₃ (MW = 305.42, Mass Spectroscopy (MH 306)).

Example B36

Synthesis of *N*-(phenylacetyl)-L-methionine *iso*-butyl ester

L-Methionine (0.129g, 0.869 mmols) (Aldrich) was taken-up in dioxane
15 (5.0 mL) and treated with a saturated solution of sodium bicarbonate (5.0 mL)
followed by phenylacetyl chloride (Aldrich) (0.114 mL, 0.822 mmols). After
stirring for 17 hours at room temperature the mixture was diluted with ethyl
acetate, the layers separated and the aqueous layer acidified to pH 2 with 5N
HCl. The crude product was extracted into ethyl acetate, dried over sodium
20 sulfate, vacuum dried and used without further purification.

N-Phenylacetyl-L-methionine (0.1285 g, 0.447 mmol) was dissolved in
3.0 mL dioxane and *iso*-butyl alcohol (0.2 mL) and treated with EDC (0.094 g,
0.492 mmol), and catalytic DMAP (0.015g). After stirring for 17 hours at
25 23°C, the mixture was evaporated at reduced pressure to an oil, the residue was
diluted in EtOAc and washed with 0.1 N HCl and saturated sodium bicarbonate.
Chromatography on silica gel using 98:2 CHCl₃/MeOH as eluant provided the
pure product.

NMR data was as follows:

-- 214 --

^1H -nmr (CDCl_3): δ = 7.4-7.23 (m, 5H), 6.14 (bd, 1H), 4.70 (m, 1H), 3.89 (d, 2H), 3.62 (s, 2H), 2.43 (m, 2H), 2.12 (m, 1H), 1.93 (m, 2H), 0.94 (d, 6H).

$\text{C}_{17}\text{H}_{25}\text{NO}_3\text{S}$ (MW = 323.17, Mass Spectroscopy (M^+ 323))

5

Example B37

Synthesis of *N*-(phenylacetyl)-L-leucine *iso*-butyl ester

L-Leucine (Aldrich) (0.114g, 0.869 mmols) was taken-up in dioxane (5.0 mL) and treated with a saturated solution of sodium bicarbonate (5.0 mL) followed by phenylacetyl chloride (Aldrich) (0.114 mL, 0.822 mmols). After stirring for 17 hours at room temperature the mixture was diluted with ethyl acetate, the layers separated and the aqueous layer acidified to pH 2 with 5N HCl. The crude product was extracted into ethyl acetate, dried over sodium sulfate, vacuum dried and used without further purification.

15

N-Phenylacetyl-L-leucine (0.0081 g, 0.038 mmol) was dissolved in 2.0 mL CHCl_3 (EtOH free) and *iso*-butyl alcohol (0.055 mL) and treated with P-EPC (100 mg, 0.87 milliequivalents). The mixture was rotated for 4 days, filtered through a plug of cotton and the filtrate evaporated at reduced pressure to an oil which was sufficiently pure for testing.

20

NMR data was as follows:

^1H -nmr (CDCl_3): δ = 7.22 (m, 5H), 5.57 (d, 1H), 4.35 (m, 1H), 3.35 (m, 3H), 1.35 (m, 4H), 0.68 (m, 9H).

$\text{C}_{18}\text{H}_{27}\text{NO}_3$ (MW = 305.40, Mass Spectroscopy (M^+ 305)).

25

Example B38

Synthesis of *N*-[(3-chlorophenyl)acetyl]alanine 3-methylbut-2-enyl ester

Following General Procedure BC above and using *N*-(3-chlorophenylacetyl) alanine (from Example BD above) and 3-methylbut-2-en-1-ol (Aldrich), the title compound can be prepared. The reaction was monitored by

30

-- 215 --

tlc on silica gel and purification was by liquid chromatography using 30% EtOAc/hexane as the eluant.

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 7.39-7.16 (m, 4H), 6.06 (bd, 1H), 5.38-5.29 (m, 1H), 4.63 (d, *J* = 9Hz, 2H), 3.56 (s, 2H), 1.79 (s, 3H), 1.7 (s, 3H), 1.39 (d, *J* = 9Hz, 3H).

Example B39

Synthesis of *N*-[(3-chlorophenyl)acetyl]alanine cyclopropylmethyl ester

Following General Procedure BC above, and using *N*-(3-chlorophenyl)acetyl alanine (from Example BD above) and cyclopropylmethanol (Aldrich), the title compound can be prepared. The reaction was monitored by tlc on silica gel and purification was by liquid chromatography using 3:7 EtOAc:hexane as the eluant.

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 7.2-7.1 (m, 4H), 6.09 (bs, 1H), 4.6 (dq, *J* = 9 Hz, 1H), 3.96 (dd, *J* = 9Hz, 2H), 3.59 (s, 2H), 1.2 (d, *J* = 9Hz, 3H), 1.2-1.0 (m, 1H), 0.603-0.503 (m, 2H), 0.300-0.203 (m, 2H).

20

Example B40

Synthesis of *N*-[(3-chlorophenyl)acetyl]alanine 2-thienylmethyl ester

Following General Procedure BC above, and using *N*-(3-chlorophenyl)acetyl alanine (from Example BD above) and 2-thiophenemethanol (Aldrich) the title compound can be prepared. The reaction was monitored by tlc on silica gel and purification was by liquid chromatography using 3:7 EtOAc:hexane as the eluant.

25

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 7.37-6.97 (m, 7H), 5.97 (q, *J* = 14 Hz, 2H), 4.6 (dq, *J* = 9 Hz, 1H), 3.76 (s, 2H), 1.38 (d, *J* = 9Hz, 3H).

30

Example B41

-- 216 --

**Synthesis of *N*-[(3-chlorophenyl)acetyl]alanine
(1-methylcyclopropyl)methyl ester**

Following General Procedure BC above, and using *N*-(3-chlorophenyl)acetyl alanine (from Example BD above) and (1-methylcyclopropyl)methanol (Aldrich) the title compound can be prepared. The reaction was monitored by tlc on silica gel and purification was by liquid chromatography using 3:7 EtOAc:hexane as the eluant.

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 8.6 (bd, *J* = 9 Hz, 1H), 3.86 (q, *J* = 14 Hz, 2H), 3.4 (s, 2H), 2.29 (q, *J* = 9 Hz, 1H), 1.3 (d, *J* = 9 Hz, 3H), 1.03 (s, 3H), 0.5-0.4 (m, 2H), 0.4-0.28 (m, 2H).

Example B42

Synthesis of *N*-[(3-chlorophenyl)acetyl]alanine 3-thienylmethyl ester

Following General Procedure BC above, and using *N*-(3-chlorophenyl)acetyl alanine (from Example BD above) and 3-thiophenemethanol (Aldrich) the title compound can be prepared. The reaction was monitored by tlc on silica gel and purification was by liquid chromatography using 3:7 EtOAc:hexane as the eluant.

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 8.03 (bd, *J* = 9 Hz, 1H), 7.56-7.5 (m, 1H), 7.47 (bs, 1H), 7.4-7.17 (m, 4H), 7.06 (d, *J* = 9 Hz, 1H), 5.1 (s, 2H), 4.3 (dq, 1H), 1.3 (d, *J* = 9 Hz, 3H).

25

Example B43

Synthesis of *N*-[(3-chlorophenyl)acetyl]alanine 2-methylcyclopentyl ester

Following General Procedure BC above, and using *N*-(3-chlorophenyl)acetyl alanine (from Example BD above) and 2-methylcyclopentanol (Aldrich) the title compound can be prepared. The reaction was monitored by tlc on silica gel and purification was by liquid chromatography using 3:7 EtOAc:hexane as the eluant.

NMR data was as follows:

-- 217 --

¹H-nmr (CDCl₃): δ = 7.39-7.16 (m, 4H), 6.3 (bd, 1H), 4.79-4.7 (m, 1H), 4.6-4.25 (m, J = 9 Hz, 1H), 3.577 (s, 2H), 2.09-1.8 (m, 2H), 1.74-1.6 (m, 2H), 1.39 (dd, J = 9 Hz, 3H), 1.2 (dt, J = 9 Hz, 1H), 0.979 (dd, J = 9 Hz, 2H)
C₁₇H₂₂NO₃Cl (MW = 323.82, Mass Spectroscopy (MH⁺ 323)).

5

Example B44

Synthesis of N-[(3-chlorophenyl)acetyl]alanine 2-methylprop-2-enyl ester

Following General Procedure BC above, and using N-(3-chlorophenyl)acetyl alanine (from Example BD above) and 2-methylprop-2-en-1-ol (Aldrich) the title compound can be prepared. The reaction was monitored by
10 tlc on silica gel and purification was by liquid chromatography using 3:7 EtOAc:hexane as the eluant.

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 7.39-7.16 (m, 4H), 6.03 (bs, 1H), 4.77 (s, 2H), 4.7-
15 4.29 (m, 3H), 2.59 (s, 2H), 1.73 (s, 3H), 1.43 (d, J = 9 Hz, 3H)
C₁₅H₁₈NO₃Cl (MW = 295.76, Mass Spectroscopy (MH⁺ 295)).

Example B45

Synthesis of N-[(3-chlorophenyl)acetyl]alanine cyclohex-2-enyl ester

Following General Procedure BC above, and using N-(3-chlorophenyl)acetyl alanine (from Example BD above) and cyclohex-2-en-1-ol (Aldrich) the title compound can be prepared. The reaction was monitored by
20 tlc on silica gel and purification was by liquid chromatography using 3:7 EtOAc:hexane as the eluant.

25 NMR data was as follows:

¹H-nmr (CDCl₃): δ = 8.6 (bd, J = 9 Hz, 1H), 7.4-7.2 (m, 4H), 6.0-5.8 (m, 1H), 5.7-5.5 (m, 1H), 5.1 (bs, 1H), 4.13-4.29 (m, 1H), 3.5 (s, 2H), 2.1-1.9 (m, 2H), 1.8-1.69 (m, 1H), 1.69-1.49 (m, 4H), 1.3 (dd, J = 9 Hz, 3H)
C₁₇H₂₀NO₃Cl (MW = 321.8, Mass Spectroscopy (MH⁺ 321.2)).

30

Example B46

-- 218 --

Synthesis of *N*-[(2-phenylbenzoxazol-5-yl)acetyl]alanine *iso*-butyl ester

Following General Procedure BI above, and using 5-(2-phenylbenzoxazol-5-yl)-acetic acid (CAS# 62143-69-5) and alanine *iso*-butyl ester (prepared following General Procedure BJ above), the title compound was prepared.

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 8.24 (m, 3H), 7.68 (m, 1H), 7.51 (m, 5H), 6.04 (m, 1H), 4.58 (m, 1H), 3.85 (m, 2H), 3.68 (s, 2H), 1.9 (m, 1H), 1.35 (d, 3H), 0.87 (d, 6H).

C₂₂H₂₄N₂O₄ (MW = 380, Mass Spectroscopy (MH⁺ 381)).

Example B47**Synthesis of *N*-[(3-methylthiophenyl)acetyl]alanine *iso*-butyl ester**

Following General Procedure BI above, and using 3-methylthiophenylacetic acid (CAS# 18698-73-2) and alanine *iso*-butyl ester (prepared following General Procedure BJ above), the title compound was prepared. The reaction was monitored by tlc on silica gel and purification was by filtration as described in the general procedure.

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 7.14 (m, 2H), 7.01 (m, 1H), 4.56 (m, 1H), 3.88 (m, 2H), 3.54 (s, 2H), 2.46 (s, 3H), 1.89 (m, 1H), 1.35 (d, 3H) 0.85 (d, 6H).

C₁₆H₂₃NO₃S (MW = 309, Mass Spectroscopy (MH⁺ 310)).

Example B48**Synthesis of *N*-4-[(2-furyl)acetyl]alanine *iso*-butyl ester**

Following General Procedure BI above, and using 2-furylacetic acid (CAS# 2745-26-8) and alanine *iso*-butyl ester (prepared following General Procedure BJ above), the title compound was prepared. The reaction was monitored by tlc on silica gel and purification was by filtration as described in the general procedure.

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 7.36 (m, 1H), 6.34 (m, 1H), 6.21 (m, 1H), 4.56 (m, 1H), 3.91 (m, 2H), 3.61 (s, 2H), 1.92 (m, 1H), 1.38 (d, 3H) 0.89 (d, 6H).

C₁₃H₁₉NO₄ (MW = 253, Mass Spectroscopy (MH⁺ 254)).

5

Example B49

Synthesis of *N*-[(benzofuran-2-yl)acetyl]alanine *iso*-butyl ester

Following General Procedure BI above, and using benzofuran-2-ylacetic acid (Maybridge) and alanine *iso*-butyl ester (prepared following General Procedure BJ above), the title compound was prepared. The reaction was monitored by tlc on silica gel and purification was by filtration as described in the general procedure.

10

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 7.51 (m, 1H), 7.44 (m, 1H), 7.25 (m, 2H), 6.67 (s, 1H), 4.60 (m, 1H), 3.87 (m, 2H), 3.77 (s, 2H), 1.88 (m, 1H), 1.38 (d, 3H), 0.87 (d, 6H).

15

C₁₇H₂₁NO₄ (MW = 303, Mass Spectroscopy (MH⁺ 304)).

Example B50

Synthesis of *N*-[(benzothiophen-3-yl)acetyl]alanine *iso*-butyl ester

Following General Procedure BI above, and using thianaphthen-3-ylacetic acid (Lancaster) and alanine *iso*-butyl ester (prepared following General Procedure BJ above), the title compound was prepared. The reaction was monitored by tlc on silica gel and purification was by filtration as described in the general procedure.

20

25

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 7.89 (m, 1H), 7.76 (m, 1H), 7.38 (m, 3H), 6.07 (m, 1H), 4.57 (m, 1H), 3.92 (m, 2H), 3.82 (s, 4H), 1.84 (m, 1H), 1.32 (d, 3H) 0.85 (d, 6H).

C₁₇H₂₁NO₃S (MW = 319, Mass Spectroscopy (MH⁺ 320)).

30

Example B51

Synthesis of *N*-[(2-chloro-5-thienyl)acetyl]alanine *iso*-butyl ester

Following General Procedure BI above, and using 5-chloro-2-thienyl)acetic acid (CAS# 13669-19-7) and alanine *iso*-butyl ester (prepared following General Procedure BJ above), the title compound was prepared. The reaction was monitored by tlc on silica gel and purification was by filtration as described in the general procedure.

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 6.77 (m, 1H), 6.68 (d, 1H), 6.31 (bm, 1H), 4.59 (m, 1H), 3.91 (m, 2H), 3.38 (s, 2H), 1.90 (m, 1H), 1.39 (d, 3H) 0.89 (d, 6H).

C₁₃H₁₈NO₃SCl (MW = 303, Mass Spectroscopy (MH⁺ 303)).

Example B52**Synthesis of *N*-[(3-methylisoxazol-5-yl)acetyl]alanine *iso*-butyl ester**

Following General Procedure BI above, and using (3-methyl-isoxazol-5-yl)acetic acid (CAS# 19668-85-0) and alanine *iso*-butyl ester (prepared following General Procedure BJ above), the title compound was prepared. The reaction was monitored by tlc on silica gel and purification was by filtration as described in the general procedure.

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 6.07 (s, 2H), 4.56 (m, 1H), 3.92 (m, 2H), 3.68 (s, 2H), 2.29 (s, 3H), 1.94 (m, 1H), 1.89 (d, 3H) 0.91 (d, 6H).

C₁₃H₂₀N₂O₄ (MW = 268, Mass Spectroscopy (MH⁺ 269)).

Example B53**Synthesis of *N*-[(2-phenylthiothienyl)acetyl]alanine *iso*-butyl ester**

Following General Procedure BI above, and using (2-phenyl-thiothienyl)acetic acid and alanine *iso*-butyl ester (prepared following General Procedure BJ above), the title compound was prepared. The reaction was monitored by tlc on silica gel and purification was by filtration as described in the general procedure.

NMR data was as follows:

-- 221 --

¹H-nmr (CDCl₃): δ = 7.21-7.11 (m, 6H), 6.92 (d, 1H), 4.56(m, 1H), 3.87 (m, 2H), 3.72 (s, 2H), 1.94 (m, 1H), 1.38 (d, 3H) 0.89 (d, 6H).

C₁₉H₂₃NO₃S₂ (MW = 377, Mass Spectroscopy (MH⁺ 378)).

5

Example B54

Synthesis of *N*-[(6-methoxybenzothiophen-2-yl)acetyl]alanine *iso*-butyl ester

Following General Procedure BI above, and using (6-methoxythianaphthen-2-yl)acetic acid and alanine *iso*-butyl ester (prepared following General Procedure BJ above), the title compound was prepared. The reaction was monitored by tlc on silica gel and purification was by filtration as described in the general procedure.

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 7.59 (d, 1H), 7.33 (d, 1H), 7.16 (s, 1H), 7.03 (dd, 1H), 4.56 (m, 1H), 3.87(s, 3H), 3.84 (m, 2H), 3.76 (s, 2H), 1.85 (m, 1H), 1.30 (d, 3H) 0.86 (d, 6H).

C₁₈H₂₃NO₄S (MW = 349, Mass Spectroscopy (MH⁺ 350)).

Example B55

Synthesis of *N*-[(3-phenyl-1,2,4-thiadiazol-5-yl)acetyl]alanine *iso*-butyl ester

Following General Procedure BI above, and using (3-phenyl-1,2,4-thiadiazol-5-yl)acetic acid (CAS# 90771-06-5) and alanine *iso*-butyl ester (prepared following General Procedure BJ above), the title compound was prepared. The reaction was monitored by tlc on silica gel and purification was by filtration as described in the general procedure.

25

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 7.47 (m, 5H), 4.66 (m, 1H), 4.16 (s, 2H), 3.91 (m, 2H), 1.93 (m, 1H), 1.48 (d, 3H) 0.93 (d, 6H).

C₁₇H₂₁N₃O₃S (MW = 347, Mass Spectroscopy (MH⁺ 348)).

30

Example B56

Synthesis of *N*-[2-phenyloxazol-4-yl)acetyl]alanine *iso*-butyl ester

-- 222 --

Following General Procedure BI above, and using (2-phenyloxazol-4-yl)acetic acid (CAS# 22086-89-1) and alanine *iso*-butyl ester (prepared following General Procedure BJ above), the title compound was prepared. The reaction was monitored by tlc on silica gel and purification was by filtration as described in the general procedure.

Example B57

Synthesis of *N*-[(3-methylphenyl)acetyl]alanine *iso*-butyl ester

Following General Procedure BI above, and using 3-methylphenylacetic acid (Aldrich) and alanine *iso*-butyl ester (prepared following General Procedure BJ above), the title compound was prepared. The reaction was monitored by tlc on silica gel and purification was by filtration as described in the general procedure.

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 7.21 (m, 1H), 7.07 (m, 3H), 4.54 (m, 1H), 3.83 (m, 2H), 3.52 (s, 2H), 2.35 (s, 3H), 1.87 (m, 1H), 1.32 (d, 3H), 0.88 (d, 6H).

C₁₆H₂₃NO₃ (MW = 277, Mass Spectroscopy (MH⁺ 278)).

Example B58

Synthesis of *N*-[(2,5-difluorophenyl)acetyl]alanine *iso*-butyl ester

Following General Procedure BI above, and using 2,5-difluorophenylacetic acid (Aldrich) and alanine *iso*-butyl ester (prepared following General Procedure BJ above), the title compound was prepared. The reaction was monitored by tlc on silica gel and purification was by filtration as described in the general procedure.

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 7.08-6.94 (m, 3H), 4.57 (m, 1H), 3.91 (m, 2H), 3.56 (s, 2H), 1.92 (m, 1H), 1.41 (d, 3H) 0.91 (d, 6H).

C₁₅H₁₉NO₃F₂ (MW = 299, Mass Spectroscopy (MH⁺ 300)).

Example B59

Synthesis of *N*-[(3,5-difluorophenyl)acetyl]alanine *iso*-butyl ester

Following General Procedure BI above, and using 3,5-difluorophenylacetic acid (Aldrich) and alanine *iso*-butyl ester (prepared following General Procedure BJ above), the title compound was prepared. The reaction was monitored by tlc on silica gel and purification was by filtration as described in the general procedure.

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 6.81 (m, 2H), 6.74 (m, 1H), 6.06 (m, 1H), 4.57 (m, 1H), 3.92 (m, 2H), 3.51 (s, 2H), 1.94 (m, 1H), 1.36 (d, 3H) 0.87 (d, 6H).

C₁₅H₁₉NO₃F₂ (MW = 299, Mass Spectroscopy (MH⁺ 300)).

Example B60**Synthesis of *N*-[(3-thienyl)acetyl]alanine *iso*-butyl ester**

Following General Procedure BI above, and using 3-thiopheneacetic acid (Aldrich) and alanine *iso*-butyl ester (prepared following General Procedure BJ above), the title compound was prepared. The reaction was monitored by tlc on silica gel and purification was by filtration as described in the general procedure.

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 7.33 (m, 1H), 7.14 (m, 1H), 7.01 (m, 1H), 6.09 (m, 1H), 4.58 (m, 1H), 3.88 (m, 2H), 3.60 (s, 2H), 1.91 (m, 1H), 1.37 (d, 3H) 0.92 (d, 6H).

Optical Rotation: [α]₂₃ -52 (c 1 MeOH) @ 589 nm.

C₁₃H₁₉NO₃S (MW = 269, Mass Spectroscopy (MH⁺ 269)).

Example B61**Synthesis of *N*-[(4-methylphenyl)acetyl]-L-alanine *iso*-butyl ester**

Following General Procedure BI above, and using 4-methylphenylacetic acid (Aldrich) and L-alanine *iso*-butyl ester (prepared following General Procedure BJ above), the title compound was prepared. The reaction was monitored by tlc on silica gel and purification was by filtration as described in the general procedure.

-- 224 --

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 7.11 (s, 4H), 5.93 (m, 1H), 4.58 (m, 1H), 3.88 (m, 2H), 3.54 (s, 2H), 2.33 (s, 3H), 1.89 (m, 1H), 1.32 (d, 3H), 0.89 (d, 6H).

C₁₆H₂₃NO₃ (MW = 277.35, Mass Spectroscopy (MH⁺ 278)).

5

Example B62

Synthesis of *N*-(phenylacetyl)-L-alanine S-1-(methoxycarbonyl) *iso*-butyl ester

Following General Procedure BK and using (S)-(+)-2-hydroxy-2-methylbutyric acid (Aldrich) in place of the amino acid, methyl (S)-(+)-2-hydroxy-2-methylbutyrate was prepared.

Methyl (S)-(+)-2-hydroxy-2-methylbutyrate was then coupled with carbobenzyloxy-L-alanine (Aldrich) using General Procedure BE to provide carbobenzyloxy-L-alanine S-1-(methoxycarbonyl) *iso*-butyl ester.

15 Carbobenzyloxy-L-alanine S-1-(methoxycarbonyl) *iso*-butyl ester (1.0 g) was then dissolved in 20 mL of methanol and 6N HCl (0.5 mL) and 10% palladium on carbon (0.1 g) were added. This reaction mixture was hydrogenated at 40 psi of hydrogen on a Parr apparatus for 5 hours at room temperature and then filtered through a pad of Celite. The filtrate was
20 concentrated at reduced pressure to provide L-alanine S-1-(methoxycarbonyl) *iso*-butyl ester hydrochloride (98% yield).

L-Alanine S-1-(methoxycarbonyl) *iso*-butyl ester hydrochloride was then coupled to phenylacetic acid using General Procedure BG to provide the title compound.

25 NMR data was as follows:

¹H-nmr (CDCl₃): δ = 7.35 - 7.20 (m, 5H), 6.22 (bd, 1H), 4.83 (d, 1H), 4.65 (p, 1H), 3.68 (s, 3H), 3.55 (s, 2H), 2.21 (m, 1H), 1.40 (d, 3H), 0.97 (d, 3H), 0.93 (d, 3H).

¹³C-nmr (CDCl₃): δ = 173.25, 171.18, 170.22, 135.11, 129.94, 129.50,
30 127.88, 52.67, 48.49, 43.98, 30.53, 19.21, 18.75, 17.58.

Example B63

Synthesis of *N*-[(3-nitrophenyl)acetyl]-L-alanine *iso*-butyl ester

Following General Procedure BH above and using 3-nitrophenylacetic acid (Aldrich) and L-alanine *iso*-butyl ester hydrochloride (from Example BB above), the title compound was prepared. The reaction was monitored by tlc on silica gel and purification was by recrystallization from butyl chloride.

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 8.17 (m, 2H), 7.68 (d, 1H), 7.52 (t, 1H), 6.18 (m, 1H), 4.48 (m, 1H), 3.94 (m, 2H), 3.67 (s, 2H), 1.93 (m, 1H), 1.42 (d, 3H), 0.91 (d, 3H).

Optical Rotation: [α]₂₃ -49 (c 5, MeOH).

Example B64**Synthesis of *N*-[(3,5-difluorophenyl)acetyl]alanine ethyl ester**

Following General Procedure BG and using 3,5-difluorophenylacetic acid (Aldrich) and alanine ethyl ester (Aldrich), the title compound was prepared as a solid with a melting point of 93°-95°C. The reaction was monitored by tlc on silica gel (R_f = 0.8 in EtOAc) and purification was by chromatography on silica gel using EtOAc as the eluant followed by recrystallization from 1-chlorobutane.

NMR data was as follows:

¹H-nmr (DMSO-*d*₆): δ = 1.30 (d, 3H); 3.52 (s, 2H).

C₁₃H₁₅NO₃F₂ (MW = 271.26, Mass Spectroscopy (MH⁺ 271)).

Example B65**Synthesis of *N*-[(3-nitrophenyl)acetyl]methionine ethyl ester**

Following General Procedure BG above and using 3-nitrophenylacetic acid (Aldrich) and methionine ethyl ester hydrochloride (Aldrich), the title compound was prepared. The reaction was monitored by tlc on silica gel and purification was by recrystallization from butyl chloride.

NMR data was as follows:

-- 226 --

¹H-nmr (CDCl₃): δ = 8.18 (s, 1H), 8.15 (d, 1H), 7.66 (d, 1H), 7.48 (t, 1H), 6.30 (m, 1H), 4.67 (m, 1H), 4.21 (t, 2H), 3.67 (s, 2H), 2.47 (t, 2H), 2.12 (m, 2H), 2.08 (s, 3H), 1.27 (t, 3H).

Optical Rotation: [α]₂₃ -30 (c 5, MeOH).

5

Example B66

Synthesis of *N*-[(3-chlorophenyl)acetyl]alanine *iso*-butyl ester

Following General Procedure BG above and using 3-chlorophenylacetic acid (Aldrich) and alanine *iso*-butyl ester (prepared following General Procedure BJ above), the title compound was prepared. The reaction was monitored by tlc on silica gel.

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 7.29 (m, 3H), 7.18 (m, 1H), 6.0 (m, 1H), 4.56 (m, 1H), 3.89 (m, 2H), 3.53 (s, 2H), 1.91 (m, 1H), 1.39 (d, 3H), 0.91 (d, 3H).

15

Optical Rotation: [α]₂₃ -45 (c 5, MeOH).

C₁₅H₂₀NO₃Cl (MW = 297.78, Mass Spectroscopy (MH⁺ 297)).

Example B67

Synthesis of *N*-[(3-chlorophenyl)acetyl]alanine 2-(*N,N*-dimethylamino)ethyl ester

20

Following General Procedure BC above, and using *N*-(3-chlorophenyl)acetyl)alanine (from Example BD above) and 2-(*N,N*-dimethyl amino) ethanol (Aldrich), the title compound can be prepared. The reaction was monitored by tlc on silica gel and purification was by liquid chromatography using 0.1:2:0.79 NH₄OH:EtOH:CHCl₃ as the eluant.

25

NMR data was as follows:

¹H-nmr (CDCl₃): 7.37 (s, 1H), 7.33-7.2 (m, 3H), 4.675-4.6 (m, 1H), 4.5-4.37 (m, 1H), 4.25-4.13 (m, 1H), 3.6 (d, *J* = 7 Hz, 2H), 2.86 (bs, 2H), 2.3 (s, 6H), 1.23 (d, *J* = 9 Hz, 3H).

30

C₁₅H₂₁N₂O₃Cl (MW = 313.799, Mass Spectroscopy (M⁺ 313)).

Example B68

Synthesis of 2-[(3,5-dichlorophenyl)acetamido]hexanoic acid methyl ester

Following General Procedure BF above, and using 3,5-dichlorophenylacetic acid (from Example BC above) and L-norleucine methyl ester hydrochloride (Bachem), the title compound was prepared as a solid having a melting point of 77°-78°C. The reaction was monitored by tlc on silica gel (R_f = 0.70 in 40% EtOAc/hexanes) and purification was by flash chromatography on silica gel using 40% EtOAc/hexanes as the eluant.

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 7.20 (s), 7.18 (s), 6.6 (m), 4.55 (m), 3.7 (s), 3.5 (s), 3.4 (s), 2.0 (s), 1.8 (m), 1.6 (m), 1.2 (m), 0.8 (t).

¹³C-nmr (CDCl₃): δ = 173.54, 169.67, 138.43, 135.72, 128.33, 128.07, 78.04, 77.62, 77.19, 53.04, 52.90, 43.14, 32.57, 27.87, 22.81, 14.41.

Example B69**Synthesis of N-[(3,5-dichlorophenyl)acetyl]-L-alanine *iso*-butyl ester**

Following General Procedure BF above, and using 3,5-dichlorophenylacetic acid (from Example BC above) and L-alanine *iso*-butyl ester hydrochloride (from Example BB above), the title compound was prepared as a solid having a melting point of 115°-116°C. The reaction was monitored by tlc on silica gel (R_f = 0.40 in 3% methanol/dichloromethane) and purification was by flash chromatography on silica gel using 3% methanol/dichloromethane as the eluant.

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 7.27 (d, *J* = 2 Hz, 1H), 7.19 (s, 2H), 6.22 (d, *J* = 6 Hz, 1H), 4.59 (quint., *J* = 7 Hz, 1H), 3.9 (q, *J* = 4 Hz, 2H), 3.5 (s, 2H), 1.9 (m, 1H), 1.4 (d, *J* = 7 Hz, 3H), 0.91 (d, *J* = 7 Hz, 6H).

¹³C-nmr (CDCl₃): δ = 173.45, 169.37, 138.31, 135.75, 128.39, 128.11, 78.04, 77.61, 77.19, 72.19, 54.03, 48.97, 43.12, 28.24, 19.52, 19.49, 19.09.

C₁₅H₁₉NO₃Cl₂ (MW = 331.9, Mass Spectroscopy (MH⁺ 332)).

Example B70

Synthesis of *N*-(cyclohexylacetyl)-L-alanine *iso*-butyl ester

Following General Procedure BB above, and using cyclohexylacetic acid (Aldrich) and L-alanine *iso*-butyl ester hydrochloride (from Example BB above), the title compound was prepared as a solid having a melting point of 92°C-

5 93°C. The reaction was monitored by tlc on silica gel ($R_f = 0.39$ in 1:3 EtOAc:hexane) and purification was by extraction with Et₂O followed by washes with aqueous K₂CO₃ and aqueous HCl.

NMR data was as follows:

¹H-nmr (CDCl₃): $\delta = 0.93$ (d, $J = 6.7$ Hz, 6H), 0.85-1.01 (m, 2H), 1.05-1.35 (m, 3H), 1.40 (d, $J = 7.1$ Hz, 3H), 1.60-1.85 (m, 6H), 1.95 (m, 1H), 2.06 (d, $J = 7.0$ Hz, 2H), 3.92 (m, 2H), 4.61 (m, 1H), 6.08 (bd, 1H).

¹³C-nmr (CDCl₃): $\delta = 18.7, 18.9, 26.0, 26.1, 27.6, 33.0, 35.3, 44.6, 47.9, 71.4, 171.8, 173.3$.

C₁₅H₂₇NO₃ (MW = 269.39, Mass Spectroscopy (MH⁺ 270)).

15

Example B71**Synthesis of *N*-(cyclopentylacetyl)-L-alanine *iso*-butyl ester**

Following General Procedure BB above, and using cyclopentylacetic acid (Aldrich) and L-alanine *iso*-butyl ester hydrochloride (from Example BB above), the title compound was prepared as a solid having a melting point of 62°C-64°C. The reaction was monitored by tlc on silica gel ($R_f = 0.37$ in 1:3 EtOAc:hexane) and purification was by extraction with Et₂O followed by washes with aqueous K₂CO₃ and aqueous HCl.

25 NMR data was as follows:

¹H-nmr (CDCl₃): $\delta = 0.87$ (d, $J = 6.8$ Hz, 6H), 1.01-1.17 (m, 2H), 1.34 (d, $J = 7.2$ Hz, 3H), 1.40-1.62 (m, 4H), 1.70-1.83 (m, 2H), 1.89 (m, 1H), 2.15 (m, 3H), 3.86 (m, 2H), 4.55 (m, 1H), 6.30 (d, $J = 7.1$ Hz, 1H).

¹³C-nmr (CDCl₃): $\delta = 18.4, 18.78, 18.80, 24.8$ (very high), 27.5, 32.27, 32.32, 36.9, 42.5, 47.7, 71.2, 172.2, 173.2.

30 Elemental Analysis-Calcd (%): C, 65.85; H, 9.87; N, 5.49; Found (%): C, 66.01; H, 10.08; N, 5.49.

-- 229 --

$C_{14}H_{25}NO_3$ (MW = 255.36, Mass Spectroscopy (MH^+ 256)).

Example B72

Synthesis of *N*-[(cyclohex-1-enyl)acetyl]-L-alanine *iso*-butyl ester

5 Following General Procedure BB above, and using cyclohex-1-enyl acetic acid (Alfa) and L-alanine *iso*-butyl ester hydrochloride (from Example BB above), the title compound was prepared as a solid having a melting point of 49°C-51°C. The reaction was monitored by tlc on silica gel (R_f = 0.40 in 1:3 EtOAc:hexane) and purification was by extraction with Et_2O followed by washes
10 with aqueous K_2CO_3 and aqueous HCl.

NMR data was as follows:

^1H -nmr ($CDCl_3$): δ = 0.91 (d, J = 4.5 Hz, 3H), 0.93 (d, J = 6.7 Hz, 3H), 1.40 (d, J = 7.2 Hz, 3H), 1.52-1.70 (m, 4H), 1.97 (m, 3H), 2.06 (bs, 2H), 2.89 (s, 2H), 3.92 (m, 2H), 4.59 (m, 1H), 5.65 (s, 1H), 6.33 (d, J = 6.6 Hz, 1H).

15 ^{13}C -nmr ($CDCl_3$): δ = 18.7, 18.91, 18.93, 21.9, 22.7, 25.3, 27.6, 28.3, 46.1, 47.9, 71.4, 127.1, 132.5, 170.6, 173.1.

Elemental Analysis-Calc (%): C, 67.38; H, 9.42; N, 5.24; Found (%): C, 67.34; H, 9.54; N, 5.16.

$C_{15}H_{25}NO_3$ (MW = 267.37, Mass Spectroscopy (MH^+ 268)).

20

Example B73

Synthesis of *N*-[(3-chlorophenyl)acetyl]alanine 3-methylbut-2-enyl thioester

Following General Procedure BC above, and using *N*-[(3-chlorophenyl)acetyl] alanine and 3-methyl-2-butene thioester (TCI), the title
25 compound can be prepared. The reaction was monitored by tlc on silica gel and purification was by liquid chromatography using 3:7 EtOAc:Hexane as the eluant.

NMR data was as follows:

30 ^1H -nmr ($DMSO-d_6$): δ = 5.2-5.075 (m, 1H), 4.37 (dq, J = 9 Hz, 1H), 3.56 (s), 3.43 (d, J = 12 Hz, 2H), 1.266 (d, J = 12 Hz, 6H) 1.3 (d, J = 9 Hz, 3H).

-- 230 --

$C_{16}H_{20}NO_2ClS$ (MW = 325.86, Mass Spectroscopy (M^+ 325)).

Example B74

Synthesis of *N*-[(2-phenyl)-2-fluoroacetyl]alanine ethyl ester

5 Following General Procedure BF above, and using α -fluorophenyl acetic acid (Aldrich) and alanine ethyl ester (Aldrich), the title compound was prepared. The reaction was monitored by tlc on silica gel (R_f = 0.75 in 1:1 EtOAc:hexane) and purification was by chromatography on silica gel using 1:2 ethyl acetate/hexanes as the eluent.

10 NMR data was as follows:

^1H -nmr (DMSO- d_6): δ = 1.14 (q, 3H), 1.34 (d, 3H), 4.07 (m, 2H), 4.33 (m, 1H), 5.84 (d, 1H), 6.01 (d, 1H), 7.40-7.55 (m, 5H), 8.87 (m, 1H).

$C_{13}H_{16}NO_3F$ (MW = 253.27, Mass Spectroscopy (MH^+ 253)).

15

Example B75

Synthesis of *N*-(3,5-difluorophenylacetyl)-L-phenylglycine methyl ester

Following General Procedure BF above, and using 3,5-difluorophenylacetic acid (Aldrich) and L-phenylglycine methyl ester hydrochloride (Bachem), the title compound was prepared.

20 NMR data was as follows:

^1H -nmr ($CDCl_3$): δ = 7.4-7.3 (m, 5H), 6.9-6.7 (m, 3H), 6.55 (d 1H, 7.1 Hz), 5.56 (d 1H 7 Hz), 3.72 (s 3H), 3.57 (s 2H)

^{13}C -nmr ($CDCl_3$): δ = 197.6, 177.6, 171.8, 169.3, 136.7, 129.6, 129.3, 127.8, 113.0, 112.9, 112.7, 111.4, 103.8, 103.5, 65.1, 57.2, 53.5, 45.1, 43.3,

25 43.3

$C_{17}H_{15}NO_3F_2$ (MW = 319.31, Mass Spectroscopy (MH^+ 320)).

Example B76

Synthesis of *N*-(3,5-difluorophenylacetyl)-L-phenylglycine *iso*-butyl ester

30 The 3,5-difluorophenylacetic acid (Aldrich) was EDC coupled to L-phenylglycine methyl ester hydrochloride (Bachem) via General Procedure BF

above. The resulting compound was placed in a large excess of the desired alcohol. A catalytic amount of dry NaH was added, and the reaction was followed by tlc until the presence of starting material was no longer detected. The reaction was quenched with a few milliliters of 1N HCl, and after a few
5 minutes of stirring saturated aqueous NaHCO₃ was added. The volume of the reaction mixture was reduced on a rotary evaporator until the excess alcohol was removed and then the remaining residue was taken up in ethyl acetate and additional water was added. The organic phase was washed with saturated aqueous NaCl and dried over MgSO₄. The solution was stripped free of solvent
10 on a rotary evaporator, and the crude product residue was then further purified by chromatography.

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 7.35-7.3 (m 5H), 6.8-6.7 (m 3H) 6.60 (d 1H, 7 Hz), 5.55 (d 1H 7.1 Hz), 3.9 (m 2H), 3.60 (s 2H), 1.85 (m 1H 7 Hz), 0.8 (q 6H
15 7 Hz)

¹³C-nmr (CDCl₃): δ = 171.3, 169.3, 165.4, 138.5, 137.0, 129.5, 129.2, 127.6, 113.1, 113.0, 112.8, 112.7, 103.8, 103.5, 103.2, 75.5, 57.2, 43.4, 43.3, 28.2, 19.3

C₂₀H₂₁NO₃F₂ (MW = 361.39, Mass Spectroscopy (MH +362)).

20

Example B77

Synthesis of *N*-(cyclopentylacetyl)-L-phenylglycine methyl ester

Following General Procedure BD above, and using cyclopentylacetic acid (Aldrich) with L-phenylglycine methyl ester hydrochloride (Bachem) the title
25 compound was prepared.

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 7.35 (s, 5H), 6.44 (bd, 1H), 5.6 (d, 1H), 3.72 (s, 3H), 2.24 (bs, 3H), 1.9-1.4 (m, 6H), 1.2-1.05 (m, 2H)

¹³C-nmr (CDCl₃): δ = 172.3, 171.7, 136.7, 129.0, 128.6, 127.3, 56.2,
30 52.7, 42.5, 36.9, 32.40, 32.38, 24.8

-- 232 --

Example B78

Synthesis of *N*-(cyclopentylacetyl)-L-alanine methyl ester

Following General Procedure BD above, and using cyclopentylacetic acid (Aldrich) with L-alanine methyl ester hydrochloride (Sigma) the title compound was prepared.

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 6.38 (d, 1H), 4.50 (m, 1H), 3.65 (s, 3H), 2.13 (bs, 3H), 1.80-1.00 (m (includes d at 1.30, 3H), 11H)

¹³C-nmr (CDCl₃): δ = 173.7, 172.5, 52.1, 47.6, 42.3, 36.8, 32.15, 32.14,

10 18.0

C₁₁H₁₉NO₃ (MW = 213.28, Mass Spectroscopy (MH⁺ 214)).

Example B79

Synthesis of *N*-(cyclopropylacetyl)-L-phenylglycine methyl ester

Following General Procedure BD above, and using cyclopropylacetic acid (Aldrich) with L-phenylglycine methyl ester hydrochloride (Bachem), the title compound was prepared.

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 7.35 (m, 5H) 6.97 (bd, *J* = 7.2 Hz, 1H) 5.59 (d, *J* = 7.8 Hz, 1H), 3.71 (s, 3H), 2.17 (m, 2H), 1.05-0.95 (m, 1H), 0.62 (m, 2H), 0.02 (m, 2H)

20

¹³C-nmr (CDCl₃): δ = 171.9, 174.6, 136.6, 129.0, 128.5, 127.2, 56.1, 52.7, 41.0, 6.9, 4.37, 4.33

25

Example B80

Synthesis of *N*-(cyclopropylacetyl)-L-alanine methyl ester

Following General Procedure BD above, and using cyclopropylacetic acid (Aldrich) with L-alanine methyl ester hydrochloride (Sigma), the title compound was prepared.

30

NMR data was as follows:

^1H -nmr (CDCl_3): δ = 6.60 (d, 1H), 4.55 (m, 1H), 3.69 (s, 3H), 2.10 (m, 2H), 1.34 (d, 3H), 0.95 (m, 1H), 0.58 (m, 2H) 0.15 (m, 2H)

^{13}C -nmr (CDCl_3): δ = 173.7, 172.3, 52.3, 47.7, 41.0, 18.2, 6.7, 4.27, 4.22

5

Example B81

Synthesis of *N*-[(3-nitrophenyl)acetyl]-L-methionine *iso*-butyl ester

Following General Procedure BH above, and using nitrophenylacetic acid (Aldrich) and L-methionine (Aldrich), the title compound was prepared as a tan oil. The reaction was monitored by tlc on silica gel.

10

NMR data was as follows:

^1H -nmr (CDCl_3): δ = 8.16 (m, 2H) 7.67 (d, 1H) 7.32 (t, 1H), 6.31 (bd, 1H), 4.69 (m, 1H), 3.90 (d, 2H), 3.68 (s, 2H), 2.47 (t, 2H), 2.15 (m, 1H), 2.02 (s, 3H), 1.90 (m, 2H), 0.91 (d, 6H).

$\text{C}_{17}\text{H}_{24}\text{N}_2\text{O}_5\text{S}$ (MW = 368.4, Mass Spectroscopy (MH^+ 368)).

15

The following General Procedures and Examples illustrate the synthesis of various lactams and related compounds which can be used to prepare, for example, compounds of formula VII and VIII above.

20

GENERAL PROCEDURE III-A

First EDC Coupling Procedure

To a 1:1 mixture of the corresponding carboxylic acid and the corresponding amino acid ester or amide in CH_2Cl_2 at 0°C was added 1.5 equivalents triethylamine, followed by 2.0 equivalents hydroxybenzotriazole monohydrate and then 1.25 equivalents of ethyl-3-(3-dimethylamino)propyl carbodiimide·HCl. The reaction mixture was stirred overnight at room temperature and then transferred to a separatory funnel. The mixture was washed with water, saturated aqueous NaHCO_3 , 1N HCl and saturated aqueous NaCl, and then dried over MgSO_4 . The resulting solution was stripped free of solvent on a rotary evaporator to yield the crude product.

30

-- 234 --

GENERAL PROCEDURE III-B

Second EDC Coupling Procedure

A mixture of the corresponding acid (1 eqv), N-1-hydroxybenzotriazole (1.6 eqv), the corresponding amine (1 eqv), N-methylmorpholine (3 eqv) and dichloromethane (or DMF for insoluble substrates) was cooled in an ice-water bath and stirred until a clear solution was obtained. EDC (1.3 eqv) was then added to the reaction mixture. The cooling bath was then allowed to warm to ambient temperature over 1-2 h and the reaction mixture was stirred overnight. The reaction mixture was then evaporated to dryness under vacuum. To the residue was added 20% aqueous potassium carbonate and the mixture was shaken thoroughly and then allowed to stand until the oily product solidified (overnight if necessary). The solid product was then collected by filtration, washed thoroughly with 20% aqueous potassium carbonate, water, 10% HCl, and water to give the product, usually in pure state. No racemization was observed.

GENERAL PROCEDURE III-C

Third EDC Coupling Procedure

The carboxylic acid was dissolved in methylene chloride. The corresponding amino acid ester or amide (1 eq.), N-methylmorpholine (5 eq.) and hydroxybenzotriazole monohydrate (1.2 eq.) were added in sequence. A cooling bath was applied to the round bottomed flask until the solution reached 0°C. At that time, 1.2 eq. of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride was added. The solution was allowed to stir overnight and come to room temperature under nitrogen pressure. The reaction mixture was worked up by washing the organic phase with saturated aqueous sodium carbonate, 0.1M citric acid, and brine before drying with sodium sulfate. The solvents were then removed to yield crude product.

GENERAL PROCEDURE III-D

Fourth EDC Coupling Procedure

-- 235 --

A round bottom flask was charged with the corresponding carboxylic acid (1.0 eq.), hydroxybenzotriazole hydrate (1.1 eq.) and the corresponding amine (1.0 eq.) in THF under nitrogen atmosphere. An appropriate amount (1.1 eq for free amines and 2.2 eq. for hydrochloride amine salts) of base, such as Hunig's base was added to the well stirred mixture followed by EDC (1.1 eq.). After stirring from 4 to 17 hours at room temperature the solvent was removed at reduced pressure, the residue taken up in ethyl acetate (or similar solvent) and water, washed with saturated aqueous sodium bicarbonate solution, 1 N HCl, brine, dried over anhydrous sodium sulfate and the solvent removed at reduced pressure to provide the product.

GENERAL PROCEDURE III-E

BOP Coupling Procedure

To a stirred solution of *N*-(3,5-difluorophenylacetyl)alanine (2 mmol) in DMF, cooled in an ice-water bath, was added BOP (2.4 mmol) and *N*-methylmorpholine (6 mmol). The reaction mixture was stirred for 50 min. and then a solution of α -amino- γ -lactam (2 mmol) in DMF cooled at 0 °C was added. The cooling bath was allowed to warm to ambient temperature over 1-2 h and the reaction mixture was then stirred overnight. A 20% aqueous potassium carbonate solution (60 mL) was added and this mixture shaken thoroughly. No solid formed. The mixture was then washed with ethyl acetate (150 mL) and evaporated to dryness under vacuum to give a white solid. Water (50 mL) was then added and this mixture shaken thoroughly. The precipitate that formed was collected by filtration, then washed thoroughly with water, followed by 1 mL of diethyl ether to give the product (51 mg, 0.16 mmol, 7.8%).

GENERAL PROCEDURE III-F

Coupling of an Acid Chloride with an Amino Acid Ester

To a stirred solution of (D,L)-alanine isobutyl ester hydrochloride (4.6 mmol) in 5 ml of pyridine was added 4.6 mmol of the acid chloride. Precipitation occurred immediately. The mixture was stirred for 3.5 h, dissolved

-- 236 --

in 100 mL of diethyl ether, washed with 10% HCl three times, brine once, 20% potassium carbonate once and brine once. The solution was dried over magnesium sulfate, filtered, and evaporated to yield the product. Other amino acid esters may also be employed in this procedure.

5

GENERAL PROCEDURE III-G

Coupling of a Carboxylic Acid with an Amino Acid Ester

A solution of the carboxylic acid (3.3 mmol) and 1,1'-carbodiimidazole (CDI) in 20 mL THF was stirred for 2 h. (D,L)-alanine isobutyl ester hydrochloride (3.6 mmol) was added, followed by 1.5 mL (10.8 mmol) of triethylamine. The reaction mixture was stirred overnight. The reaction mixture was dissolved in 100 mL of diethyl ether, washed with 10% HCl three times, brine once, 20% potassium carbonate once and brine once. The solution was dried over magnesium sulfate, filtered, and evaporated to yield the product. Other amino acid esters may also be employed in this procedure.

15

GENERAL PROCEDURE III-H

Fifth EDC Coupling Procedure

In a round bottom flask was added a carboxylic acid (1.1 eq.) in THF, an amine hydrochloride (1.0 eq.), 1-hydroxybenzotriazole hydrate (1.1 eq.), N,N-diisopropylethylamine (2.1 eq.), followed by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) (1.1 eq.). The reaction mixture stirred at room temperature for 10-20 hours under an atmosphere of nitrogen. The mixture was diluted with EtOAc and washed with 0.1 M HCl (1 x 10 mL), saturated NaHCO₃ (1 x 10 mL), H₂O (1 x 10 mL), and brine and dried over MgSO₄. The drying agent was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel followed by trituration from EtOAc and hexanes.

25

30

GENERAL PROCEDURE III-I

Sixth EDC Coupling Procedure

-- 237 --

To a solution or suspension of the amine or amine hydrochloride (1.0 eq.) in THF (0.05-0.1 M) under N₂ at 0°C was added the carboxylic acid (1.0-1.1 eq.), hydroxybenzotriazole monohydrate (1.1-1.15 eq.), Hunig's base (1.1 eq. for free amines and 1.1-2.3 eq. for hydrochloride amine salts), followed by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.1-1.15 eq.). The cooling bath was removed and the mixture allowed to warm to room temperature for 10-24 hours. The solution or mixture was diluted with EtOAc, in a 3-5 volume multiple of the initial THF volume, and washed with 0.1-1.0 M aq. HCl (1 or 2x), dilute NaHCO₃ (1 or 2x), and brine (1x). Then, the organic phase was dried over either MgSO₄ or Na₂SO₄, filtered, concentrated to provide the crude product, which was either further purified or utilized without further purification.

GENERAL PROCEDURE III-J

15

EEDQ Coupling Procedure

To a solution of the amine in THF (1.0 eq., 0.05-0.08 M, final molarity) under N₂ at room temperature was added the N-t-Boc protected amino acid (1.1 eq., either as a solid or in THF via cannula), followed by EEDQ (Aldrich, 1.1 eq.). The pale yellow solution was stirred at room temperature for 16-16.5 hours, then diluted with EtOAc (in a 3-5 volume multiple of the initial THF volume), and washed with 1M aq. HCl (2x), dilute aq. NaHCO₃ (2x), and brine (1x). The organic phase was dried over either Na₂SO₄ or MgSO₄, filtered, and concentrated.

25

Example 2-A

Synthesis of

5-Amino-5,7-dihydro-6H-dibenzo[a,c]cyclohepten-6-ol Hydrochloride

30

Step A - Synthesis of 5-Oximo-5,7-dihydro-6H-dibenzo[a,c]cyclohepten-6-one

A round bottom flask was charged with 5,7-dihydro-6H-dibenzo[a,c]cyclohepten-6-one (1.0 g, 4.81 mmol)(CAS# 1139-82-8, prepared as

-- 238 --

described in *Tetrahedron Letters*, Vol. 28, No. 23, (1987), pp 2633-2636) and butyl nitrite (0.673 ml, 5.77 mmol) (Aldrich) in Et₂O. The solution was cooled to 0°C and treated drop-wise with a saturated solution of HCl(g)/Et₂O. After 5 h at 0°C the resulting precipitate was filtered, rinsed with cold Et₂O and vacuum dried to give the title compound as a colorless solid.

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 7.26-7.74 (m, 8H), 3.84 (m, 2H).

C₁₅H₁₁NO₂ (MW = 237.26); mass spectroscopy (MH⁺) 238.

Anal. Calcd for C₁₅H₁₁NO₂; C, 75.93 H, 4.67 N, 5.90. Found: C, 75.67

10 H, 4.83 N, 5.67.

Step B- Synthesis of 5-Amino-5,7-dihydro-6H-dibenzo[a,c]cyclohepten-6-ol Hydrochloride

The compound isolated above (0.489 g, 2.04 mmol) was dissolved in THF and added drop-wise to a well-stirred mixture of LAH (10.2 ml, 10.2 mmol)/THF. After heating to reflux for 25 h under N₂ atmosphere the solution was quenched and worked-up according to Fieser's method. The resulting solid was rinsed with NH₃ sat/CHCl₃, the filtrate evaporated and the title compound purified by chromatography (SiO₂, CHCl₃).

20 C₁₅H₁₅NO (MW = 225.290); mass spectroscopy (MH⁺) 226.

Anal. Calcd for C₁₅H₁₅NO; C, 79.97 H, 6.71 N, 6.22. Found: C, 80.19 H, 6.71 N, 5.91.

GENERAL PROCEDURE 5-A

25 N-Alkylation of Lactams

To a stirred solution of a BOC-protected α-aminocaprolactam (6.87 g, 30 mmol) in DMF (150 mL) was added in portions 97% NaH (1.08g, 45 mmol). Bubbling occurred immediately and followed by heavy precipitation. After 10 min., benzyl bromide (3.93 mL, 33 mmol) was added. The precipitate dissolved quickly and in about 10 min. a clear solution was obtained. The reaction mixture was stirred overnight and then evaporated as completely as possible on a rotovap at 30°C. Ethyl acetate (100 mL) was added to the residue and this

mixture was washed with water, brine, and dried over magnesium sulfate. After filtration and concentration, a thick liquid (10 g) was obtained which was then chromatographed over silica gel with 1:3 ethyl acetate/hexane as the eluant to provide 5.51 g (58%) of the N-benzylated product as an oil. Other lactams and
5 alkylating agents may be used in this procedure to obtain a wide variety of N-alkylated lactams. Various bases, such as $\text{LiN}(\text{SiMe}_3)_2$, may also be employed.

GENERAL PROCEDURE 5-B

BOC Removal Procedure

10 The BOC-protected compound in a 1:1-2:1 mixture of CH_2Cl_2 and trifluoroacetic acid was stirred until tlc indicated complete conversion, typically 2 hours. The solution was then stripped to dryness and the residue was taken up in ethyl acetate or CH_2Cl_2 . The solution was washed with saturated aqueous NaHCO_3 and the aqueous phase was adjusted to a basic pH, then extracted with
15 ethyl acetate or CH_2Cl_2 . The organic phase was washed with saturated aqueous NaCl and dried over MgSO_4 . The solution was stripped free of solvent on a rotary evaporator to yield the product.

GENERAL PROCEDURE 5-C

Synthesis of α -Aminolactams

20 The Schmidt reaction was conducted on 4-ethylcyclohexanone using hydroxyamine sulfonic acid as described in Olah, *Org. Synth. Collective*, Vol. VII, page 254, to provide 5-ethylcaprolactam in 76% yield. Using the procedure described in Watthey, et al., *J. Med. Chem.*, 1985, 28, 1511-1516, this lactam
25 was then dichlorinated with PCl_5 at the alpha position and reduced by hydrogenation to provide four isomeric monochlorides (two racemic mixtures). The two racemic mixtures were separated from each other by column chromatography using silica gel and each racemic mixture was reacted with sodium azide to yield the corresponding azide which was hydrogenated to
30 provide the corresponding α -aminolactams. Other cycloalkanones may be employed in this procedure to provide a wide variety of α -aminolactams. In

-- 240 --

some cases, such as when preparing the 9-membered ring α -aminolactam, longer reaction times, higher reaction temperatures and an excess of sodium azide may be required. For example, the 9-membered ring α -aminolactam required 5 equivalents of sodium azide, a reaction temperature of 120°C and a reaction time of 4 days. Such conditions can be readily determined by those of ordinary skill in the art.

GENERAL PROCEDURE 5-D

Synthesis of 4-Amino-1,2,3,4-tetrahydroisoquinoline-3-ones

10 The 4-amino-1,2,3,4-tetrahydroisoquinoline-3-one derivatives employed in this invention can be prepared by the following art-recognized procedures. The conditions for these reactions are further described in D. Ben-Ishai, et al., *Tetrahedron*, 43, 439-450 (1987). The following intermediates were prepared via this procedure:

15 3-amino-1,2,3,4-tetrahydroisoquinolin-3-one
4-amino-7-benzyl-1,2,3,4-tetrahydroisoquinolin-3-one
4-amino-1-phenyl-1,2,3,4-tetrahydroisoquinolin-3-one
cis and *trans*-4-amino-1-phenyl-1,2,3,4-tetrahydroisoquinolin-3-one
4-amino-2-phenethyl-1,2,3,4-tetrahydroisoquinolin-3-one
20 4-amino-2-methyl-1,2,3,4-tetrahydroisoquinolin-3-one
9-amino(flouren-1-yl)glycine δ -lactam-1,2,3,4-tetrahydroisoquinolin-3-one.

Step A - Preparation of N-Bismethoxycarbonylaminoacetic Acid: To one mole equivalent of glyoxylic acid in 2 liters of ethanol-free chloroform was added two mole equivalents of methyl carbamate and 0.1 mole equivalent of naphthalene sulfonic acid. The reaction mixture was then brought to a reflux for 6 hours. Water was removed using an inverse Dean Stark trap. The reaction was then cooled and the product filtered and washed with chloroform. The white solid was recrystallized from ethyl acetate/hexanes to give a white powder in 65% yield.

-- 241 --

Step B - Coupling Procedure: To 0.0291 moles of N-bismethoxycarbonylaminoacetic acid (or the appropriate carboxylic acid) in 200 mL of THF was added one mole equivalent of EDC•HCl, a benzylamine, HOBT, and diisopropylethylamine. The reaction was allowed to stir at room temperature for 18 hours and then poured into a separatory funnel and extracted into ethyl acetate. The ethyl acetate solution was washed with 1 molar K_2CO_3 and then 1 molar HCl. The organic layer was dried over Na_2SO_4 , filtered and solvent removed to give the crystalline benzylamide of N-bismethoxycarbonylaminoacetic acid. This material was used without further purification. Typical yields range from 40 - 55%.

Step C - Cyclization Procedure: The benzylamide of N-bismethoxycarbonylaminoacetic acid (0.008 moles) was dissolved in 75 mL of methanesulfonic acid and allowed to stir over night at room temperature. The reaction mixture was poured over ice and extracted into ethyl acetate. The ethyl acetate extract was washed with 1 molar K_2CO_3 and then 1 N HCl. The organic layer was dried over Na_2SO_4 , filtered and the solvent removed to give the crystalline 4-methoxycarbonylamino-1,2,3,4-tetrahydroisoquinoline-3-one in 50-90% yield. This material was used without further purification.

Step D - Removal of the Methoxyoxycarbonyl Group (MOC): To the 4-methoxycarbonylamino-1,2,3,4-tetrahydroisoquinoline-3-one (3.4 mmoles) in 30 mL of acetonitrile was added 2 mole equivalents of trimethylsilyliodide (TMSI). The reaction mixture was heated to 50-80°C for 3 hrs and then cooled and poured into a separatory funnel. The reaction mixture was diluted with ethyl acetate and washed with 1 molar K_2CO_3 and then with 5% $NaHSO_3$. The organic layer was dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure to give the 4-amino-1,2,3,4-tetrahydroisoquinoline-3-one derivative. Typical yields range from 50-87%.

-- 242 --

Step E - Alternative Procedure for Removal of the Methoxyoxycarbonyl

Group: To 3.8 mmoles of the MOC-protected compound was added 10 mL of 30% HBr in acetic acid and this reaction mixture was heated to 60°C for 3 hrs. The mixture was then cooled and hexanes were added. The hexanes layer was decanted off and the residue as placed under reduced pressure to give a tan solid. This solid was slurried in ether and filtered to give the 4-amino-1,2,3,4-tetrahydroisoquinoline-3-one hydrobromide salt. Typical yields range from 57-88%.

Example 5-A

Synthesis of

3-Amino-1,2,3,4-tetrahydroquinolin-2-one

Step A: Sodium (0.30g, 110M%) was added to anhydrous ethanol (45 mL) and the reaction mixture was stirred until homogenous. Diethyl N-acetylaminomalonate (2.51 g, 100 M%) was added in one portion and this mixture was stirred for 1 h. 2-Nitrobenzyl bromide (2.5g, 100M%) was then added in one portion and the reaction mixture was stirred for 3 h. The reaction was poured into water and extracted with ethyl acetate (3x) and then backwashed with water (3x) and brine (1x). Treatment with MgSO₄, rotoevaporation, and chromatography (30% EtOAc/hexanes) yielded diethyl N-acetyl-amino-2-nitrobenzylmalonate in 82% yield.

Step B: Diethyl N-acetyl-amino-2-nitrobenzylmalonate (1g, 100M%) was dissolved in a minimum amount of EtOH. Pd/C (10%, 0.05g) was added and the reaction mixture was subjected to 50 psi of H₂ for 3 hours. The reaction was then filtered thru a pad of celite. Additional EtOH (25mL) and TsOH (catalytic amount, 0.01g) were added and this mixture was refluxed for 2 hours. The reaction was rotoevaporated to a residue and then partitioned between water and ethyl acetate. The water layer was extracted with ethyl acetate (3x) and the combined ethyl acetate extracts were washed with water (3x) and then brine (1x). Treatment with MgSO₄ and rotoevaporation yielded pure 3-(N-acetyl-amino)-3-carboethoxy-1,2,3,4-tetrahydroquinolin-2-one (89% yield).

Step C: 3-(N-Acetylamino)-3-carboethoxy-1,2,3,4-tetrahydroquinolin-2-one (0.75 g, 100M%) was suspended in 6N HCl (25 mL) and the mixture was heated to 100°C for 3 hours. The reaction was cooled, rotoevaporated to a residue and then partitioned between water and ethyl acetate. The water was extracted with ethyl acetate (3x) and the combined ethyl acetate extracts were then washed with water (3x) and then brine (1x). Treatment with MgSO₄ followed by rotoevaporation yielded 3-(R,S)-amino-1,2,3,4-tetrahydroquinolin-2-one (72% yield).

Example 5-B

10

Synthesis of 4-Amino-1-(pyrid-4-yl)-1,2,3,4-tetrahydroisoquinolin-3-one

Step A: To a solution of 4-cyanopyridine (Aldrich) (0.150 moles) in 300 mL of dry ether was added 1.1 eq. of phenylmagnesium bromide (Aldrich) dropwise. The reaction was refluxed for 2 hours and then stirred overnight at room temperature. Sodium borohydride (1.0 eq.) was added dropwise as a solution in 200 mL of methanol (CAUTION -- very exothermic). The reaction was then heated to reflux for 6 hours, cooled and quenched with a saturated solution of ammonium chloride. The solution was decanted from the salt in the reaction mixture and acidified with 1N HCl. After washing the aqueous layer with ethyl acetate, the pH of aqueous layer was adjusted to about 9.0 with 1N sodium hydroxide (cold). The aqueous layer was then extracted with ethyl acetate and the organic extracts washed with brine, dried over Na₂SO₄, filtered and concentrated to give 4-pyridyl- α -benzyl amine as a thick yellow oil.

25

Step B: Following General Procedure 5-D and using 4-pyridyl- α -benzyl amine, the title compound was prepared.

Example 5-C

30

Synthesis of 4-Amino-1-(pyrid-2-yl)-1,2,3,4-tetrahydroisoquinolin-3-one

-- 244 --

Step A: 2-Pyridyl- α -benzyl amine was prepared by substituting 2-cyanopyridine (Aldrich) for 4-cyanopyridine in the procedure described in Example 5-B.

5 Step B: Following General Procedure 5-D and using 4-pyridyl- α -benzyl amine, the title compound was prepared.

Example 5-D

Synthesis of

10 4-Amino-1-(pyrid-3-yl)-1,2,3,4-tetrahydroisoquinolin-3-one

Step A: Following the procedure described in J. Med. Chem., 1982, 25, 1248, and using 3-benzoyl-pyridine (Aldrich), 3-pyridyl- α -benzyl amine was prepared.

15 Step B: Following General Procedure 5-D and using 3-pyridyl- α -benzyl amine, the title compound was prepared.

Example 5-E

Synthesis of

20 4-Amino-7-benzyl-1,2,3,4-tetrahydroisoquinolin-3-one

Step A: To a Parr bottle containing 3-benzoylbenzoic acid (0.044 moles) (Aldrich) in 150 mL of ethyl acetate and 4.5 mL of concentrated H₂SO₄ was added 10 grams of 5% Pd/C. The mixture was hydrogenated on a Parr apparatus under hydrogen (45 psi) overnight. The reaction mixture was then
25 filtered through Hyflo, washing with ethyl acetate. The filtrate was dried over Na₂SO₄, filtered and concentrated to give an oil. The oil was slurried in hexane and the resulting white solid was collected by filtration to afford 3-benzylbenzoic acid, which was used without further purification.

30 Step B: To the product from Step A (0.0119 moles) was added 150 mL of CH₂Cl₂, one drop of DMF, 10 mL of oxalyl chloride, and the mixture was stirred at room temperature for 3 hours. After cooling to 10°C, 30 mL of

-- 245 --

NH₄OH (exothermic) was added and the mixture was stirred for 30 min. The reaction mixture was then concentrated and the resulting residue diluted with ethyl acetate. The organic layer was washed with 1N NaOH, brine, dried over Na₂SO₄, and concentrated to give the 3-(benzyl)benzamide as a white solid,
5 which was used without further purification.

Step C: To a solution of 3-(benzyl)benzamide (.0094 moles) from Step B in 70 of toluene was added 8 mL of Red-Al® (65+ wt. % solution of sodium bis(2-methoxyethoxy)aluminum hydride in toluene, Aldrich) (CAUTION --
10 reaction very exothermic). The reaction mixture was then heated at 60°C for 2 hours and then poured over ice. The resulting mixture was extracted with ethyl acetate and the combined extracts were washed with water and brine. The organic layer was extracted with 1N HCl and the aqueous layer washed with ethyl acetate. The pH of the aqueous layer was then adjusted to about 9.0 with
15 1N NaOH and extracted with ethyl acetate. The organic extracts were washed with water and brine and then concentrated to give 3-(benzyl)benzyl amine.

Step D: Following General Procedure 5-D and using 3-(benzyl)benzyl amine, the title compound was prepared.

20

Example 5-F

Synthesis of

4-Amino-6-phenyl-1,2,3,4-tetrahydroisoquinolin-3-one

Step A: To a solution of 4-biphenylcarboxamide (Aldrich) (0.025 mole)
25 in 150 mL of THF cooled to 10°C was added a solution of 1.5 eq of LAH (1M in THF) dropwise. The reaction mixture turned from a white slurry to a green homogenous solution and then to a yellow homogeneous solution. The reaction was then quenched with 2.5 mL of 1N NaOH. The mixture was then filtered through Hyflo and extracted with ethyl acetate. The organic layer was then
30 washed with 1N HCl. The pH of the resulting aqueous layer was adjusted to about 9 with 1N NaOH and extracted with ethyl acetate. The organic extracts

-- 246 --

were washed with water and brine, and then dried over Na_2SO_4 , filtered and concentrated to give 4-(phenyl)benzyl amine as a white solid.

5 Step B: Following General Procedure 5-D and using 4-(phenyl)benzyl amine, the title compound was prepared.

Example 5-G

Synthesis of *cis*- and *trans*-4-Amino-1-phenyl-1,2,3,4-tetrahydroisoquinolin-3-one

10 Step A: Following General Procedure 5-D and using α -phenylbenzylamine (Aldrich), 4-amino-1-phenyl-1,2,3,4-tetrahydroisoquinolin-3-one was prepared.

15 Step B: To a solution of 4-amino-1-phenyl-1,2,3,4-tetrahydroisoquinolin-3-one (0.00158 moles) from Step A in 20 mL of CH_2Cl_2 was added 2.0 eq. of triethylamine and Boc anhydride (1.1 eq.). The reaction was stirred overnight at room temperature and then concentrated. The residue was diluted with ethyl acetate and water. The pH of the aqueous layer was adjusted to 3.0 with sodium bisulfate and the layers were separated. The organic layer was dried
20 over Na_2SO_4 , filtered and concentrated. The residue was purified by LC 2000, eluting with ethyl acetate/hexanes (70:30) to give a white solid containing a 1:1 mixture of *cis*- and *trans*-4-(N-Boc-amino)-1-phenyl-1,2,3,4-tetrahydroisoquinolin-3-one isomers. This mixture was recrystallized from ethyl acetate to give the pure *trans* isomer and a *cis* isomer-enriched mixture of *cis*
25 and *trans* isomers. This mixture was recrystallized again from ethyl acetate/hexanes (70:30) to give the pure *cis* isomer.

30 Step C: The *cis* isomer and the *trans* isomer from Step B were separately deprotected using General Procedure 8-J to give *cis*-4-amino-1-phenyl-1,2,3,4-tetrahydroisoquinolin-3-one and *trans*-4-amino-1-phenyl-1,2,3,4-tetrahydroisoquinolin-3-one.

-- 247 --

Example 5-H

Synthesis of

4-Amino-7-phenyl-1,2,3,4-tetrahydroisoquinolin-3-one

Step A: To a solution of 1-bromo-3-phenylbenzene (Aldrich) (0.0858 moles) in 300 mL of dry THF cooled to -78°C was added tert-butyl lithium (2 eq.) (1.7M in hexane) dropwise. The reaction mixture was stirred for 40 min. at -78°C and then quenched with 2 eq. of DMF (13.24 mL). The resulting mixture was stirred for 20 min. and then poured into a separatory funnel and extracted with CH_2Cl_2 . The organic extracts were washed with water, dried over Na_2SO_4 , filtered and concentrated to give a brown oil. This oil was purified by LC 2000 chromatography, eluting with ethyl acetate/hexanes (5:95) to give 3-biphenylcarboxaldehyde.

Step B: To a solution of 3-biphenylcarboxaldehyde (0.011 eq.) in 30 mL of methanol was added 10 eq. of 7N NH_3/MeOH and NaCNBH_4 (2 eq.). A yellow gum precipitated from solution. The solution was then heated at 60°C until gum dissolved and the solution was stirred at room temperature overnight. The reaction mixture was then concentrated and the resulting residue diluted with ice water and ethyl acetate. The organic layer was then washed with brine and extracted with 5N HCl. The pH of the aqueous layer was then adjusted to 12 and the aqueous layer was extracted with cold ethyl acetate. The organic layer was dried over Na_2SO_4 , filtered and concentrated to give 3-(phenyl)benzyl amine as an oil.

Step C: Following General Procedure 5-D and using 3-(phenyl)benzyl amine, the title compound was prepared.

Example 5-I

Synthesis of

4-Amino-1-benzyl-1,2,3,4-tetrahydroisoquinolin-3-one

Step A: To a solution of benzoyl chloride (0.123 moles) (Aldrich) in 600 mL of CH_2Cl_2 was added 2.0 eq. of phenethylamine (Aldrich) dropwise.

-- 248 --

The reaction mixture was stirred at room temperature for 3 hours and then poured into a separatory and extracted with CH_2Cl_2 . The organic extracts were washed with water and 1N HCl, and then dried over Na_2SO_4 , filtered and concentrated to give N-phenethyl benzamide.

5

Step B: Reduction of N-phenethyl benzamide using the procedure of Example 5-E, Step C afforded N-benzyl-N-phenethylamine as an oil.

Step C: Following General Procedure 5-D and using N-benzyl-N-phenethylamine, the title compound was prepared.

10

Example 5-J

Synthesis of

3-Amino-1-methyl-2-indolinone Monohydrochloride

15

Step A: (2,3-Dihydro-1-methyl-2-oxo-1H-indol-3-yl)carbamic acid methyl ester (CAS No. 110599-56-9) was prepared using the procedure described in Ben-Ishai, D.; Sataty, I.; Peled, N.; Goldshare, R. *Tetrahedron* 1987, 43, 439-450. The starting materials for this preparation were N-methylaniline (CAS# 100-61-8, Eastman Kodak Co.), glyoxylic acid (CAS# 298-12-4, Aldrich), and methyl carbamate (CAS# 598-55-0, Aldrich).

20

Step B: The product from Step A (333.5 mg) in 31% HBr in AcOH (10 mL) was heated to 50-60°C for 2 hours. The resulting orange solution was concentrated to a thick orange oil which was dissolved in EtOAc (15 mL) and the product extracted into 1 M aq. HCl (10 mL). The aqueous acid was neutralized with aq. NaHCO_3 and the product extracted into CH_2Cl_2 (10 x 10 mL). HCl (gas) was passed through the combined CH_2Cl_2 extracts to form a purple solution. The solution was concentrated to provide the title compound (262.8 mg) as a purple solid.

25

30

Example 5-K

Synthesis of

-- 249 --

3-Amino-1-methyl-4-phenyl-3,4-trans-dihydrocarbostyryl/Tin Complex**Step A: - Synthesis of 4-Phenyl-3,4-dihydrocarbostyryl**

4-Phenyl-3,4-dihydrocarbostyryl (CAS# 4888-33-9) was prepared in two steps using the procedure described by Conley, R. T.; Knopka, W. N. *J. Org. Chem.* 1964, 29, 496-497. The starting materials for this preparation were cinnamoyl chloride (Aldrich) and aniline (Aldrich). The title compound was purified by flash chromatography eluting with CH₂Cl₂/EtOAc (4:1).

Step B: - Synthesis of 1-Methyl-4-phenyl-3,4-dihydrocarbostyryl

To a suspension of NaH (1.2 eq., 0.537 g of 60% dispersion in mineral oil) in THF (50 mL) under N₂ at 0°C was added the product from Step A (1.0 eq., 2.50 g) in THF (50 mL) via cannula over a period of 5 minutes. The resulting pale yellow mixture was stirred at 0°C for 10 minutes, then MeI (2.0 eq., 1.39 mL) was added. The opaque yellow mixture was allowed to slowly (ice bath not removed) warm to ambient temperature with stirring for 15 hours. 1M Aq. HCl (50 mL) and EtOAc (250 mL) were added and the phases partitioned. The organic phase was washed with dilute NaHCO₃ (1 x 100 mL), brine (1 x 100 mL), then dried over MgSO₄, filtered, concentrated, and the residue purified by flash chromatography eluting with CH₂Cl₂/EtOAc (19:1 gradient to 15:1) to provide 1-methyl-4-phenyl-3,4-dihydrocarbostyryl.

Step C: - Synthesis of 3-Azido-1-methyl-4-phenyl-3,4-trans-dihydrocarbostyryl

Following General Procedure 8-K, 3-azido-1-methyl-4-phenyl-3,4-trans-dihydrocarbostyryl was prepared as a white solid. The product was purified by flash chromatography eluting with CH₂Cl₂/hexanes/EtOAc 15:15:1.

Selected ¹H-NMR data for the title compound (CDCl₃): δ = 4.46 (d, 1H, J = 10.57 Hz), 4.18 (d, 1H, J = 10.63 Hz).

Step D: - Synthesis of 3-Amino-1-methyl-4-phenyl-3,4-trans-dihydrocarbostyryl/Tin Complex

-- 250 --

To a mixture of SnCl_2 (350.7 mg) in MeOH (7 mL) under N_2 at 0°C was added the product from Step C (257.4 mg) in MeOH/THF (5 mL/5 mL) via cannula over a period of 1 minute. The cooling bath was removed the solution allowed to warm to ambient temperature for 8 hours (No starting material by TLC). The solution was concentrated to a yellow foam, THF (10 mL) was added and the mixture was re-concentrated and used without further purification.

Example 5-L

Synthesis of

10 3-Amino-1-methyl-4-phenyl-3,4-*cis*-dihydrocarbostyryl

Step A: - Synthesis of 3-Amino-1-methyl-4-phenyl-3,4-*trans*-
dihydrocarbostyryl

3-Amino-1-methyl-4-phenyl-3,4-*trans*-dihydrocarbostyryl was prepared following General Procedure 8-F using 3-azido-1-methyl-4-phenyl-3,4-*trans*-
15 dihydrocarbostyryl from Example 5-K, Step C. The product was purified by L.C. 2000 eluting with EtOAc/hexanes (4:1) to yield a white solid.

Selected $^1\text{H-NMR}$ data for the title compound (CDCl_3): $\delta = 4.03$ (d, 1H, $J = 12.8$ Hz), 3.92 (d, 1H, $J = 12.7$ Hz).

20 Step B: - Synthesis of 3-(4-Chlorobenzylimine)-1-methyl-4-
phenyl-3,4-*trans*-dihydrocarbostyryl

To a solution of the product from Step A (1 eq., 239.6 mg) in CH_2Cl_2 (10 mL) under N_2 at ambient temperature was added 4-chlorobenzaldehyde (1.05 eq., 140 mg, Aldrich), Et_3N (1.4 eq., 185 mL), and MgSO_4 (3.6 eq., 411 mg).
25 The resultant mixture was stirred at room temperature for 73 hours. The solids were removed by filtration through a plug of Celite, rinsing with CH_2Cl_2 , and the filtrate concentrated to provide 3-(4-chlorobenzylimine)-1-methyl-4-phenyl-3,4-*trans*-dihydrocarbostyryl as a thick white foam.

30 Step C: - Synthesis of 3-Amino-1-methyl-4-phenyl-3,4-*cis*-
dihydrocarbostyryl

To a solution of diisopropylamine (1.05 eq., 0.132 mL) in THF (5 mL) under N_2 at -78°C was added a solution of $n\text{-BuLi}$ (1.05 eq., 0.588 mL of a 1.6

-- 251 --

M solution in hexanes) and the result solution was stirred for 30 minutes. To this solution was added the product from Step B (1.0 eq., 336 mg) in THF (2 mL) via cannula. The solution was allowed to warm to 0°C, then quenched with 1 M aq. HCl (3 mL) and allowed to warm to room temperature with stirring overnight. The product was extracted into H₂O and washed with EtOAc (1 x), then the aqueous acid was basified with 1 M aq. K₂CO₃ and the product extracted into EtOAc. The EtOAc extract was dried over Na₂SO₄, filtered, and concentrated to give 3-amino-1-methyl-4-phenyl-3,4-*cis*-dihydrocarbostyryl.

Selected ¹H-NMR data for the title compound (CDCl₃): δ = 4.31 (d, 1H, J = 6.6 Hz).

Example 5-M

Synthesis of 3-Amino-1-*tert*-butoxycarbonyl-4-phenyl- 3,4-*trans*-dihydrocarbostyryl/Tin Complex

Step A: - Synthesis of 1-*tert*-Butoxycarbonyl-4-phenyl-3,4-dihydrocarbostyryl

1-*tert*-Butoxycarbonyl-4-phenyl-3,4-dihydrocarbostyryl was prepared from the product of Example 5-K, Step A (CAS# 4888-33-9) by the Boc procedure for aryl amides described by Grehn, L.; Gunnarsson, K.; Ragnarsson, U. *Acta Chemica Scandinavica B* 1986, 40, 745-750; employing (Boc)₂O (Aldrich) and catalytic DMAP (Aldrich) in acetonitrile. The product was purified by flash chromatography eluting with CH₂Cl₂ gradient to CH₂Cl₂/EtOAc (19:1) and isolated as a pale yellow oil.

Step B - Synthesis of 3-Azido-1-*tert*-butoxycarbonyl-4-phenyl-3,4-*trans*-dihydrocarbostyryl

Following General Procedure 8-K using the product from Step A, the title compound was prepared as a 12.4:1 mixture of *trans/cis* isomers which were separated by flash chromatography eluting with hexanes/Et₂O (6:1 gradient to 4:1) in the first column and hexanes/EtOAc (12:1) in a second column. The pure *trans* isomer was used in Step C.

-- 252 --

Selected ¹H-NMR data for the title compound (CDCl₃): δ = 4.45 (d, 1H, J = 11.1 Hz), 4.24 (d, 1H, J = 11.2 Hz).

5 **Step C: - Synthesis of 3-Amino-1-*tert*-butoxycarbonyl-4-phenyl-3,4-*trans*-dihydrocarbostyryl/Tin Complex**

To a mixture of SnCl₂ (450.6 mg) in MeOH (9 mL) under N₂ at 0°C was added the product from Part D (433.0 mg) in MeOH (15 mL) via cannula over a period of 1 minute. The cooling bath was removed the solution allowed to warm to ambient temperature for 17 hours. The solution was concentrated to an
10 amorphous yellow solid and used without further purification.

Example 5-N

**Synthesis of
(S)-3-Amino-1-benzyl-δ-valerolactam**

15 **Step A: - Synthesis of L-(+)-Ornithine Methyl Ester Hydrochloride**

Into a stirred suspension of L-(+)-ornithine hydrochloride (Aldrich) in methanol was bubbled anhydrous hydrochloric acid gas until the solution was saturated. The reaction mixture was capped with a rubber septum and stirring
20 was continued overnight at room temperature. The solvent was then stripped under reduced pressure and the residue triturated with ether. The resulting solid was dried under reduced pressure to afford L-(+)-ornithine methyl ester hydrochloride as a white solid (97% yield).

25 **Step B: - Synthesis of (S)-3-Amino-δ-valerolactam**

Sodium spheres in oil (2.0 eq.) (Aldrich) were washed with hexanes (2x) and methanol (2.3 mL/mmol) was slowly added. The reaction mixture was stirred under nitrogen until the sodium dissolved and then L-(+)-ornithine methyl ester hydrochloride (1 eq.) in methanol (2.3 mL/mmol) was added dropwise.
30 The reaction mixture was stirred for 16 hours and then diluted with diethyl ether (5 mL/mmol) and filtered to remove the solids. The solvent was then removed under reduced pressure and the residue was heated at 70°C for 3 hours under

-- 253 --

reduced pressure. The residue was then triturated with dichloromethane/ether, the solvent decanted and the resulting residue dried under reduced pressure to afford (S)-3-amino- δ -valerolactam (44% yield).

5 **Step C: - Synthesis of N-Boc-(S)-3-Amino- δ -valerolactam**

(S)-3-Amino- δ -valerolactam (1 eq.) was dissolved in dioxane and the solution was chilled to 0°C. BOC-anhydride (1.3 eq.) was added and the ice bath was removed allowing the solution to come to room temperature and stirring was continued for 16 hours. The solution was rotary evaporated to
10 afford N-Boc-(S)-3-amino- δ -valerolactam.

Step D: - Synthesis of (S)-3-Amino-1-benzyl- δ -valerolactam

Following General Procedure 5-A and using N-Boc-(S)-3-amino- δ -valerolactam and benzyl bromide provided N-Boc-(S)-3-amino-1-benzyl- δ -
15 valerolactam. Removal of the Boc group using General Procedure 5-B afford the title compound.

Example 5-O

20 **Synthesis of
4-Amino-2-aza-2-benzyl-3-oxobicyclo[3.2.1]octane Hydrochloride**

Step A: - Synthesis of 2-Aza-3-oxobicyclo[3.2.1]octane and 3-Aza-2-oxobicyclo[3.2.1]octane (9:1 Mixture)

To ($\pm$)-norcamphor (Aldrich) in 1 mL/mmol of acetic acid was added 1.5 eq. of hydroxylamine-O-sulfonic acid. The reaction mixture was
25 heated to reflux under nitrogen for 1 hour and then saturated sodium carbonate and dilute sodium hydroxide were added. The resulting mixture was extracted with dichloromethane and the organic extracts washed with brine, dried over sodium sulfate, and the solvent removed under reduced pressure. Purification of the residue by column chromatography afforded a 9:1 mixture of 2-aza-3-oxobicyclo[3.2.1]octane and 3-aza-2-oxobicyclo[3.2.1]octane.
30

Step B: - Synthesis of 2-Aza-2-benzyl-3-oxobicyclo[3.2.1]octane

-- 254 --

Following General Procedure 5-A and using the product for Step A and benzyl bromide, 2-aza-2-benzyl-3-oxobicyclo[3.2.1]octane was prepared.

5 **Step C: - Synthesis of 2-Aza-2-benzyl-4-oximino-3-oxobicyclo[3.2.1]octane**

To a solution of 2-aza-2-benzyl-3-oxobicyclo[3.2.1]octane in THF was added 2.5 eq. of 1M t-BuOK/THF (Aldrich) and the resulting mixture was stirred for 30 minutes. Isoamyl nitrite (1.5 eq.) was then added dropwise and the reaction mixture was stirred overnight. To the reaction mixture was added
10 3N HCl and this mixture was extracted with ethyl acetate and the organic extracts washed with water, dried, and concentrated under reduced pressure. The residue was triturated with ether/hexanes, the solvents decanted and the residue dried under reduced pressure to afford 2-aza-2-benzyl-4-oximino-3-oxobicyclo[3.2.1]octane as a tan liquid (41% yield). This procedure is further
15 described in Y. Kim, *Tetrahedron Lett.* 30(21), 2833-2636 (1989).

Step D: - Synthesis of 2-Aza-2-benzyl-4-amino-3-oxobicyclo[3.2.1]octane

A solution of 2-aza-2-benzyl-4-oximino-3-oxobicyclo[3.2.1]octane in 10
20 mL/mmmole of ethanol and 5.8 mL/mmmole of 3N HCl containing 0.5 g/mmmole of 10% Pd/C was saturated with hydrogen gas to 45 psi. The mixture was shaken for 3 hours and then filtered through a layer of Celite. The filtrate was dried over sodium sulfate and concentrated under reduced pressure to afford the title compound as a solid (86% yield). This procedure is further described in E.
25 Reimann, *Arch. Pharm.* 310, 102-109 (1977).

GENERAL PROCEDURE 6-A

Alkylation of
1-Amino-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one

30 **Step A:** 1-Ethoxycarbonylamino-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one was prepared according to the procedure of Ben-Ishai et al., *Tetrahedron*, 1987, 43, 430.

-- 255 --

Step B: 1-Ethoxycarbonylamino-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one (2.0 g, 100 M%) was dissolved in DMF (30 mL) and NaH (95%, 0.17 g, 100M%) was added in one portion. The reaction mixture was stirred for 1 hour and then the appropriate alkyl iodide (300M%) was added and the mixture was stirred for 12 hours. The reaction was poured into water and extracted with ethyl acetate (3x). The ethyl acetate extracts were then washed with water (3x) and brine (1x). Treatment with MgSO₄, rotoevaporation, and chromatography (30% EtOAc/hexanes) yielded 1-ethoxycarbonylamino-3-alkyl-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one in 87% yield.

Step C: 1-Ethoxycarbonylamino-3-alkyl-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one (1.0g, 100M%) was suspended in 30 mL of 30% HBr/HOAc and heated to 100°C. The reaction mixture was stirred for 5 hours at this temperature and then the reaction was cooled and rotoevaporated to yield 1-amino-3-alkyl-1,3,4,5-tetrahydro-2H-3-benzazepin-2-one as the hydrobromide salt (100% yield).

GENERAL PROCEDURE 6-B

Alkylation of 3-Amino-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

Step A: 3-Amino-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one was prepared from α -tetralone using the methods described in Armstrong et al. *Tetrahedron Letters*, 1994, 35, 3239. The following compounds were as prepared by this procedure for use in the following steps:

5-methyl-3-amino-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (from 4-methyl- α -tetralone (Aldrich)); and

5,5-dimethyl-3-amino-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (from 4,4-dimethyl- α -tetralone (Aldrich)).

Step B: 3-Amino-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (4.43 g, 100M%) was suspended in t-butanol (30mL) and BOC-anhydride (7.5 mL, 130M%) was added dropwise. The reaction was stirred for 2 hours and then it

-- 256 --

was rotoevaporated to a residue which was chromatographed with 60% ethyl acetate/hexanes to yield BOC-protected 3-amino-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one in 87% yield.

5 Step C: BOC-protected 3-amino-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (1.5 g, 100M%) was dissolved in DMF (20mL) and NaH (95%, 0.13g, 100M%) was added in one portion. The reaction mixture was stirred for 1 hour and then the appropriate alkyl iodide (300M%) was added and stirring was continued for 12 hours. The reaction was poured into water and extracted with
10 ethyl acetate (3x). The ethyl acetate extracts were washed with water (3x) and then brine (1x). Treatment with MgSO₄, rotoevaporation, and chromatography (30% EtOAc/hexanes) yielded a BOC-protected 3-amino-1-alkyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one in 80% yield.

15 Step D: The BOC-protected 3-amino-1-alkyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (1.0g, 100M%) was suspended in 30 mL of 1:1 CH₂Cl₂/trifluoroacetic acid and the mixture was stirred for 4 hours. The reaction was then rotoevaporated to yield the 3-amino-1-alkyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (100% yield).

20

Example 6-A

Synthesis of

3-Amino-1,5-dimethyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

25 Step A: 3-Amino-5-methyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one was prepared from 4-methyl- α -tetralone using the methods described in Armstrong et al. *Tetrahedron Letters*, 1994, 35, 3239.

30 Step B: 3-Amino-5-methyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (9.3g 100M%) was dissolved in dioxane (300mL) and the solution was chilled to 0°C. BOC-anhydride (13.89g 130M%) was added and the ice bath was removed allowing the solution to come to room temperature and stirring was continued for 16 hours. The solution was rotary evaporated to remove dioxane

to provide an off white solid. This solid was recrystallized from CHCl_3 to yield BOC-protected 3-amino-5-methyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one in 55% yield.

5 Step C: BOC-protected 3-amino-5-methyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (100 M%) was dissolved in DMF (20mL) and NaH (95%, 100 M%) was added in one portion and the reaction mixture was stirred for 1 hour. Methyl iodide (300 M%) was added and this mixture was stirred for 12 hours. The reaction was then poured into water and extracted with ethyl acetate (3x) then backwashed with water (3x) and then brine (1x). Treatment
10 with MgSO_4 , rotoevaporation, and chromatography (5% MeOH/ CH_2Cl_2) yielded BOC-protected 3-amino-1,5-dimethyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one in 75% yield.

15 Step D: BOC-protected 3-amino-1,5-dimethyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (100 M%) was suspended in 30 mL of 1:1 CH_2Cl_2 /trifluoroacetic acid. The reaction mixture was stirred for 4 hours. The reaction was then rotoevaporated to yield 3-amino-1,5-dimethyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one (100% yield).

20

Example 6-B

Synthesis of

5-(L-Alaninyl)-amino-3,3,7-trimethyl-5,7-dihydro-6H-benz[b]azepin-6-one Hydrochloride

25 Following the procedure of Example 7-I and using 5-amino-3,3,7-trimethyl-5,7-dihydro-6H-benz[b]azepin-6-one hydrochloride (Example 6-C), the title compound was prepared.

Example 6-C

30

Synthesis of

5-Amino-3,3,7-trimethyl-5,7-dihydro-6H-benz[b]azepin-6-one Hydrochloride

-- 258 --

Step A: Following General Procedure 5-A and using N-t-Boc-5-amino-3,3-dimethyl-5,7-dihydro-6H-benz[b]azepin-6-one (General Procedure 6-B, following by Boc protection) and methyl iodide, N-t-Boc-5-amino-3,3,7-trimethyl-5,7-dihydro-6H-benz[b]azepin-6-one was prepared.

5

Step B: Following General Procedure 8-N and using N-t-Boc-5-amino-3,3,7-trimethyl-5,7-dihydro-6H-benz[b]azepin-6-one, the title compound was prepared.

10

Example 6-D

Synthesis of

3-(S)-Amino-1-methyl-5-oxa-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

Step A: 3-(S)-Amino-5-oxa-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one was prepared from N-Boc-serine (Bachem) and 2-fluoro-1-nitrobenzene (Aldrich) using the method of R. J. DeVita et al., *Bioorganic and Medicinal Chemistry Lett.* **1995**, 5(12) 1281-1286.

15

Step B: Following General Procedure 5-A and using the product from Step A, the title compound was prepared.

20

Example 6-E

Synthesis of

3-(S)-Amino-1-ethyl-5-oxa-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

25

Step A: 3-(S)-Amino-5-oxa-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one was prepared from N-Boc-serine (Bachem) and 2-fluoro-1-nitrobenzene (Aldrich) using the method of R. J. DeVita et al., *Bioorganic and Medicinal Chemistry Lett.* **1995**, 5(12) 1281-1286.

30

Step B: Following General Procedure 5-A and using the product from Step A, the title compound was prepared.

Example 6-F

Synthesis of
3-(S)-Amino-1-methyl-5-thia-1,3,4,5-
tetrahydro-2H-1-benzazepin-2-one

5 The title compound was prepared from N-Boc-cystine (Novabio) and 2-fluoro-1-nitrobenzene (Aldrich) using the method of R. J. DeVita et al., *Bioorganic and Medicinal Chemistry Lett.* 1995, 5(12) 1281-1286, followed by General Procedure 5-A.

10

GENERAL PROCEDURE 7-A

Preparation of
5-Amino-7-alkyl-5,7-dihydro-
6H-dibenz[b,d]azepin-6-one Derivatives

15 Step A: Following General Procedure 5-A and using 5,7-dihydro-6H-dibenz[b,d]azepin-6-one and an alkyl halide, the 7-alkyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one was prepared.

20 Step B: The 7-alkyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (1 eq.) was dissolved in THF and isoamyl nitrite (1.2 eq.) was added. The mixture was cooled to 0°C in an ice bath. NaHMDS (1.1 eq., 1M in THF) was added dropwise. After stirring for 1 hour or until the reaction was complete, the mixture was concentrated then acidified with 1N HCl and extracted with EtOAc. The organic portion was dried and concentrated to yield a crude product which was purified by silica gel chromatography.

25

Step C: The resulting oxime was dissolved in EtOH/NH₃ (20:1) and hydrogenated in a bomb using Raney nickel and hydrogen (500 psi) at 100°C for 10 hours. The resulting mixture was filtered and concentrated to provide an oil which was purified by silica gel chromatography to yield the title compound.

30

GENERAL PROCEDURE 7-B

Preparation of
Fluoro-substituted 5,7-dihydro-6H-

-- 260 --

dibenz[b,d]azepin-6-one Derivatives

A modification of the procedure of Robin D. Clark and Jahangir, *Tetrahedron*, Vol. 49, No. 7, pp. 1351-1356, 1993 was used. Specifically, an appropriately substituted N-t-Boc-2-amino-2'-methylbiphenyl was dissolved in THF and cooled to -78°C. s-Butyl lithium (1.3M in cyclohexane, 2.2 eq.) was added slowly so that the temperature remained below -65°C. The resulting mixture was allowed to warm to -25°C and was stirred at that temperature for 1 hour. The mixture was cooled to -78°C. Dry CO₂ was bubbled through the mixture for 30 seconds. The mixture was allowed to warm to ambient temperature then was carefully quenched with water. The mixture was concentrated under reduced pressure then was adjusted to pH 3 with 1N HCl. The mixture was extracted with EtOAc and the organic portion was dried and concentrated to yield a crude material. The crude material was dissolved in methanol and the solution was saturated with HCl. The mixture was heated at reflux for 12 hours then was allowed to cool. The mixture was concentrated to provide crude lactam which was purified by chromatography or crystallization.

GENERAL PROCEDURE 7-C

Resolution of

20 5-Amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

In a round bottom flask was added the racemic freebase amine (1.0 eq.) in methanol followed by di-*p*-toluoyl-D-tartaric acid monohydrate (1.0 eq.). The mixture was concentrated *in vacuo* to a residue and redissolved in a moderate volume of methanol and allowed to stir at room temperature open to the atmosphere (8-72 hours). The solid was removed by filtration. The enantiomeric excess was determined by chiral HPLC (Chiracel ODR) using 15% acetonitrile and 85% H₂O with 0.1% trifluoroacetic acid and a flow rate of 1.0 mL/min at 35°C. The resolved di-*p*-toluoyl-D-tartaric salt was then dissolved in EtOAc and saturated NaHCO₃ until pH 9-10 was reached. The layers were separated and the organic layer was washed again with saturated NaHCO₃, H₂O, and brine. The organic layer was dried over MgSO₄ and the drying agent was removed by filtration. The filtrate was concentrated *in vacuo*.

The free amine was dissolved in MeOH and HCl (12M, 1.0 eq.) was added. The salt was concentrated *in vacuo* and the resulting film was triturated with EtOAc. The HCl salt was filtered and rinsed with EtOAc. The ee was determined by chiral HPLC.

5

Example 7-A

Synthesis of 5-Amino-7-methyl-5,7-dihydro- 6H-dibenz[b,d]azepin-6-one Hydrochloride

10 Step A - Synthesis of 7-Methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

A round bottom flask was charged with sodium hydride (0.295 g, 7.46 mmol) in 9.0 ml of DMF and treated with 5,7-dihydro-6H-dibenz[b,d]azepin-6-one (1.3 g, 6.22 mmol) (CAS # 20011-90-9, prepared as described in Brown, et. al., Tetrahedron Letters, No. 8, 667-670, (1971) and references cited therein). After stirring at 60°C for 1 h, the solution was treated with methyl iodide (1.16 ml, 18.6 mmol) and stirring continued for 17 h with the exclusion of light. After cooling, the reaction was diluted with CH₂Cl₂/H₂O, washed with NaHSO₄ solution, H₂O, and dried over Na₂SO₄. Evaporation and flash chromatography (SiO₂, CHCl₃) gave 0.885 g (63%) of the title compound as a colorless solid.

20

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 7.62 (d, 2H), 7.26-7.47 (m, 6H), 3.51 (m, 2H), 3.32 (s, 3H).

C₁₅H₁₃NO (MW = 223.27); mass spectroscopy (MH⁺) 223.

25 Anal. Calcd for C₁₅H₁₃NO; C, 80.69 H, 5.87 N, 6.27. Found: C, 80.11 H, 5.95 N, 6.23.

Step B - Synthesis of 7-Methyl-5-oximo-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

30 The compound isolated above (0.700 g, 3.14 mmol) was dissolved in 20 ml of toluene and treated with butyl nitrite (0.733 ml, 6.28 mmol). The reaction temperature was lowered to 0°C and the solution was treated with KHMDS

Anal. Calcd for $C_{15}H_{12}N_2O_2$; C, 71.42 H, 4.79 N, 11.10. Found: C, 71.24
9 N, 10.87.

The oxime isolated above (0.99 g, 3.92 mmol) was hydrogenated in a Parr apparatus at 35 psi over 10 % Pd/C (0.46 g) in 3A ethanol. After 32 h the reaction mixture was filtered through a plug of celite, the filtrate evaporated to a foam and treated with a saturated solution of HCl (g) in Et₂O. The resulting colorless solid was filtered, rinsed with cold Et₂O and vacuum dried to give 0.66 g (61 %) of the title compound.

¹H-nmr (DMSOd6): δ = 9.11 (bs, 3H), 7.78-7.41(m, 8H), 4.83 (s, 1H), 3.25 (s, 3H).

Anal. Calcd for $C_{15}H_{14}N_2O \cdot HCl$; C, 65.57 H, 5.50 N, 10.19 Found: C, 65.27 H, 5.67 N, 10.13.

**Synthesis of
(S)- and (R)-5-(L-Alaninyl)-amino-7-methyl-
5,7-dihydro-6H-dibenz[b,d]azepin-6-one**

Boc-L-Alanine (0.429 g, 2.26 mmol) (Aldrich) was dissolved in THF and treated with HOBt hydrate (0.305 g, 2.26 mmol), and 5-amino-7-methyl-5,7-

dihydro-6H-dibenz[b,d]azepin-6-one (0.45 g, 1.89 mmol) (Example 7-A). The temperature was lowered to 0°C and the reaction mixture treated with EDC (0.449 g, 2.26 mmol) (Alrich) and stirred 17 hours under N₂. The reaction mixture was evaporated, the residue diluted with EtOAc/H₂O, washed 1.0 N HCl, sat. NaHCO₃, brine and dried over Na₂SO₄. The diastereomers were separated on a Chiralcel OD column using 10% IPA/heptane at 1.5 ml/minute.

Isomer 1: Retention time 3.37 minutes.

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 7.62-7.33 (m, 9H), 5.26 (d, 1H), 5.08 (m, 1H), 4.34 (m, 1H), 3.35 (s, 3H), 1.49 (s, 9H), 1.40 (d, 3H).

Optical Rotation: [α]₂₀ = - 96 @ 589 nm (c = 1, MeOH).

C₂₃H₂₇N₃O₄ (MW = 409.489); mass spectroscopy (MH⁺) 409.

Anal. Calcd for C₂₃H₂₇N₃O₄; C, 67.46 H, 6.64 N, 10.26. Found: C, 68.42 H, 7.02 N, 9.81.

Isomer 2: Retention time 6.08 minutes.

NMR data was as follows:

¹H-nmr (CDCl₃): δ = 7.74 (bd, 1H), 7.62-7.32 (m, 8H), 5.28 (d, 1H), 4.99 (m, 1H), 4.36 (m, 1H), 3.35 (s, 3H), 1.49 (s, 9H), 1.46 (d, 3H).

Optical Rotation: [α]₂₀ = 69 @ 589 nm (c = 1, MeOH).

C₂₃H₂₇N₃O₄ (MW = 409.489); mass spectroscopy (MH⁺) 409.

Anal. Calcd for C₂₃H₂₇N₃O₄; C, 67.46 H, 6.64 N, 10.26. Found: C, 67.40 H, 6.62 N, 10.02

Step B - Synthesis of (S)- and (R)-5-(L-Alaninyl)-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride

The compounds isolated in Part A (each isomer separately) were dissolved in dioxane and treated with excess HCl (g). After stirring for 17 hours, the title compounds were isolated as colorless solids after evaporation and vacuum drying.

Isomer 1:

C₁₈H₁₉N₃O₂.HCl (MW = 345.832); mass spectroscopy (MH⁺ free base) 309.

-- 264 --

Optical Rotation: $[\alpha]_{20} = -55$ @ 589 nm ($c = 1$, MeOH).

Isomer 2:

$C_{18}H_{19}N_3O_2 \cdot HCl$ (MW = 345.832); mass spectroscopy (MH⁺ free base)

309.

5 Optical Rotation: $[\alpha]_{20} = 80$ @ 589 nm ($c = 1$, MeOH).

Example 7-C

Synthesis of

10 (S)- and (R)-5-(L-Valinyl)-amino-7-methyl-
5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Step A - Synthesis of (S)- and (R)-5-(N-Boc-L-Valinyl)-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

15 Boc-L-Valine (0.656 g, 3.02 mmol) (Aldrich) was dissolved in THF and treated with HOBt hydrate (0.408, 3.02 mmol), DiPea (1.05 ml, 6.05 mmol) and 5-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one hydrochloride (0.75 g, 2.75 mmol) (Example 7-A). The temperature was lowered to 0°C and the reaction mixture treated with EDC (0.601 g, 3.02 mmol) (Alrich) and stirred 17 hours under N₂. The reaction mixture was evaporated, the residue diluted with EtOAc/H₂O, washed 1.0 N HCl, sat. NaHCO₃, brine and dried over 20 Na₂SO₄. The diastereomers were separated on a Chiralcel OD column using 10% IPA/heptane at 1.5 ml/minute.

Isomer 1: Retention time 3.23 minutes.

Optical Rotation: $[\alpha]_{20} = -120$ @ 589 nm ($c = 1$, MeOH).

$C_{25}H_{31}N_3O_4$ (MW = 437.544); mass spectroscopy (MH⁺) 438

25 Isomer 2: Retention time 6.64 minutes.

Optical Rotation: $[\alpha]_{20} = 50$ @ 589 nm ($c = 1$, MeOH).

$C_{25}H_{31}N_3O_4$ (MW = 437.544); mass spectroscopy (MH⁺) 438

30 Step B - Synthesis of (S)- and (R)-5-(L-Valinyl)-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride

The compounds isolated in Part A (each isomer separately) were dissolved in dioxane and treated with excess HCl (g). After stirring for 17

hours, the title compounds were isolated as colorless solids after evaporation and vacuum drying.

Isomer 1:

$C_{20}H_{23}N_3O_2 \cdot HCl$ (MW = 373.88); mass spectroscopy (MH⁺ free base)

5 338.

Optical Rotation: $[\alpha]_{20} = -38$ @ 589 nm (c = 1, MeOH).

Isomer 2:

$C_{20}H_{23}N_3O_2 \cdot HCl$ (MW = 373.88); mass spectroscopy (MH⁺ free base)

338.

10 Optical Rotation: $[\alpha]_{20} = 97$ @ 589 nm (c = 1, MeOH).

Example 7-D

Synthesis of

(S)- and (R)-5-(L-tert-Leucine)-amino-7-methyl-
5,7-dihydro-6H-dibenz[b,d]azepin-6-one

15

Step A - Synthesis of (S)- and (R)-5-(N-Boc-L-tert-Leuciny)-
amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

Boc-L-tert-Leucine (0.698 g, 3.02 mmol) (Fluka) was dissolved in THF and treated with HOBt hydrate (0.408, 3.02 mmol), Dipea (1.05 ml, 6.05 mmol) and 5-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one hydrochloride (0.75 g, 2.75 mmol)(Example 7-A). The temperature was lowered to 0°C and the reaction mixture treated with EDC (0.601 g, 3.02 mmol) (Alrich) and stirred 17 hours under N₂. The reaction mixture was evaporated, the residue diluted with EtOAc/H₂O, washed 1.0 N HCl, sat. NaHCO₃, brine and dried over Na₂SO₄. The diastereomers were separated on a Chiralcel OD column using 10% IPA/heptane at 1.5 ml/minute.

20

25

Isomer 1: Retention time 3.28minutes.

Optical Rotation: $[\alpha]_{20} = -128$ @ 589 nm (c = 1, MeOH).

$C_{26}H_{33}N_3O_4$ (MW = 451.571); mass spectroscopy (MH⁺) 452

30

Isomer 2: Retention time 5.52 minutes.

Optical Rotation: $[\alpha]_{20} = 26$ @ 589 nm (c = 1, MeOH).

-- 266 --

$C_{26}H_{33}N_3O_4$ (MW = 451.571); mass spectroscopy (MH+) 452

Step B - Synthesis of (S)- and (R)-5-(L-tert-Leucynyl)-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride

The compounds isolated in Part A (each isomer separately) were dissolved in dioxane and treated with excess HCl (g). After stirring for 17 hours, the title compounds were isolated as colorless solids after evaporation and vacuum drying.

Isomer 1:

$C_{21}H_{25}N_3O_2 \cdot HCl$ (MW = 387.91); mass spectroscopy (MH+ free base)

352.

Optical Rotation: $[\alpha]_{20} = -34$ @ 589 nm (c = 1, MeOH).

Isomer 2:

$C_{21}H_{25}N_3O_2 \cdot HCl$ (MW = 387.91); mass spectroscopy (MH+ free base)

352.

Optical Rotation: $[\alpha]_{20} = 108$ @ 589 nm (c = 1, MeOH).

Example 7-E

Synthesis of

5-(N-Boc-Amino)-5,7-dihydro-6H,7H-dibenz[b,d]azepin-6-one

Step A - Synthesis of 5-Iodo-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

A solution of 5,7-dihydro-6H-dibenz[b,d]azepin-6-one (1.0 g, 4.77 mmol) (Example 7-A) and Et_3N (2.66 ml, 19.12 mmol) were stirred for 5.0 minutes at $-15^\circ C$ in CH_2Cl_2 and treated with TMSI (1.36 ml, 9.54 mmol). After stirring for 15 minutes I_2 (1.81 g, 7.16 mmol) was added in a single portion and the reaction allowed to warm to $5-10^\circ C$ over 3 h. The reaction was quenched with sat. Na_2SO_3 , diluted with CH_2Cl_2 and separated. The organics were washed with Na_2SO_3 and $NaHSO_3$ and dried over $MgSO_4$. After filtration, the organics were concentrated to approximately 20 ml and diluted with an additional 20 ml of hexanes. The title compound was isolated as a tan precipitate by filtration.

Step B - Synthesis of 5-Azido-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

The iodide isolate above was dissolved in DMF and treated with 1.2 equivalents of NaN_3 . After stirring 17 h at 23°C the mixture was diluted with EtOAc/ H_2O , separated, washed with brine and dried over MgSO_4 . The title compound was triturated from hot EtOAc as a tan powder.

Step C - Synthesis of 5-(N-Boc-Amino)-5,7-dihydro-6H,7H-dibenz[b,d]azepin-6-one

The azide was dissolved in THF/ H_2O and stirred at 23°C for 17 h in the presence of 3.0 equivalents of Ph_3P . The reaction was diluted with 50 % HOAc/toluene, separated, the aqueous layer extracted with toluene and evaporated to an oily residue. This was taken to pH 7.0 by the addition of 1 N NaOH, the resulting HOAc salt was collected and vacuum dried. Finally, the compound was treated with Boc anhydride (1.05 equivalents) and Et_3N (2.1 equivalents) in THF. After stirring for 5 h at 23°C the reaction was filtered and the title compound isolated as a colorless powder.

Example 7-F

20 Synthesis of
5-Amino-7-(2-methylpropyl)-5,7-dihydro-
6H-dibenz[b,d]azepin-6-one Hydrochloride

Step A - Synthesis of 5-(N-Boc-Amino)-7-(2-methylpropyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

25 A solution of 5-(N-Boc-amino)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (0.2g, 0.617 mmol) (Example 7-E) in DMF was treated with Cs_2CO_3 (0.22 g, 0.678 mmol) and warmed to 60°C. To the reaction mixture was added 1-iodo-2-methylpropane (0.078 ml, 0.678 mmol) and stirring continued for 17 h. After cooling to 23 °C the mixture was diluted with CH_2Cl_2 , washed with several portions of brine and dried over Na_2SO_4 . The title compound was purified by chromatography (SiO_2 , $\text{CHCl}_3/\text{MeOH}$ 9:1).

30 $\text{C}_{23}\text{H}_{28}\text{N}_2\text{O}_3$ (MW = 380.41); mass spectroscopy (MH+) 381

-- 268 --

Anal. Calcd for $C_{23}H_{28}N_2O_3$; C, 72.61 H, 7.42 N, 7.36. Found: C, 72.31 H, 7.64 N, 7.17.

5

Step B - Synthesis of 5-Amino-7-(2-methylpropyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride

The compound isolated in Part A was deprotected in dioxane saturated with gaseous HCl. The title compound was isolated as a slightly colored solid after evaporation and vacuum drying.

10

Example 7-G

**Synthesis of
5-Amino-7-(methoxyacetyl)-5,7-dihydro-
6H-dibenz[b,d]azepin-6-one Hydrochloride**

15

Step A- Synthesis of 5-(N-Boc-Amino)-7-(methoxyacetyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

20

A solution of 5-(N-Boc-amino)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (1.03, 3.08 mmol) (Example 7-E) in DMF was treated with Cs_2CO_3 (1.10 g, 3.39 mmol) and warmed to 60°C. To the reaction mixture was added bromomethyl acetate (0.321 ml, 3.39 mmol) (Aldrich) and stirring continued for 17 h. After cooling to 23 °C the mixture was diluted with CH_2Cl_2 , washed with several portions of brine and dried over Na_2SO_4 . The title compound was purified by chromatography (SiO_2 , $CHCl_3$).

$C_{22}H_{24}N_2O_5$ (MW = 396.44); mass spectroscopy (MH⁺) 397

25

Anal. Calcd for $C_{22}H_{24}N_2O_5$; C, 66.65 H, 6.10 N, 7.07. Found: C, 66.28 H, 5.72 N, 6.50.

Step B - Synthesis of 5-Amino-7-(methoxyacetyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride

30

The compound isolated in Part A was deprotected in dioxane saturated with gaseous HCl. The title compound was isolated as a colorless solid after evaporation and vacuum drying.

$C_{17}H_{16}N_2O_3$ HCl (MW = 332.78); mass spectroscopy (MH⁺ free base) 297.

Example 7-H

**Synthesis of
5-Amino-7-(3,3-dimethyl-2-butanonyl)-
5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride**

5 Step A- Synthesis of 5-(N-Boc-Amino)-7-(3,3-dimethyl-butanonyl)-
5,7-dihydro-6H-dibenz[b,d]azepin-6-one

A solution of 5-(N-Boc-amino)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (0.2 g, 0.617 mmol) (Example 7-E) in DMF was treated with Cs_2CO_3 (0.3 g, 0.925 mmol) and warmed to 60°C. To the reaction mixture was added 1-chloro-
10 3,3-dimethyl-2-butanone (0.096 ml, 0.74 mmol) (Aldrich) and stirring continued for 17 h. After cooling to 23 °C, the mixture was diluted with CH_2Cl_2 , washed with several portions of brine and dried over Na_2SO_4 . The title compound was isolated as a colorless solid.

$\text{C}_{25}\text{H}_{30}\text{N}_2\text{O}_4$ (MW = 422.522); mass spectroscopy (MH⁺) 423

15

Step B - Synthesis of 5-Amino-7-(3,3-dimethyl-2-butanonyl)-5,7-
dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride

The compound isolated in Part A was deprotected in dioxane saturated with gaseous HCl. The title compound was isolated as a colorless solid after
20 evaporation and vacuum drying.

Example 7-I

**Synthesis of
L-Alaninyl-5-amino-7-methyl-5,7-dihydro-
6H-dibenz[b,d]azepin-6-one Hydrochloride**

25

Step A: Following General Procedure III-D and using N-t-Boc-L-alanine and 5-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one, N-t-Boc-L-alaninyl-5-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one was prepared.

30

Step B: Following General Procedure 8-N and using the N-t-Boc-L-alaninyl-5-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one, the title compound was prepared. Other substituted N-t-Boc-L-alaninyl-5-amino-7-

-- 270 --

methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-ones can also be prepared by this procedure.

Example 7-J

5

Synthesis of L-Valinyl-5-amino-7-methyl-5,7-dihydro- 6H-dibenz[b,d]azepin-6-one Hydrochloride

Step A: Following General Procedure III-D and using N-t-Boc-L-valine and 5-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one, N-t-Boc-L-valinyl-5-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one was prepared.

Step B: Following General Procedure 8-N and using the N-t-Boc-L-valinyl-5-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one, the title compound was prepared. Other substituted N-t-Boc-L-valinyl-5-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-ones can also be prepared by this procedure.

Example 7-K

Synthesis of 5-Amino-7-phenbutyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

20

Following General Procedure 7-A and using 5,7-dihydro-6H-dibenz[b,d]azepin-6-one (prepared as described in Brown, et. al., Tetrahedron Letters, No. 8, 667-670, (1971) and references cited therein) and 1-chloro-4-phenylbutane (Aldrich), the title compound was prepared.

25

Example 7-L

Synthesis of 5-Amino-7-cyclopropymethyl-5,7-dihydro- 6H-dibenz[b,d]azepin-6-one

30

Following General Procedure 7-A and using 5,7-dihydro-6H-dibenz[b,d]azepin-6-one (prepared as described in Brown, et. al., Tetrahedron Letters, No. 8, 667-670, (1971) and references cited therein) and (bromomethyl)cyclopropane (Aldrich), the title compound was prepared.

-- 271 --

Example 7-M.

Synthesis of

5-Amino-7-(2',2',2'-trifluoroethyl)-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

5 Following General Procedure 7-A and using 5,7-dihydro-6H-dibenz[b,d]azepin-6-one (prepared as described in Brown, et. al., Tetrahedron Letters, No. 8, 667-670, (1971) and references cited therein) and 1-bromo-2,2,2-trifluoroethane (Aldrich), the title compound was prepared.

10

Example 7-N

Synthesis of

5-Amino-7-cyclohexyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one

15 Following General Procedure 7-A and using 5,7-dihydro-6H-dibenz[b,d]azepin-6-one (prepared as described in Brown, et. al., Tetrahedron Letters, No. 8, 667-670, (1971) and references cited therein) and bromocyclohexane (Aldrich), the title compound was prepared.

Example 7-O

20

Synthesis of

5-(L-Alaninyl)amino-9-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride

25 Step 1: 2-Bromo-5-fluorotoluene was stirred in THF at -78C. s-BuLi (1.05 eq., 1.3 M in cyclohexane) was slowly added and the mixture was stirred for 45 minutes. Trimethylborate (1.5 eq) was added and the mixture was allowed to warm to ambient temperature. After stirring for 1 hour, pinacol (2 eq.) was added. The mixture was stirred for 16 hours then was concentrated under reduced pressure. The resulting residue was slurried in CH₂Cl₂ and filtered through Celite. The filtrate was concentrated to yield an oil which was
30 purified by chromatography on deactivated silica gel (Et₃N) to yield the arylboronate ester.

-- 272 --

Step 2: 2-Bromoaniline (1 eq.) and di-*t*-butyl-dicarbonate (1.1 eq.) were stirred at 80°C for 20 hours. The resulting mixture was allowed to cool and was directly distilled using house vacuum to provide N-*t*-Boc-2-bromoaniline.

5 Step 3: N-*t*-Boc-2-bromoaniline (Step 2, 1 eq.), the arylboronate ester (Step 1, 1.1 eq.), K₂CO₃ (1.1 eq.) and tetrakis(triphenylphosphine)palladium(0) (0.02 eq) were stirred in 20% water/dioxane under nitrogen. The solution was heated at reflux for 10 hours. The mixture was allowed to cool then was concentrated. The resulting residue was partitioned between water and
10 chloroform. The organic portion was dried and concentrated to yield an oil which was purified by silica gel chromatography using 1:1 CH₂Cl₂/hexanes.

Step 4: Following General Procedure 7-B and using the substituted biphenyl from step 3, the 9-fluoro-5,7-dihydro-6H-dibenz[b,d]azepin-6-one was
15 prepared.

Step 5: 9-Fluoro-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (1 eq., Step 4), cesium carbonate (1.1 eq., Aldrich) and methyl iodide (1.1 eq., Aldrich) were stirred in dry DMF at ambient temperature for 16 hours. The mixture was
20 concentrated under reduced pressure to provide a residue which was partitioned between EtOAc and water. The organic portion was dried and concentrated to yield an oil which was purified by silica gel chromatography to 9-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one.

25 Step 6: Following General Procedure 7-A, Step B and 9-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one from Step 5, 5-amino-9-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one was prepared.

Step 7: Following the procedure of Example 7-I and using 5-amino-9-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one from Step 6, the title
30 compound was prepared.

-- 273 --

Example 7-P

Synthesis of

**5-(L-Alaninyl)amino-13-fluoro-7-methyl-
5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride**

5 Following the procedure of Example 7-O and using 2-bromo-4-fluoroaniline (Step 2, Lancaster) and o-tolylboronic acid (Step 3, Aldrich), the title compound was prepared.

10

Example 7-Q

Synthesis of

**5-(L-Alaninyl)amino-10-fluoro-7-methyl-
5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride**

15 Following the procedure of Example 7-O and using 2-bromo-4-fluorotoluene (Step 1), the title compound was prepared.

Example 7-R

Synthesis of

20 **5-(L-Alanyl)-amino-7-cyclopropylmethyl-
5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride**

Following the procedure of Example 7-I and using 5-amino-7-cyclopropylmethyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (Example 7-L), the title compound was prepared.

25

Example 7-S

Synthesis of

**5-(L-Alaninyl)amino-7-phenbutyl-
5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride**

30 Following the procedure of Example 7-I and using 5-amino-7-phenbutyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (Example 7-K), the title compound was prepared.

Example 7-T

Synthesis of

-- 274 --

**5-(L-Valinyl)amino-7-cyclopropylmethyl-
5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride**

Following the procedure of Example 7-J and using 5-amino-7-cyclopropylmethyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (Example 7-L), the
5 title compound was prepared.

Example 7-U

**Synthesis of
5-(L-Valinyl)amino-7-phenbutyl-
10 5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride**

Following the procedure of Example 7-J and using 5-amino-7-phenbutyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (Example 7-U), the title compound was prepared.

15 Example 7-V

**Synthesis of
5-(L-Valinyl)amino-7-hexyl-5,7-dihydro-
6H-dibenz[b,d]azepin-6-one Hydrochloride**

Step A: Following General Procedure 7-A and using 5,7-dihydro-6H-dibenz[b,d]azepin-6-one (prepared as described in Brown, et. al., Tetrahedron Letters, No. 8, 667-670, (1971) and references cited therein) and 1-bromohexane (Aldrich), 5-amino-7-hexyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one was
20 prepared.

Step B: Following the procedure of Example 7-J and using 5-amino-7-hexyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one, the title compound was prepared.
25

Example 7-W

**Synthesis of
5-(L-Valinyl)amino-10-fluoro-7-methyl-
30 5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride**

Following the procedure of Example 7-J and using 5-amino-10-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (as prepared in Example 7-Q), the title compound was prepared.

-- 275 --

Example 7-X

**Synthesis of
5-(L-Valinyl)amino-13-fluoro-7-methyl-
5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride**

5 Following the procedure of Example 7-J and using the 5-amino-13-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (as prepared in Example 7-P), the title compound was prepared.

Example 7-Y

**Synthesis of
5-(L-Valinyl)amino-13-fluoro-7-methyl-
5,7-dihydro-6H-dibenz[b,d]azepin-6-one Hydrochloride**

10 Following the procedure of Example 7-J and using the 5-amino-9-fluoro-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (as prepared in Example 7-O),
15 the title compound was prepared.

Example 7-Z

**Synthesis of
(5-Amino-7-methyl-1,2,3,4,5,7-hexahydro-
6H-dicyclohexyl[b,d]azepin-6-one**

20 The 5-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one hydrochloride (Example 7-A) was dissolved in a 1:1 mixture of EtOAc/HOAc. 5% Rh/C was added and the mixture was stirred at 60°C under 60 psi of hydrogen. After 3 days, the mixture was filtered and the filtrate was
25 concentrated to provide an oil which was purified by SCX-cation exchange chromatography to yield the title compound.

Example 7-AA

**Synthesis of
5-(S)-Amino-7-methyl-5,7-dihydro-
6H-dibenz[b,d]azepin-6-one Hydrochloride**

30 Following General Procedure 7-C using racemic 5-amino-7-methyl-5,7-dihydro-6H-dibenz[b,d]azepin-6-one (1.0 eq.) and di-*p*-toluoyl-D-tartaric acid monohydrate (1.0 eq.) in methanol, the title compound was prepared as a solid.

-- 276 --

The product was collected by filtration. Enantiomeric excess was determined by chiral HPLC.

Desired enantiomer 1: retention time of 9.97 minutes.

Undesired enantiomer 2: retention time of 8.62 minutes.

5 NMR data was as follows:

¹H-nmr (CDCl₃): δ = 9.39 (s, 2H), 7.75-7.42 (m, 8H), 4.80 (s, 1H), 3.30 (s, 3H).

C₁₅H₁₅ClN₂O (MW = 274.75); mass spectroscopy (MH⁺) 239.1.

Anal Calcd for C₁₅H₁₅ClN₂O₃; C, 65.57; H, 5.50; N, 10.20; Found: C, 65.51, H, 5.61; N, 10.01.

GENERAL PROCEDURE 8-A

N-1-Methylation of Benzodiazepines

15 A solution of benzodiazepine (1 eq.) in DMF (0.1 M concentration) at 0°C was treated with potassium tert-butoxide (1.0 eq., 1.0 M solution in THF). After stirring for 30 minutes at 0°C, iodomethane (1.3 eq.) was added and stirring continued for 25 minutes. The mixture was diluted with methylene chloride and washed with water and brine. The organic phase was dried over Na₂SO₄, filtered, and concentrated. The crude product was then either purified 20 by trituration with 1:1 ether/hexanes or chromatographed via HPLC using ethyl acetate/hexanes as the eluent.

GENERAL PROCEDURE 8-B

Cbz Removal Procedure

25 A flask was charged with the Cbz-protected 3-aminobenzodiazepine (1 eq.). To this was added HBr (34 eq.; 30% solution in acetic acid). Within 20 minutes all of the starting material dissolves. The reaction was stirred for 5 hours at ambient temperature. Ether was added to the orange solution causing the HBr•amine salt to precipitate. The mixture was decanted. This process of 30 adding ether and decanting was repeated thrice in an effort to remove acetic acid and benzyl bromide. Toluene was added and the mixture concentrated *in vacuo*.

-- 277 --

This step was also repeated. The HBr salt was partitioned between ethyl acetate and 1 M K_2CO_3 . The aqueous layer was back-extracted with ethyl acetate. The combined organics were washed with brine, dried over Na_2SO_4 , filtered, and concentrated.

5

GENERAL PROCEDURE 8-C

Boc Removal Procedure

A solution of Boc-protected amine (1 eq.) in methylene chloride (0.15 M concentration) was cooled to 0°C and treated with trifluoroacetic acid (30 eq.).

10 After 10 minutes at 0°C, the cooling bath was removed and stirring continued at ambient for 20 minutes to 1 hour. The mixture was concentrated *in vacuo* to remove excess trifluoroacetic acid. The residue was dissolved in methylene chloride and washed with saturated aqueous $NaHCO_3$ or 1 M K_2CO_3 and brine. The organic layer was dried over Na_2SO_4 , filtered, and concentrated.

15

GENERAL PROCEDURE 8-D

Azide Transfer Reaction Using KHMDS

The azido derivative was prepared using the procedure described in John W. Butcher et al., *Tet. Lett.*, 37, 6685-6688 (1996).

20

GENERAL PROCEDURE 8-E

Azide Transfer Reaction Using LDA

To a solution of diisopropylamine (1.1 eq.) in 1 mL of dry THF cooled to -78°C was added n-butyl lithium (1.6M in hexane) (1.1 eq.) dropwise
25 maintaing the reaction temperature at -78°C. The reaction mixture was stirred for 30 min. at -78°C and then the lactam (0.471 mM) was added dropwise as a solution in 1 mL of dry THF. The reaction mixture was stirred at -78°C for 30 min. and then a pre-cooled solution of trisyl azide (1.2 eq.) was added as a solution in 1 mL of dry THF. The reaction mixture was stirred at -78°C for 20
30 min. and then quenched with acetic acid (4.0 eq.). The reaction mixture was then stirred at 40°C for 2 hrs. The reaction was then poured into EtOAc and

-- 278 --

washed with water, sodium bicarbonate and brine, and then dried over sodium sulfate, filtered and concentrated. The residue was purified by LC 2000 chromatography.

5

GENERAL PROCEDURE 8-F

Azido Group Reduction

The azido group was reduced to the corresponding primary amine using the procedure described in John W. Butcher et al., *Tet. Lett.*, 37, 6685-6688 (1996).

10

GENERAL PROCEDURE 8-G

N-Alkylation of Amides or Lactams

Using Sodium Hydride or Potassium tert-Butoxide

To a slurry of sodium hydride or potassium tert-butoxide (1.1 eq) in 15 mL of dry DMF was added the appropriate amide (0.0042 moles) as a solution in 10 mL of DMF. The alkyl iodide was then added and a thick slurry resulted. The reaction became less thick as time elapsed and when complete by TLC the reaction had become homogeneous. The reaction mixture was poured over ice and extracted into ethyl acetate. The organic layer was washed with water, followed by brine. The organic layer was then dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by HPLC (LC 2000), eluting with an ethyl acetate/hexane system.

20

GENERAL PROCEDURE 8-H

25

N-Alkylation of

Amides or Lactams Using KHMDS

To the appropriate amide or lactam in THF cooled to -78°C was added KHMDS dropwise and the reaction mixture was stirred for 30 min. at -78°C. The alkyl iodide was then added dropwise while maintaining the temperature at -70°C. The cooling bath was then removed and reaction was allowed to warm to room temperature and stirring was continued for 2 hours. The reaction mixture was then poured over ice and extracted into ethyl acetate. The organic

30

extracts were washed with water, followed by brine. The organic layer was then dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by HPLC (LC 2000), eluting with an ethyl acetate/hexane system.

5

GENERAL PROCEDURE 8-I

N-Alkylation of Amides or Lactams Using Cesium Carbonate

To a solution of the amide or lactam in DMF was added cesium carbonate (1.05 eq) and an alkyl iodide (1.1 eq). The mixture was allowed to stir overnight at room temperature and then the reaction mixture was diluted with ethyl acetate and washed with water, followed by brine. The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by HPLC (LC 2000), eluting with an ethyl acetate/hexane system.

15

GENERAL PROCEDURE 8-J

BOC Removal Procedure

To an N-Boc protected compound was added $\text{CH}_2\text{Cl}_2/\text{TFA}$ (4:1) at room temperature. The reaction mixture was stirred at room temperature for 3 hours and then concentrated. The residue was extracted into dichloromethane and washed with water, saturated sodium bicarbonate, dried over Na_2SO_4 , filtered and concentrated to give the free amine.

20

GENERAL PROCEDURE 8-K

Azide Transfer Procedure

25

This azide transfer procedure is a modification of the procedure described in Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 4011-4030. To a solution of the lactam substrate (1.0 eq.) in THF (~0.1 M) under N_2 at -78°C was added a solution of $\text{KN}(\text{TMS})_2$ (1.1 eq. of 0.5 M in Toluene, Aldrich) dropwise over a period of 2-10 minutes. A slight exotherm was often observed by an internal thermometer, and the resulting

30

-- 280 --

solution was stirred for 5-15 minutes, while re-cooling to -78°C . Then, trisyl azide (1.1-1.5 eq., CAS No. 36982-84-0, prepared as described by references in the Evans reference above) in THF (~ 0.5 M), either precooled to -78°C or at room temperature, was added via cannula over a period of 0.5-5 minutes.

- 5 Again, a slight exotherm was generally noted. The resulting solution was stirred for from 5-10 minutes, while re-cooling to -78°C . Then, AcOH (4.5-4.6 eq., glacial) was added, the cooling bath removed and the mixture allowed to warm to room temperature with stirring for 12-16 hours. The mixture was diluted with EtOAc, in a 2-5 volume multiple of the initial THF volume, and washed
10 with dilute aq. NaHCO_3 (1-2x), 0.1-1.0 M aq. HCl (0-2x), and brine (1x). The organic phase was then dried over MgSO_4 , filtered, concentrated to provide the crude product.

GENERAL PROCEDURE 8-L

15 Azide Reduction to an Amine

- A mixture of the azide in absolute EtOH (0.03-0.07 M) and 10% Pd/C ($\sim 1/3$ by weight of the azide) was shaken in a Parr apparatus under H_2 (35-45 psi) at room temperature for 3-6 hours. The catalyst was removed by filtration through a plug of Celite, rinsing with absolute EtOH, and the filtrate
20 concentrated to provide the crude amine product.

GENERAL PROCEDURE 8-M

Amide Alkylation Using Cesium Carbonate

- This procedure is a modification of the procedure described in Claremon,
25 D. A.; et al, PCT Application: WO 96-US8400 960603. To a mixture of 2,4-dioxo-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine (CAS No. 49799-48-6) in DMF (1.0 eq., 0.7 M) under N_2 at room temperature was added Cs_2CO_3 (2.2 eq.) and the appropriate alkyl halide (2.2 eq.). The mixture was stirred at room temperature for 5.5-16 hours. The mixture was partitioned between EtOAc and
30 sat. NaHCO_3 . The aqueous layer was extracted with EtOAc (1-2x) and the

combined EtOAc extracts were dried over Na_2SO_4 , filtered, and concentrated to provide the crude product.

GENERAL PROCEDURE 8-N

5

BOC Removal Procedure

A stream of anhydrous HCl gas was passed through a stirred solution of the N-t-Boc protected amino acid in 1,4-dioxane (0.03-0.09 M), chilled in a ice bath to $\sim 10^\circ\text{C}$ under N_2 , for 10-15 minutes. The solution was capped, the cooling bath removed, and the solution was allowed to warm to room temperature with stirring for 2-8 hours, monitoring by TLC for the consumption of starting material. The solution was concentrated (and in some instances dissolved in CH_2Cl_2 then re-concentrated and placed in vacuum oven at $60-70^\circ\text{C}$ to remove most of the residual dioxane) and used without further purification.

15

Example 8-A

Synthesis of

3-Amino-1,3-dihydro-5-(1-piperidinyl)-2H-1,4-benzodiazepin-2-one

Step A - Preparation of 1,2-Dihydro-3H-1-methyl-5-(1-piperidinyl)-1,4-benzodiazepin-2-one

A solution of phosphorous pentachloride (1.2 eq) in methylene chloride was added dropwise to a solution of 1-methyl-1,2,3,4-tetrahydro-3H-1,4-benzodiazepin-2,5-dione (Showell, G. A.; Bourrain, S.; Neduvellil, J. G.; Fletcher, S. R.; Baker, R.; Watt, A. P.; Fletcher, A. E.; Freedman, S. B.; Kemp, J. A.; Marshall, G. R.; Patel, S.; Smith, A. J.; Matassa, V. G. *J. Med. Chem.* 1994, 37, 719.) in methylene chloride. The resultant yellowish-orange solution was stirred at ambient temperature for 2.5 hours; the solvent was removed *in vacuo*. The orange residue was redissolved in methylene chloride, cooled to 0°C , and treated with a solution of piperidine (2 eq) and triethylamine (2 eq) in methylene chloride. The cooling bath was removed and the reaction stirred for 18 hours. The reaction mixture was washed with saturated aqueous NaHCO_3 (back-extracted with methylene chloride) and brine. The organic phase was dried over Na_2SO_4 , filtered, and concentrated. The residue was purified via

-- 282 --

HPLC eluting with a gradient of 4 to 10% methanol/methylene chloride affording the title intermediate as a yellow solid having a melting point of 103-105°C.

$C_{15}H_{19}N_3O$ (MW 257.37); mass spectroscopy 257.

5 Anal. Calcd for $C_{15}H_{19}N_3O$: C, 70.01; H, 7.44; N, 16.33. Found: C, 69.94; H, 7.58; N, 16.23.

Step B - Preparation of 1,2-Dihydro-3H-1-methyl-3-oximido-5-(1-piperidiny)-1,4-benzodiazepin-2-one

10 Potassium tert-butoxide (2.5 eq) was added in two portions to a -20°C solution of 1,2-dihydro-3H-1-methyl-5-(1-piperidiny)-1,4-benzodiazepin-2-one (1 eq) in toluene). After stirring at -20°C for 20 min, isoamyl nitrite (1.2 eq.; Aldrich) was added to the red reaction mixture. The reaction was stirred at -20°C for 5 hours at which time the reaction was done by TLC. The cooling bath
15 was removed and the reaction quenched with 0.5 M citric acid. After stirring for 10 minutes, diethyl ether was added. The suspension was stirred at ambient temperature overnight then filtered washing with ether. The resultant cream colored solid had a melting point of 197-200°C.

¹H NMR data of the E/Z isomers was as follows:

20 ¹H NMR (300 MHz, CDCl₃): δ = 7.64 (1H, bs), 7.48 (2H, d, J=7.4 Hz), 7.35-7.20 (6H, m), 6.75 (1H, bs), 3.8-3.2 (8H, m), 3.46 (3H, s), 3.42 (3H, s), 1.90-1.40 (12H, m).

$C_{15}H_{18}N_4O_2$ (MW = 286.37); mass spectroscopy 286.

25 Step C - Preparation of 1,2-dihydro-3H-1-methyl-3-[O-(ethylaminocarbonyl)oximido]-5-(1-piperidiny)-1,4-benzodiazepin-2-one

A mixture of 1,2-dihydro-3H-1-methyl-3-oximido-5-(1-piperidiny)-1,4-benzodiazepin-2-one (1 eq) in THF was treated with ethyl isocyanate (1.7 eq)
30 and triethylamine (0.6 eq). The mixture was heated to 64°C for 4 hours. The mixture was concentrated and the residue purified by HPLC eluting with 5% methanol/methylene chloride.

¹H NMR data of the E/Z isomers was as follows:

¹H NMR (300 MHz, CDCl₃): δ = 7.50 (2H, dd, J=8.4, 1.5 Hz), 7.35-7.22 (6H, m), 6.42 (1H, bt), 6.20 (1H, bt), 3.7-3.4 (8H, m), 3.46 (3H, s), 3.44 (3H, s), 3.25 (4H, m), 1.9-1.4 (12H, m), 1.12 (3H, t, J=6.3 Hz), 1.10 (3H, t, J=6.3 Hz).

C₁₈H₂₃N₅O₃ (MW = 357.46); mass spectroscopy 357.

Step D - Preparation of 3-Amino-1,3-dihydro-2H-1-methyl-5-(1-piperidiny)-1,4-benzodiazepin-2-one

The 1,2-dihydro-3H-1-methyl-3-[O-(ethylaminocarbonyl)oximido]-5-(1-piperidiny)-1,4-benzodiazepin-2-one (1 eq) was hydrogenated in methanol over 5% palladium on carbon (0.15 eq) at 43 psi for 3.25 hours. The reaction was filtered through celite and concentrated *in vacuo*. The residue was taken up in methylene chloride and filtered a second time through celite. The filtrate was concentrated and the resultant foam was used immediately.

Example 8-B

Synthesis of
3-(L-Alaniny)-amino-2,3-dihydro-
1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

Step A - Preparation of (S)-3-amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one, (1S)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptane-1-methanesulfonate

The title intermediate was prepared according to Reider, P. J.; Davis, P.; Hughes, D. L.; Grabowski, E. J. J. *J. Org. Chem.* 1987, 52, 955 using 3-amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (Bock M. G.; DiPardo, R. M.; Evans, B. E.; Rittle, K. E.; Veber, D. F.; Freidinger, R. M.; Hirshfield, J.; Springer, J. P. *J. Org. Chem.* 1987, 52, 3232.) as the starting material.

Step B - Preparation of 3-[N'-(tert-Butylcarbamate)-L-alaniny]-amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

-- 284 --

(S)-3-Amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one, (1S)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptane-1-methanesulfonate was free based by partitioning between methylene chloride and 1M potassium carbonate. The free amine was then coupled with N-Boc-alanine following General Procedure III-D.

$C_{24}H_{28}N_4O_4$ (MW = 436.56); mass spectroscopy 436.

Anal. Calc. for $C_{24}H_{28}N_4O_4$: C, 66.03; H, 6.47; N, 12.84. Found: C, 65.79; H, 6.68; N, 12.80.

10 Step C - Preparation of 3-(L-Alaninyl)-amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

Following General Procedure 8-C using 3-[N'-(tert-butylcarbamate)-L-alaninyl]-amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one, the title compound was prepared as a white foam.

15 Anal. Calc. for $C_{19}H_{19}N_4O_2$: C, 69.21; H, 6.64; N, 15.37. Found: C, 70.11; H, 6.85; N, 15.01.

Example 8-C

Synthesis of

20 3-(L-Alaninyl)-amino-7-chloro-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

Step A - Preparation of 3-(Benzyloxycarbonyl)-amino-7-chloro-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

A solution of 3-(benzyloxycarbonyl)-amino-7-chloro-2,3-dihydro-5-phenyl-1H-1,4-Benzodiazepin-2-one (1 eq; Neosystem) in DMF was cooled to 0°C and treated with potassium *tert*-butoxide (1 eq; 1.0M solution in THF). The resultant yellow solution was stirred at 0°C for 30 minutes then quenched with methyl iodide (1.3 eq). After stirring an addition 25 minutes the reaction was diluted with methylene chloride and washed with water and brine. The organic phase was dried over Na_2SO_4 , filtered, and concentrated. The residue was purified via HPLC chromatography eluting with a gradient of 20→30% ethyl acetate/hexanes.

$C_{24}H_{20}ClN_3O_3$ (MW = 433.92); mass spectroscopy 433.

Anal. calcd for $C_{24}H_{20}ClN_3O_3$: C, 66.44; H, 4.65; N, 9.68. Found: C, 66.16; H, 4.50; N, 9.46.

5 Step B - Preparation of 3-Amino-7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one

Following General Procedure 8-B using 3-(benzyloxycarbonyl)-amino-7-chloro-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one, the title intermediate was prepared as a white foam which was used immediately in Step C.

10

Step C - Preparation of 3-[N'-tert-Butylcarbamate)-L-alaninyl]-amino-7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one

Following General Procedure III-D using N-Boc-L-alanine and 3-amino-15 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one, the title intermediate was prepared as a white foam.

$C_{24}H_{28}ClN_4O_4$ (MW = 471.18); mass spectroscopy 471

Anal. calcd for $C_{24}H_{28}ClN_4O_4$: C, 61.21; H, 5.78; N, 11.90. Found: C, 61.24; H, 5.59; N, 11.67.

20

Step D - Preparation of 3-(L-Alaninyl)amino-7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one

Following General Procedure 8-C using 3-[N'-tert-butylcarbamate)-L-alaninyl]-amino-7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-25 2-one, the title intermediate was prepared as a white foam. The crude material was used immediately.

Example 8-D

Synthesis of

30

3-(L-Alaninyl)amino-7-bromo-2,3-dihydro-1-methyl-5-(2-fluorophenyl)-1H-1,4-benzodiazepin-2-one

Step A - Preparation of 3-(Benzyloxycarbonyl)-amino-7-bromo-2,3-dihydro-1-methyl-5-(2-fluorophenyl)-1H-1,4-benzodiazepin-2-one

-- 286 --

Following General Procedure 8-A using 3-(benzyloxycarbonyl)-amino-7-bromo-2,3-dihydro-5-(2-fluorophenyl)-1H-1,4-benzodiazepin-2-one (Neosystem), the title intermediate was prepared as a white foam.

$C_{24}H_{19}BrFN_3O_3$ (MW = 496.36); mass spectroscopy 497.

5 Anal. calcd for $C_{24}H_{19}BrFN_3O_3$: C, 58.08; H, 3.86; N, 8.47. Found: C, 57.90; H, 4.15; N, 8.20.

Step B - Preparation of 3-Amino-7-bromo-1,3-dihydro-1-methyl-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one

10 Following General Procedure 8-B using 3-(benzyloxycarbonyl)-amino-7-bromo-2,3-dihydro-1-methyl-5-(2-fluorophenyl)-1H-1,4-benzodiazepin-2-one, the title intermediate was prepared as a white foam which was used immediately in Step C.

15 Step C - Preparation of 3-[N'-(tert-Butylcarbamate)-L-alaninyl]-amino-7-bromo-1,3-dihydro-1-methyl-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one

20 Following General Procedure III-D using N-Boc-L-alanine (Novo) and 3-amino-7-bromo-1,3-dihydro-1-methyl-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one, the title intermediate was prepared as a white foam.

$C_{24}H_{26}BrFN_4O_4$ (MW = 533.12); mass spectroscopy 533.2.

Anal. calcd for $C_{24}H_{26}BrFN_4O_4$: C, 54.04; H, 4.91; N, 10.50. Found: C, 53.75; H, 4.92; N, 10.41.

25 Step D - Preparation of 3-(L-Alaninyl)-amino-7-bromo-1,3-dihydro-1-methyl-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one

30 Following General Procedure 8-C using 3-[N'-(tert-butylcarbamate)-L-alaninyl]-amino-7-bromo-1,3-dihydro-1-methyl-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one, the title intermediate was prepared as a white foam. The crude material was used immediately.

Example 8-E

Synthesis of

**3-(N'-Methyl-L-alaninyl)-amino-2,3-dihydro-
1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one**

Step A - Preparation of 3-[N'-(*tert*-Butylcarbamate)-N'-methyl-L-
alaninyl]-amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-
benzodiazepin-2-one

5

Following General Procedure III-D and using (S)-3-amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (Example 8-B) and N-*tert*-Boc-N-methyl-alanine (Sigma), the title intermediate was obtained as a white solid.

$C_{25}H_{30}N_4O_4$ (MW = 450.2); mass spectroscopy (M+1) 451.2.

10

Anal. calcd for $C_{25}H_{30}N_4O_4$: C, 66.65; H, 6.71; N, 12.44. Found: C, 66.66; H, 6.89; N, 12.21.

Step A - Preparation of 3-(N'-Methyl-L-alaninyl)-amino-2,3-
dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

15

Following General Procedure 8-C and using 3-[N'-(*tert*-butylcarbamate)-N'-methyl-L-alaninyl]-amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one, the title intermediate was prepared as a white foam.

$C_{20}H_{22}N_4O_2$ (MW = 350.46); mass spectroscopy (M+1) 351.4.

20

Anal. calcd for $C_{20}H_{22}N_4O_2$: C, 68.55; H, 6.33; N, 15.99. Found, C, 68.36; H, 6.20; N, 15.79.

Example 8-F

Synthesis of

**3-(L-Alaninyl)amino-7-chloro-2,3-dihydro-
1-methyl-5-(2-chlorophenyl)-1H-1,4-benzodiazepin-2-one**

25

Step A - Preparation of 3-(Benzyloxycarbonyl)-amino-7-chloro-2,3-
dihydro-1-methyl-5-(2-chlorophenyl)-1H-1,4-
benzodiazepin-2-one

30

Following General Procedure 8-A using 3-(benzyloxycarbonyl)-amino-7-chloro-2,3-dihydro-5-(2-chlorophenyl)-1H-1,4-benzodiazepin-2-one (Neosystem), the title intermediate was prepared as a white solid having a melting point of 232-233°C.

$C_{24}H_{19}Cl_2N_3O_3$ (MW = 468.36); mass spectroscopy 468.

-- 288 --

¹H NMR (300 MHz, CDCl₃): δ = 7.67 (1H, m), 7.52 (1H, dd, J=2.4, 8.7 Hz), 7.42-7.26 (9H, m), 7.07 (1H, d, J=2.4 Hz), 6.70 (1H, d, J=8.3 Hz), 5.35 (1H, d, J=8.4 Hz), 5.14 (2H, ABq, J=19.6 Hz), 3.47 (3H, s).

¹³C NMR (75 MHz, CDCl₃): δ = 166.66, 165.65, 155.72, 140.52, 136.99, 136.0, 132.87, 131.99, 131.47, 131.40, 131.38, 131.16, 130.54, 130.06, 128.45, 128.08, 128.03, 127.72, 127.22, 123.28, 122.01, 68.95, 67.02, 35.32.

Step B - Preparation of 3-Amino-7-chloro-1,3-dihydro-1-methyl-5-(2-chlorophenyl)-2H-1,4-benzodiazepin-2-one

Following General Procedure 8-B using 3-(benzyloxycarbonyl)-amino-7-chloro-2,3-dihydro-1-methyl-5-(2-chlorophenyl)-1H-1,4-benzodiazepin-2-one, the title intermediate was prepared as a white foam which was used immediately in Step C.

Step C - Preparation of 3-[N'-(tert-Butylcarbamate)-L-alaninyl]-amino-7-chloro-1,3-dihydro-1-methyl-5-(2-chlorophenyl)-2H-1,4-benzodiazepin-2-one

Following General Procedure III-D using N-Boc-L-alanine and 3-amino-7-chloro-1,3-dihydro-1-methyl-5-(2-chlorophenyl)-2H-1,4-benzodiazepin-2-one, the title intermediate was prepared as a white foam.

C₂₄H₂₆Cl₂N₄O₄ (MW = 505.44); mass spectroscopy 505.2.

Step D - Preparation of 3-(L-Alaninyl)-amino-7-chloro-1,3-dihydro-1-methyl-5-(2-chlorophenyl)-2H-1,4-benzodiazepin-2-one

Following General Procedure 8-C using 3-[N'-(tert-butylcarbamate)-L-alaninyl]-amino-7-chloro-1,3-dihydro-1-methyl-5-(2-chlorophenyl)-2H-1,4-benzodiazepin-2-one, the title intermediate was prepared as a white foam. The crude material was used immediately.

Example 8-G

Synthesis of

3-(L-Alaninyl)amino-5-cyclohexyl-2,3-dihydro-1-methyl-1H-1,4-Benzodiazepin-2-one

Step A - Preparation of 3-(Benzyloxycarbonyl)-amino-5-cyclohexyl-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-2-one

Following General Procedure 8-A using 3-(benzyloxycarbonyl)-amino-5-cyclohexyl-2,3-dihydro-1H-1,4-benzodiazepin-2-one (Neosystem), the title intermediate was prepared as a white solid having a melting point of 205-206°C.

$C_{24}H_{27}N_3O_3$ (MW = 405.54); mass spectroscopy 405.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.54 (1H, d, J=7.9 Hz), 7.48 (1H, d, J=7.7 Hz), 7.36-7.26 (7H, m), 6.54 (1H, d, J= 8.3 Hz), 5.15 (1H, d, J=8.0 Hz), 5.09 (2H, ABq, J=17.1 Hz), 3.39 (3H, s), 2.77 (1H, m), 2.01 (1H, bd, J=13.6 Hz), 1.85 (1H, bd, J=12.4 Hz), 1.68-1.49 (4H, m), 1.34-1.02 (4H, m).

Step B - Preparation of 3-Amino-5-cyclohexyl-1,3-dihydro-1-methyl-2H-1,4-benzodiazepin-2-one

Following General Procedure 8-B using 3-(benzyloxycarbonyl)-amino-5-cyclohexyl-2,3-dihydro-1-methyl-1H-1,4-benzodiazepin-2-one, the title intermediate was prepared as a white foam which was used immediately in Step C.

$C_{16}H_{21}N_3O$ (MW+H = 272.1763); mass spectroscopy 272.1766

Step C - Preparation of 3-[N'-(tert-Butylcarbamate)-L-alaninyl]-amino-5-cyclohexyl-1,3-dihydro-1-methyl-2H-1,4-benzodiazepin-2-one

Following General Procedure III-D using N-Boc-L-alanine and 3-amino-5-cyclohexyl-1,3-dihydro-1-methyl-2H-1,4-benzodiazepin-2-one, the title intermediate was prepared as a white foam.

$C_{24}H_{34}N_4O_4$ (MW = 442.62); mass spectroscopy (M+H) 443.2.

Step D - Preparation of 3-(L-Alaninyl)amino-5-cyclohexyl-1,3-dihydro-1-methyl-2H-1,4-benzodiazepin-2-one

Following General Procedure 8-C using 3-[N'-(tert-butylcarbamate)-L-alaninyl]-amino-5-cyclohexyl-1,3-dihydro-1-methyl-2H-1,4-benzodiazepin-2-one,

-- 290 --

the title intermediate was prepared as a white foam. The crude material was used immediately.

$C_{19}H_{26}N_4O_2$ (M+H = 343.2136); mass spectroscopy found 343.2139.

5

Example 8-H

Synthesis of

3-(L-Alaninyl)amino-2,3-dihydro-1-methyl-7-nitro-5-phenyl-1H-1,4-benzodiazepin-2-one

10

Step A - Preparation of 2-[N-(α -Isopropylthio)-N'-(benzyloxycarbonyl)-glyciny]-amino-5-nitrobenzophenone

15

A solution of α -(isopropylthio)-N-(benzyloxycarbonyl)glycine (1 eq; prepared according to Zoller, V.; Ben-Ishai, D. *Tetrahedron* 1975, 31, 863.) in dry THF was cooled to 0 °C and treated with oxalyl chloride (1 eq.) and 3 drops of DMF. After stirring for 15 minutes at 0°C, the cooling bath was removed and stirring continued at ambient temperature for 40 minutes. The solution was recooled to 0°C. A solution of 2-amino-5-nitrobenzophenone (0.9 eq.; Acros) and 4-methylmorpholine (2.0 eq.) in dry THF was added via cannulation to the acid chloride. The cooling bath was removed and the reaction stirred at ambient for 5 hours. The reaction was diluted with methylene chloride and washed with 0.5 M citric acid, saturated aqueous $NaHCO_3$, and brine. The organic phase was dried over Na_2SO_4 , filtered, and concentrated. The residue was purified via preparative LC2000 eluting with a gradient of 15→20% ethyl acetate/hexanes giving an off-white foam.

20

$C_{26}H_{25}N_3O_6S$ (MW = 507.61); mass spectroscopy found 507.9.

25

Anal. calcd for $C_{26}H_{25}N_3O_6S$: C, 61.53; H, 4.96; N, 8.28. Found: C, 61.70; H, 4.99; N, 8.22.

Step B - Preparation of 2-[N-(α -Amino)-N'-(benzyloxycarbonyl)-glyciny]-amino-5-nitrobenzophenone

30

Ammonia gas was bubbled into a solution 2-[N-(α -isopropylthio)-N'-(benzyloxycarbonyl)-glyciny]-amino-5-nitrobenzophenone (1 eq) in THF at 0°C. After 35 minutes mercury(II) chloride (1.1 eq) was added. The ice bath was removed and ammonia gas was continued to bubble through the suspension for 4

hours. The bubbler was removed and the reaction continued to stir for 16 hours. The mixture was filtered through celite washing with THF. The filtrate was concentrated-*in vacuo*. The crude solid was used in step C without further purification.

5

Step C - Preparation of 3-(Benzyloxycarbonyl)-amino-2,3-dihydro-7-nitro-5-phenyl-1H-1,4-benzodiazepin-2-one

2-[N-(α -Amino)-N'-(benzyloxycarbonyl)-glyciny]-amino-5-nitrobenzophenone (1 eq) was treated with glacial acetic acid and ammonium acetate (4.7 eq). The suspension was stirred at ambient temperature for 21 hours. After concentrating the reaction in *vacuo*, the residue was partitioned between ethyl acetate and 1 N NaOH. The aqueous layer was back-extracted with ethyl acetate. The combined organics were washed with brine, dried over Na₂SO₄, filtered, and concentrated. The residue was purified via flash chromatography eluting with a gradient of 2→3% isopropyl alcohol/methylene chloride.

15

C₂₃H₁₈N₄O₅ (MW = 430.45); mass spectroscopy found (M+H) 431.2.

Anal. calcd for C₂₃H₁₈N₄O₅: C, 64.18; H, 4.22; N, 13.02. Found: C, 64.39; H, 4.30; N, 13.07.

20

Step D - Preparation of 3-(Benzyloxycarbonyl)-amino-2,3-dihydro-1-methyl-7-nitro-5-phenyl-1H-1,4-benzodiazepin-2-one

Following General Procedure 8-A and using 3-(benzyloxycarbonyl)-amino-2,3-dihydro-7-nitro-5-phenyl-1H-1,4-benzodiazepin-2-one, the title intermediate was prepared as a yellow foam.

25

C₂₄H₂₀N₄O₅ (MW = 444.48); mass spectroscopy found (M+H) 445.2.

Anal. calcd for C₂₄H₂₀N₄O₅: C, 64.86; H, 4.54; N, 12.60. Found: C, 65.07; H, 4.55; N, 12.46.

30

Step E - Preparation of 3-Amino-1,3-dihydro-1-methyl-7-nitro-5-phenyl-2H-1,4-benzodiazepin-2-one

-- 292 --

Following General Procedure 8-B and using 3-(benzyloxycarbonyl)-amino-2,3-dihydro-1-methyl-7-nitro-5-phenyl-1H-1,4-benzodiazepin-2-one, the title intermediate was prepared as a yellow foam which was used immediately in Step F.

5

Step F - Preparation of 3-[N'-(*tert*-Butylcarbamate)-L-alaninyl]-amino-2,3-dihydro-1-methyl-7-nitro-5-phenyl-1H-1,4-benzodiazepin-2-one

Following General Procedure III-D using N-Boc-L-alanine and 3-amino-1,3-dihydro-1-methyl-7-nitro-5-phenyl-2H-1,4-benzodiazepin-2-one, the title intermediate was prepared as a yellow solid.

10

$C_{24}H_{27}N_5O_6$ (MW = 481.56); mass spectroscopy found (M+H) 482.3.

Anal. calcd for $C_{24}H_{27}N_5O_6$: C, 59.88; H, 5.61; N, 14.55. Found: C, 60.22; H, 5.75; N, 13.91.

15

Step G - Preparation of 3-(L-Alaninyl)-amino-2,3-dihydro-1-methyl-7-nitro-5-phenyl-1H-1,4-benzodiazepin-2-one

Following General Procedure 8-C using 3-[N'-(*tert*-butylcarbamate)-L-alaninyl]-amino-2,3-dihydro-1-methyl-7-nitro-5-phenyl-1H-1,4-benzodiazepin-2-one, the title intermediate was prepared as a yellow foam. The crude material was used immediately.

20

Example 8-I

Synthesis of

25

3-(L-Alaninyl)amino-2,3-dihydro-1-methyl-5-(2-fluorophenyl)-1H-1,4-benzodiazepin-2-one

Step A - Preparation of 3-Amino-1,3-dihydro-1-methyl-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one

30

A flask was charged with 3-(benzyloxycarbonyl)-amino-7-bromo-2,3-dihydro-1-methyl-5-(2-fluorophenyl)-1H-1,4-benzodiazepin-2-one (1 eq.; Example 8-D, Step A) and 10% palladium on carbon. Methanol was added, and the flask was placed under a balloon of H_2 . The reaction was stirred for 21

hours. The mixture was filtered through celite washing with methanol. The filtrate was concentrated to a white solid.

$C_{16}H_{14}FN_3O$ (MW = 283.33); mass spectroscopy found (M+H) 284.1.

5 Step B - Preparation of 3-[N'-(*tert*-Butylcarbamate)-L-alaninyl]-amino-1,3-dihydro-1-methyl-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one

Following General Procedure III-D using N-Boc-L-alanine and 3-amino-1,3-dihydro-1-methyl-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one, the title
10 intermediate was prepared as a white solid.

$C_{24}H_{27}FN_4O_4$ (MW = 454.50); mass spectroscopy found (M+H) 455.4.

Anal. calcd for $C_{24}H_{27}FN_4O_4$: C, 63.44; H, 5.95; N, 12.33. Found: C, 63.64; H, 6.08; N, 12.16.

15 Step C - Preparation of 3-(L-Alaninyl)-amino-7-bromo-1,3-dihydro-1-methyl-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one

Following General Procedure 8-C using 3-[N'-(*tert*-butylcarbamate)-L-alaninyl]-amino-1,3-dihydro-1-methyl-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one, the title intermediate was prepared as a white foam. The crude material
20 was used immediately.

Example 8-J

Synthesis of

25 3-(L-Alaninyl)-amino-2,3-dihydro-1-methyl-5-(3-fluorophenyl)-1H-1,4-benzodiazepin-2-one

Step A - Preparation of 2-Amino-3'-fluorobenzophenone

A solution of 3-bromofluorobenzene (1 eq.) in THF was cooled to -78°C under nitrogen and treated with *tert*-butyllithium (2.05 eq., 1.6 M solution in pentane) at a rate of 40 ml/h. The internal temperature did not rise above -
30 74°C. The orange solution was stirred at -78°C for 30 minutes prior to the addition of anthranilonitrile (0.6 eq.) as a solution in THF. The reaction was warmed to 0°C and stirred for 2 hours. 3N HCl was added to the mixture and stirring continued for 30 minutes. The reaction was diluted with ethyl acetate

-- 294 --

and the layers were separated. The aqueous layer was back-extracted thrice with ethyl acetate. The combined extracts were washed with brine, dried over Na_2SO_4 , filtered, and concentrated. The residue was purified via HPLC eluting with 93:7 hexanes/ethyl acetate.

5 $\text{C}_{13}\text{H}_{10}\text{FNO}$ (MW = 215.24); mass spectroscopy found (M+H) 216.3.

^1H NMR (300 MHz, CDCl_3) δ 7.44-7.19 (6H, m), 6.74 (1H, d, $J=8.0$ Hz), 6.61 (1H, dd, $J=0.94, 7.9$ Hz), 6.10 (2H, bs).

10 Step B - Preparation of 2-[N-(α -Isopropylthio)-N'-(benzyloxycarbonyl)-glyciny]-amino-3'-fluorobenzophenone

A solution of α -(isopropylthio)-N-(benzyloxycarbonyl)glycine (1 eq; prepared according to Zoller, V.; Ben-Ishai, D. *Tetrahedron* 1975, 31, 863.) in dry THF was cooled to 0°C and treated with oxalyl chloride (1 eq.) and 3 drops of DMF. After stirring for 15 minutes at 0°C , the cooling bath was removed and stirring continued at ambient temperature for 40 minutes. The solution was recooled to 0°C . A solution of 2-amino-3'-fluorobenzophenone (0.9 eq.) and 4-methylmorpholine (2.0 eq.) in dry THF was added via cannulation to the acid chloride. The cooling bath was removed and the reaction stirred at ambient for 20 5 hours. The reaction was diluted with methylene chloride and washed with 0.5 M citric acid, saturated aqueous NaHCO_3 , and brine. The organic phase was dried over Na_2SO_4 , filtered, and concentrated. The residue was purified via preparative LC2000 eluting with a gradient of 15 $\rightarrow$ 20% ethyl acetate/hexanes giving an off-white foam.

25 $\text{C}_{26}\text{H}_{25}\text{N}_2\text{O}_4\text{S}$ (MW = 480.60); mass spectroscopy found (M+ NH_4^+) 498.3.

^1H NMR (300 MHz, CDCl_3) δ 11.39 (1H, s), 8.59 (1H, d, $J=6.0$ Hz), 7.63-7.55 (2H, m), 7.48-7.27 (9H, m), 7.14 (1H, dt, $J=1.2, 8.4$ Hz), 5.94 (1H, d, $J=7.2$ Hz), 5.58 (1H, d, $J=8.7$ Hz), 5.17 (2H, ABq, $J=14.7$ Hz), 3.25 (1H, sep, $J=6.6$ Hz), 1.44 (3H, d, $J=6.0$ Hz), 1.28 (3H, d, $J=6.6$ Hz).

30

Step C - Preparation of 2-[N-(α -Amino)-N'-(benzyloxycarbonyl)-glyciny]-amino-3'-fluorobenzophenone

Ammonia gas was bubbled into a solution 2-[N-(α -isopropylthio)-N'-(benzyloxycarbonyl)-glyciny]-amino-3'-fluorobenzophenone (1 eq) in THF at 0°C. After 35 minutes mercury(II) chloride (1.1 eq) was added. The ice bath was removed and ammonia gas was continued to bubble through the suspension for 4 hours. The bubbler was removed and the reaction continued to stir for 16 hours. The mixture was filtered through celite washing with THF. The filtrate was concentrated *in vacuo*. The crude solid was used in step D without further purification.

10 Step D - Preparation of 3-(Benzyloxycarbonyl)-amino-2,3-dihydro-5-(3-fluorophenyl)-1H-1,4-benzodiazepin-2-one

2-[N-(α -Amino)-N'-(benzyloxycarbonyl)-glyciny]-amino-3'-fluorobenzophenone (1 eq) was treated with glacial acetic acid and ammonium acetate (4.7 eq). The suspension was stirred at ambient temperature for 21 hours. After concentrating the reaction in *vacuo*, the residue was partitioned between ethyl acetate and 1 N NaOH. The aqueous layer was back-extracted with ethyl acetate. The combined organics were washed with brine, dried over Na₂SO₄, filtered, and concentrated. The residue was purified via flash chromatography eluting with a gradient of 2→3% isopropyl alcohol/methylene chloride.

C₂₃H₁₈FN₃O₃ (MW = 403.44); mass spectroscopy found (M+H) 404.4.

Anal. calcd for C₂₃H₁₈FN₃O₃•0.5H₂O: C, 66.98; H, 4.64; N, 10.18.

Found: C, 67.20; H, 4.64; N, 9.77.

25 Step E - Preparation of 3-(Benzyloxycarbonyl)-amino-2,3-dihydro-1-methyl-5-(3-fluorophenyl)-1H-1,4-benzodiazepin-2-one

Following General Procedure 8-A and using 3-(benzyloxycarbonyl)-amino-2,3-dihydro-5-(3-fluorophenyl)-1H-1,4-benzodiazepin-2-one, the title intermediate was prepared as a yellow foam.

30 C₂₄H₂₀FN₃O₃ (MW = 417.47); mass spectroscopy found (M+H) 418.3.

Anal. calcd for C₂₄H₂₀FN₃O₃: C, 69.06; H, 4.83; N, 10.07. Found: C, 69.33; H, 4.95; N, 9.82.

Step F - Preparation of 3-Amino-1,3-dihydro-1-methyl-5-(3-fluorophenyl)-2H-1,4-benzodiazepin-2-one

Following General Procedure 8-B and using 3-(benzyloxycarbonyl)-amino-2,3-dihydro-1-methyl-5-(3-fluorophenyl)-1H-1,4-benzodiazepin-2-one, the title intermediate was prepared as a yellow foam which was used immediately in Step G.

Step G - Preparation of 3-[N'-(*tert*-Butylcarbamate)-L-alaninyl]-amino-2,3-dihydro-1-methyl-5-(3-fluorophenyl)-1H-1,4-benzodiazepin-2-one

Following General Procedure III-D using N-Boc-L-alanine and 3-amino-1,3-dihydro-1-methyl-5-(3-fluorophenyl)-2H-1,4-benzodiazepin-2-one, the title intermediate was prepared as a yellow solid.

$C_{24}H_{27}FN_4O_4$ (MW = 454.50); mass spectroscopy found (M+H) 455.3.

Anal. calcd for $C_{24}H_{27}FN_4O_4$: C, 63.42; H, 5.99; N, 12.33. Found: C, 63.34; H, 6.01; N, 12.08.

Step H - Preparation of 3-(L-Alaninyl)-amino-2,3-dihydro-1-methyl-5-(3-fluorophenyl)-1H-1,4-benzodiazepin-2-one

Following General Procedure 8-C using 3-[N'-(*tert*-butylcarbamate)-L-alaninyl]-amino-2,3-dihydro-1-methyl-5-(3-fluorophenyl)-1H-1,4-benzodiazepin-2-one, the title intermediate was prepared as a yellow foam. The crude material was used immediately.

Example 8-K

Synthesis of

3-(L-Alaninyl)amino-2,3-dihydro-1-methyl-5-(4-fluorophenyl)-1H-1,4-benzodiazepin-2-one

Step A - Preparation of 2-Amino-4'-fluorobenzophenone

A solution of 4-bromofluorobenzene (1 eq.) in THF was cooled to -78°C under nitrogen and treated with *tert*-butyllithium (2.05 eq., 1.6 M solution in pentane) at a rate of 40 ml/h. The internal temperature did not rise above -74°C. The orange solution was stirred at -78°C for 30 minutes prior to the

addition of anthranilonitrile (0.6 eq.) as a solution in THF. The reaction was warmed to 0°C and stirred for 2 hours. 3N HCl was added to the mixture and stirring continued for 30 minutes. The reaction was diluted with ethyl acetate and the layers were separated. The aqueous layer was back-extracted thrice with ethyl acetate. The combined extracts were washed with brine, dried over Na₂SO₄, filtered, and concentrated. The residue was purified via HPLC eluting with 93:7 hexanes/ethyl acetate.

C₁₃H₁₀FNO (MW = 215.24); mass spectroscopy found (M+H) 216.3.

Anal. calcd for C₁₃H₁₀FNO: C, 72.55; H, 4.68; N, 6.51. Found: C, 72.80; H, 4.51; N, 6.74.

Step B - Preparation of 2-[N-(α -Isopropylthio)-N'-(benzyloxycarbonyl)-glyciny]-amino-4'-fluorobenzophenone

A solution of α -(isopropylthio)-N-(benzyloxycarbonyl)glycine (1 eq; prepared according to Zoller, V.; Ben-Ishai, D. *Tetrahedron* 1975, 31, 863.) in dry THF was cooled to 0°C and treated with oxalyl chloride (1 eq.) and 3 drops of DMF. After stirring for 15 minutes at 0°C, the cooling bath was removed and stirring continued at ambient temperature for 40 minutes. The solution was recooled to 0°C. A solution of 2-amino-4'-fluorobenzophenone (0.9 eq.) and 4-methylmorpholine (2.0 eq.) in dry THF was added via cannulation to the acid chloride. The cooling bath was removed and the reaction stirred at ambient for 5 hours. The reaction was diluted with methylene chloride and washed with 0.5 M citric acid, saturated aqueous NaHCO₃, and brine. The organic phase was dried over Na₂SO₄, filtered, and concentrated. The residue was purified via preparative LC2000 eluting with a gradient of 15→20% ethyl acetate/hexanes giving an off-white foam.

C₂₆H₂₅N₂O₄S (MW = 480.60); mass spectroscopy found (M+NH₄⁺) 498.2.

¹H NMR (300 MHz, CDCl₃) δ 11.28 (1H, s), 8.56 (1H, d, J=8.4 Hz), 7.78-7.73 (2H, m), 7.61-7.53 (2H, m), 7.36-7.32 (5H, m), 7.20-7.14 (3H, m), 5.98 (1H, d, J=7.5 Hz), 5.57 (1H, d, J=7.8 Hz), 5.16 (2H, ABq, J=14.7 Hz), 3.25 (1H, sep, J=6.0 Hz), 1.43 (3H, d, J=6.3 Hz), 1.27 (3H, d, J=6.6 Hz).

-- 298 --

Step C - Preparation of 2-[N-(α -Amino)-N'-(benzyloxycarbonyl)-glyciny]-amino-4'-fluorobenzophenone

Ammonia gas was bubbled into a solution 2-[N-(α -isopropylthio)-N'-(benzyloxycarbonyl)-glyciny]-amino-3'-fluorobenzophenone (1 eq) in THF at 0°C. After 35 minutes mercury(II) chloride (1.1 eq) was added. The ice bath was removed and ammonia gas was continued to bubble through the suspension for 4 hours. The bubbler was removed and the reaction continued to stir for 16 hours. The mixture was filtered through celite washing with THF. The filtrate was concentrated *in vacuo*. The crude solid was used in step D without further purification.

Step D - Preparation of 3-(Benzyloxycarbonyl)amino-2,3-dihydro-5-(4-fluorophenyl)-1H-1,4-benzodiazepin-2-one

2-[N-(α -Amino)-N'-(benzyloxycarbonyl)-glyciny]-amino-4'-fluorobenzophenone (1 eq) was treated with glacial acetic acid and ammonium acetate (4.7 eq). The suspension was stirred at ambient temperature for 21 hours. After concentrating the reaction in *vacuo*, the residue was partitioned between ethyl acetate and 1 N NaOH. The aqueous layer was back-extracted with ethyl acetate. The combined organics were washed with brine, dried over Na₂SO₄, filtered, and concentrated. The residue was purified via flash chromatography eluting with a gradient of 2→3% isopropyl alcohol/methylene chloride.

C₂₃H₁₈FN₃O₃ (MW = 403.44); mass spectroscopy found (M+H) 404.4.

Anal. calcd for C₂₃H₁₈FN₃O₃•1.25H₂O: C, 64.85; H, 4.85. Found: C, 64.80; H, 4.55.

Step E - Preparation of 3-(Benzyloxycarbonyl)-amino-2,3-dihydro-1-methyl-5-(4-fluorophenyl)-1H-1,4-benzodiazepin-2-one

Following General Procedure 8-A and using 3-(benzyloxycarbonyl)-amino-2,3-dihydro-5-(4-fluorophenyl)-1H-1,4-benzodiazepin-2-one, the title intermediate was prepared as a yellow foam.

C₂₄H₂₀FN₃O₃ (MW = 417.47); mass spectroscopy found (M+H) 418.2.

Anal. calcd for $C_{24}H_{20}FN_3O_3$: C, 69.06; H, 4.83; N, 10.07. Found: C, 69.35; H, 4.93; N, 9.97.

5 Step F - Preparation of 3-Amino-1,3-dihydro-1-methyl-5-(4-fluorophenyl)-2H-1,4-benzodiazepin-2-one

Following General Procedure 8-B and using 3-(benzyloxycarbonyl)-amino-2,3-dihydro-1-methyl-5-(4-fluorophenyl)-1H-1,4-benzodiazepin-2-one, the title intermediate was prepared as a yellow foam which was used immediately in Step G.

10

Step G - Preparation of 3-[N'-(tert-Butylcarbamate)-L-alaninyl]-amino-2,3-dihydro-1-methyl-5-(3-fluorophenyl)-1H-1,4-benzodiazepin-2-one

Following General Procedure III-D using N-Boc-L-alanine and 3-amino-1,3-dihydro-1-methyl-5-(3-fluorophenyl)-2H-1,4-benzodiazepin-2-one, the title intermediate was prepared as a yellow solid.

15

$C_{24}H_{27}FN_4O_4$ (MW = 454.50); mass spectroscopy found (M+H) 455.4.

Anal. calcd for $C_{24}H_{27}FN_4O_4 \cdot 1.5H_2O$: C, 59.86; H, 6.28; N, 11.64.

Found: C, 60.04; H, 5.62; N, 11.27.

20

Step H - Preparation of 3-(L-Alaninyl)-amino-2,3-dihydro-1-methyl-5-(4-fluorophenyl)-1H-1,4-benzodiazepin-2-one

Following General Procedure 8-C using 3-[N'-(tert-butylcarbamate)-L-alaninyl]-amino-2,3-dihydro-1-methyl-5-(4-fluorophenyl)-1H-1,4-benzodiazepin-2-one, the title intermediate was prepared as a yellow foam. The crude material was used immediately.

25

Example 8-L

Synthesis of

30

3-(N'-L-Alaninyl)amino-2,3-dihydro-1-isobutyl-5-phenyl-1H-1,4-benzodiazepin-2-one

Step A: 1,3-Dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one (prepared according to the procedure of M. G. Bock et al., *J. Org. Chem.* **1987**, *52*, 3232-

Step C: The product from Step B and N-Boc-L-alanine (Sigma) were coupled using General Procedure III-D, followed by removal of the Boc group using General Procedure 8-J, to afford 3-(N'-L-alaninyl)amino-1,3-dihydro-1-isobutyl-5-phenyl-2H-1,4-benzodiazepin-2-one.

3-(N'-L-alaninyl)amino-1,3-dihydro-1-isopropyl-5-phenyl-2H-1,4-benzodiazepin-2-one

3-(N'-L-alaninyl)amino-1,3-dihydro-1-propyl-5-phenyl-2H-1,4-benzodiazepin-2-one

20 3-(N'-L-alaninyl)amino-1,3-dihydro-1-cyclopropylmethyl-5-phenyl-2H-1,4-benzodiazepin-2-one

3-(N'-L-alaninyl)amino-1,3-dihydro-1-ethyl-5-phenyl-2H-1,4-benzodiazepin-2-one.

25 Example 8-M

Synthesis of

3-(N'-L-Alaninyl)amino-1-methyl-5-phenyl-1,3,4,5-tetrahydro-2H-1,5-benzodiazepin-2-one

Step A: 1,3,4,5-Tetrahydro-5-phenyl-2H-1,5-benzodiazepin-2-one (CAS No. 32900-17-7) was methylated using General Procedure 8-I to afford 1-methyl-5-phenyl-1,3,4,5-tetrahydro-2H-1,5-benzodiazepin-2-one.

-- 301 --

Step B: Following General Procedures 8-E and 8-F and using the product from Step A, 3-amino-1-methyl-5-phenyl-1,3,4,5-tetrahydro-2H-1,5-benzodiazepin-2-one was prepared.

5 **Step C:** The product from Step B and N-Boc-L-alanine (Sigma) were coupled using General Procedure III-D, followed by removal of the Boc group using General Procedure 8-N, to afford 3-(N'-L-alaninyl)amino-1-methyl-5-phenyl-1,3,4,5-tetrahydro-2H-1,5-benzodiazepin-2-one.

10

Example 8-N**Synthesis of****3-(N'-L-Alaninyl)amino-2,4-dioxo-1-methyl-5-phenyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine**

15

3-Amino-2,4-dioxo-1-methyl-5-phenyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine (CAS No. 131604-75-6) was coupled with N-Boc-L-alanine (Sigma) using General Procedure III-D, followed by removal of the Boc group using General Procedure 8-N, to afford the title compound.

20

Example 8-O**Synthesis of****3-((R)-Hydrazinopropionyl)amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one**

25

3-Amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one was coupled to (R)-N,N'-di-BOC-2-hydrazinopropionic acid (Example N) using General Procedure III-D. Removal of the Boc group using General Procedure 5-B afforded the title compound.

30

Example 8-P**Synthesis of****3-Amino-2,4-dioxo-1,5-bis-(1-methylethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine**

35

Step A: - **Synthesis of 2,4-Dioxo-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine**

-- 302 --

2,4-Dioxo-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine (CAS No. 49799-48-6) was prepared from 1,2-phenylenediamine (Aldrich) and malonic acid (Aldrich) using the procedure of Claremon, D. A.; et al, PCT Application: WO 96-US8400 960603.

5

Step B: - Synthesis of 2,4-Dioxo-1,5-bis-(1-methylethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine

2,4-Dioxo-1,5-bis-(1-methylethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine (CAS No. 113021-84-4) was prepared following General Procedure 8-M using the product from Step A and 2-iodopropane (Aldrich). Purification was by flash chromatography eluting with EtOAc/hexanes (3:7 gradient to 1:1), then recrystallization from EtOAc/hexanes.

15

Step C: - Synthesis of 3-Azido-2,4-dioxo-1,5-bis-(1-methylethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine

Following General Procedure 8-K using the product from Step B, 3-azido-2,4-dioxo-1,5-bis-(1-methylethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine (CAS No. 186490-50-6) was prepared as a white solid. The product was purified by flash chromatography eluting with hexanes/EtOAc (4:1) to provide a separable 23:1 mixture of pseudo-axial/pseudo-equatorial azides. The pure pseudo-axial azide was used in the next step.

25

Step D: - Synthesis of 3-Amino-2,4-dioxo-1,5-bis-(1-methylethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine

Following General Procedure 8-L using the product from Step C, 3-amino-2,4-dioxo-1,5-bis-(1-methylethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine (CAS No. 186490-51-7) was prepared as a white solid. Purification was by flash chromatography eluting with CH₂Cl₂/MeOH (98:2 gradient to 95:5). The isolated pseudo-axial amine atropisomer was completely converted to the pseudo-equatorial amine atropisomer by heating in toluene to 100-105 °C for 15 minutes, and the pseudo-equatorial amine atropisomer was used in the next step. The isomers were distinguished by ¹H-NMR in CDCl₃.

30

Selected ¹H-NMR (CDCl₃): Pseudo-axial amine 4.40 (s, 1H); Pseudo-equatorial amine 3.96 (s, 1H).

Example 8-Q

5

**Synthesis of
3-(R-2-Thienylglyciny)amino-2,4-dioxo-
1,5-bis-(1-methylethyl)-2,3,4,5-tetrahydro-
1H-1,5-benzodiazepine Hydrochloride**

Step A: - Synthesis of N-(*t*-Butoxycarbonyl)-R-2-thienylglycine

10

N-(*t*-Butoxycarbonyl)-R-2-thienylglycine (CAS No. 74462-03-1) was prepared from L-α-(2-thienyl)glycine (Sigma) by the procedure described in Bodansky, M. et al; *The Practice of Peptide Synthesis*; Springer Verlag; 1994, p. 17.

15

Step B: - Synthesis of 3-[N'-(*t*-Butoxycarbonyl)-R-2-thienylglyciny]amino-2,4-dioxo-1,5-bis-(1-methylethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine

Following General Procedure III-J above using the product from Example 8-P and the product from Step A above, 3-[N'-(*t*-butoxycarbonyl)-R-2-thienylglyciny]amino-2,4-dioxo-1,5-bis-(1-methylethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine was prepared as a white foam. Purification was by flash chromatography eluting with CH₂Cl₂/EtOAc (9:1 gradient to 5:1).

25

Step C: - Synthesis of 3-(R-2-Thienylglyciny)amino-2,4-dioxo-1,5-bis-(1-methylethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine Hydrochloride

Following General Procedure 8-N above using the product from Step B, the title compound was prepared as a white solid.

30

Example 8-R

**Synthesis of
3-(L-Alaniny)amino-2,4-dioxo-1,5-bis-methyl-
2,3,4,5-tetrahydro-1H-1,5-benzodiazepine Hydrochloride**

35

Step A: - Synthesis of 2,4-Dioxo-1,5-bis-methyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine

-- 304 --

2,4-Dioxo-1,5-bis-methyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine (CAS No. 23954-54-3) was prepared following General Procedure 8-M using the product from Example 8-P, Step A and iodomethane (Aldrich). The white solid product precipitated during partial concentration of the reaction after work-up, and was isolated by filtration.

Step B: - Synthesis of 3-Azido-2,4-dioxo-1,5-bis-methyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine

For this substrate, General Procedure 8-K was modified in the following manner. Initially the product from Step A was suspended (not a solution) in THF at -78°C, and following addition of the KN(TMS)₂ solution, this suspension was allowed to warm to -35°C over a period of 12 minutes, during which the suspension became a solution, and was re-cooled to -78°C; then treated as described in the General Procedure. 3-Azido-2,4-dioxo-1,5-bis-methyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine was purified by flash chromatography eluting with CHCl₃/EtOAc (7:1), then trituration from hot CHCl₃ with hexanes and cooled to -23°C. The product was isolated as a white solid.

Step C: - Synthesis of 3-Amino-2,4-dioxo-1,5-bis-methyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine

Following General Procedure 8-L using the product from Step B, 3-amino-2,4-dioxo-1,5-bis-methyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine was prepared as a white solid. The crude product was used without further purification.

Step D: - Synthesis of 3-[N'-(*t*-Butoxycarbonyl)-L-alaninyl]-amino-2,4-dioxo-1,5-bis-methyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine

Following General Procedure III-I above using N-Boc-L-alanine (Novabiochem) and the product from Step C, 3-[N'-(*t*-butoxycarbonyl)-L-alaninyl]-amino-2,4-dioxo-1,5-bis-methyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine was prepared as a white foam. Purification was by flash chromatography eluting with CH₂Cl₂/EtOAc (2:1 gradient to 1:1).

-- 305 --

Step E: - Synthesis of 3-(L-alaninyl)-amino-2,4-dioxo-1,5-bis-methyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine Hydrochloride

Following General Procedure 8-N above using the product from Step D,
5 the title compound was prepared as an off-white amorphous solid.

Example 8-S

**Synthesis of
10 3-(L-Alaninyl)amino-2,4-dioxo-1,5-bis-(2-methylpropyl)-
2,3,4,5-tetrahydro-1H-1,5-benzodiazepine Hydrochloride**

Step A: - Synthesis of 2,4-Dioxo-1,5-bis-(2-methylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine

2,4-Dioxo-1,5-bis-(2-methylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine was prepared following General Procedure 8-M using the
15 product from Example 8-P, Step A and 1-iodo-2-methylpropane (Aldrich). Purification was by flash chromatography eluting with EtOAc/hexanes (3:7 gradient to 1:1), then recrystallization from EtOAc/hexanes.

**20 Step B: - Synthesis of 3-Azido-2,4-dioxo-1,5-bis-(2-methylpropyl)-
2,3,4,5-tetrahydro-1H-1,5-benzodiazepine**

Following General Procedure 8-K (a precipitate formed during the addition of the KN(TMS)₂, but dissolved upon addition of the trisyl azide) using the product from Step A, 3-azido-2,4-dioxo-1,5-bis-(2-methylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine was prepared as a white solid. The product
25 was purified by flash chromatography eluting with hexanes/EtOAc (4:1) and a second flash chromatography eluting with CH₂Cl₂/hexanes/EtOAc (10:10:1 gradient to 8:6:1).

30 Step C: - Synthesis of 3-Amino-2,4-dioxo-1,5-bis-(2-methylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine

Following General Procedure 8-L using the product from Step B, 3-amino-2,4-dioxo-1,5-bis-(2-methylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine was prepared as a white solid. Purification was by flash

-- 306 --

chromatography eluting with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (98:2 gradient to 95:5, with 5% NH_3 in the MeOH).

5 **Step D: - Synthesis of 3-[N'-(*t*-Butoxycarbonyl)-L-alaninyl]-amino-2,4-dioxo-1,5-bis-(2-methylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine**

Following General Procedure III-I above using N-Boc-L-alanine (Novabiochem) and the product from Step C, 3-[N'-(*t*-butoxycarbonyl)-L-alaninyl]-amino-2,4-dioxo-1,5-bis-(2-methylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine was prepared as a white foam. Purification was by flash chromatography eluting with $\text{CH}_2\text{Cl}_2/\text{EtOAc}$ (3:1 gradient to 3:2).

15 **Step E: - Synthesis of 3-(L-Alaninyl)-amino-2,4-dioxo-1,5-bis-(2-methylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine Hydrochloride**

Following General Procedure 8-N above using the product from Step D, the title compound was prepared as an amorphous white solid.

Example 8-T

20 **Synthesis of
3-(S-Phenylglyciny)amino-2,4-dioxo-1,5-bis-(2-methylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine Hydrochloride**

25 **Step A: - Synthesis of 3-[N'-(*t*-Butoxycarbonyl)-S-phenylglyciny]-amino-2,4-dioxo-1,5-bis-(2-methylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine**

Following General Procedure III-J above using the product from Example 8-S, Step C and the Boc-L-phenylglycine (Novabiochem, CAS No. 2900-27-8), 3-[N'-(*t*-butoxycarbonyl)-S-phenylglyciny]-amino-2,4-dioxo-1,5-bis-(2-methylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine was prepared as a white foam. Purification was by flash chromatography eluting with $\text{CH}_2\text{Cl}_2/\text{EtOAc}$ (9:1 gradient to 5:1).

Step B: - Synthesis of 3-(S-PhenylglycinyI)-amino-2,4-dioxo-1,5-bis-(2-methylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine Hydrochloride

Following General Procedure 8-N above using the product from Step A,
5 3-(S-phenylglycinyI)-amino-2,4-dioxo-1,5-bis-(2-methylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine hydrochloride was prepared as an off-white solid.

Example 8-U

10 **Synthesis of
3-(L-AlaninyI)amino-2,4-dioxo-1,5-bis-(cyclopropylmethyl)-
2,3,4,5-tetrahydro-1H-1,5-benzodiazepine Hydrochloride**

**Step A: - Synthesis of 2,4-Dioxo-1,5-bis-(cyclopropylmethyl)-
2,3,4,5-tetrahydro-1H-1,5-benzodiazepine**

15 2,4-Dioxo-1,5-bis-(cyclopropylmethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine was prepared following General Procedure 8-M using the product from Example 8-P, Step A, and (bromomethyl)cyclopropane (Lancaster). Purification was by flash chromatography eluting with EtOAc/hexanes (3:7 gradient to straight EtOAc), then recrystallization from EtOAc/hexanes.

20

Step B: - Synthesis of 3-Azido-2,4-dioxo-1,5-bis-(cyclopropylmethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine

For this substrate General Procedure 8-K was modified in the following
25 manner. Initially the product from Step A was suspended (not a solution) in THF at -78°C, and following addition of the KN(TMS)₂ solution, this suspension was allowed to warm to -30°C, during which the suspension became a solution, and was re-cooled to -78°C. Upon re-cooling to -78°C a precipitate began to form, therefore the reaction flask containing the mixture was partially raised
30 above the cooling bath until the internal temperature rose to -50°C; then the trisyl azide solution was added. The cooling bath was removed and the mixture allowed to warm to -20°C whereupon the mixture had become a nearly homogenous solution, and the AcOH was added. Then, treated as described in the general procedure. 3-Azido-2,4-dioxo-1,5-bis-(cyclopropylmethyl)-2,3,4,5-

-- 308 --

tetrahydro-1H-1,5-benzodiazepine was purified by trituration with hot to room temperature EtOAc, followed by recrystallization from hot to -23°C CHCl₃/EtOAc/EtOH (5:5:1) and isolated as a white solid.

5 **Step C: - Synthesis of 3-Amino-2,4-dioxo-1,5-bis-(cyclopropylmethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine**

Following General Procedure 8-L using the product from Step B, 3-amino-2,4-dioxo-1,5-bis-(cyclopropylmethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine was prepared as a white solid. Purification was by flash chromatography eluting with CH₂Cl₂/MeOH (98:2 gradient to 95:5, with 5% NH₃ in the MeOH) followed by recrystallization from warm CH₂Cl₂/hexanes (1:1) to -23°C.

15 **Step D: - Synthesis of 3-[N'-(*t*-Butoxycarbonyl)-L-alaninyl]-amino-2,4-dioxo-1,5-bis-(cyclopropylmethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine**

Following General Procedure III-I above using N-Boc-L-alanine (Novabiochem) and the product from Step C, 3-[N'-(*t*-butoxycarbonyl)-L-alaninyl]-amino-2,4-dioxo-1,5-bis-(cyclopropylmethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine was prepared as a white foam. Purification was by flash chromatography eluting with CH₂Cl₂/EtOAc (3:1 gradient to 2:1).

25 **Step E: - Synthesis of 3-(L-Alaninyl)-amino-2,4-dioxo-1,5-bis-(cyclopropylmethyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine Hydrochloride**

Following General Procedure 8-N above using the product from Step D, the title compound was prepared as an off-white solid.

30

Example 8-V

**Synthesis of
3-(L-Alaninyl)-amino-2,4-dioxo-1,5-bis-(2,2-dimethylpropyl)-
2,3,4,5-tetrahydro-1H-1,5-benzodiazepine Hydrochloride**

-- 309 --

Step A: - Synthesis of 2,4-Dioxo-1,5-bis-(2,2-dimethylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine

To a stirred suspension of the product from Example 8-P, Step A (1.0 eq., 17.08 g) in DMSO (500 mL) at room temperature was added neopentyl iodide (43.01 g, 2.24 eq., Aldrich) and Cs₂CO₃ (72.65 g, 2.3 eq., Aldrich). The
5 resulting mixture was heated to 75°C for 30 minutes, then additional Cs₂CO₃ (31.59 g, 1.0 eq.) was added and the mixture rapidly stirred at 75°C for 6 hours. The mixture was allowed to cool and H₂O (500 mL) and EtOAc (1000 mL) were added. The phases were partitioned and the organic phase washed with
10 H₂O (1x500 mL), 1 M aq. HCl (2x500 mL), and brine (1x500 mL). Then, the organic phase was dried over MgSO₄, filtered, concentrated, and purified by flash chromatography eluting with hexanes/EtOAc (3:2 gradient to 2:3) to provide 2,4-dioxo-1,5-bis-(2,2-dimethylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine as a white solid.

15

Step B: - Synthesis of 3-Azido-2,4-dioxo-1,5-bis-(2,2-dimethylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine

Following General Procedure 8-K using the product from Step A, 3-
20 azido-2,4-dioxo-1,5-bis-(2,2-dimethylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine was prepared as a white solid. The product was purified by flash chromatography eluting with hexanes/CH₂Cl₂/EtOAc (10:5:1 gradient to 5:5:1) to provide a separable 13:1 mixture of pseudo-axial/pseudo-equatorial azides. The pure pseudo-axial azide was used in the next step. Selected ¹H-
25 NMR (CDCl₃): Pseudo-axial azide 5.12 (s, 1H); Pseudo-equatorial azide 4.03 (s, 1H).

Step C: - Synthesis of 3-Amino-2,4-dioxo-1,5-bis-(2,2-dimethylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine

30

Following General Procedure 8-L using the product from Step B, 3-amino-2,4-dioxo-1,5-bis-(2,2-dimethylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine was prepared as a white solid. Purification was by flash

-- 310 --

chromatography eluting with CH₂Cl₂/MeOH (98:2 gradient to 95:5, with 5% NH₃ in the MeOH). The isolated white solid product was identified as a ~4:1 mixture of pseudo-axial and pseudo-equatorial amines atropisomers by ¹H-NMR. The mixture was heated in toluene to 100 °C for 20 minutes, then re-

5 concentrated to provide the pure pseudo-equatorial amine atropisomer, as a white solid, and this was for the next step. Selected ¹H-NMR (CDCl₃): Pseudo-axial amine 4.59 (s, 1H); Pseudo-equatorial amine 4.03 (s, 1H).

10 **Step D: - Synthesis of 3-[N'-(*t*-Butoxycarbonyl)-L-alaninyl]-amino-2,4-dioxo-1,5-bis-(2,2-dimethylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine**

Following General Procedure III-I above using N-Boc-L-alanine (Novabiochem) and the product from Step C, 3-[N'-(*t*-butoxycarbonyl)-L-alaninyl]-amino-2,4-dioxo-1,5-bis-(2,2-dimethylpropyl)-2,3,4,5-tetrahydro-1H-

15 1,5-benzodiazepine was prepared as a white foam. Purification was by flash chromatography eluting with CH₂Cl₂/EtOAc (4:1 gradient to 5:2).

20 **Step E: - Synthesis of 3-(L-Alaninyl)-amino-2,4-dioxo-1,5-bis-(2,2-dimethylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine Hydrochloride**

Following General Procedure 8-N above using the product from Step D, the title compound was prepared as an off-white solid.

Example 8-W

25 **Synthesis of
3-(L-Alaninyl)amino-2,4-dioxo-1,5-bis-phenyl-
2,3,4,5-tetrahydro-1H-1,5-benzodiazepine hydrochloride**

30 **Step A: - Synthesis of 2,4-Dioxo-1,5-bis-phenyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine**

This procedure is a modification of the procedure described in Chan, D. M. T. *Tetrahedron Lett.* 1996, 37, 9013-9016. A mixture of the product from Example 8-P, Step A (1.0 eq., 7.50 g), Ph₃Bi (2.2 eq., 41.26 g, Aldrich), Cu(OAc)₂ (2.0 eq., 15.48 g, Aldrich), Et₃N (2.0 eq., 8.62 g) in CH₂Cl₂ (100 mL) was stirred under N₂ at room temperature for 6 days (monitoring by TLC). The

solids were removed by filtration through a plug of Celite rinsing with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (3x75 mL). The filtrate was concentrated, dissolved in hot $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (9:1) and filtered through a large plug of silica gel eluting with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (9:1, 2L). The filtrate was concentrated and the residue purified by flash chromatography eluting with straight CH_2Cl_2 gradient to $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (9:1). 2,4-Dioxo-1,5-bis-phenyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine crystallized during concentration of the fractions containing the product, and was isolated by filtration as a white solid.

10 **Step B: - Synthesis of 3-Azido-2,4-dioxo-1,5-bis-phenyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine**

For this substrate, General Procedure 8-K was modified in the following manner. Initially the product from Step A was suspended (not a solution) in THF at -70°C , and following addition of the $\text{KN}(\text{TMS})_2$ solution, this suspension was allowed to warm to -20°C over a period of 10 minutes, during which the suspension became a solution, and was re-cooled to -70°C ; then treated as described in the general procedure. The title compound was purified by trituration with hot $\text{CHCl}_3/\text{hexanes}$ (1:1) to yield 3-azido-2,4-dioxo-1,5-bis-phenyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine as a white solid.

20

Step C: - Synthesis of 3-Amino-2,4-dioxo-1,5-bis-phenyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine

Following General Procedure 8-L using the product from Step B, 3-amino-2,4-dioxo-1,5-bis-phenyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine was prepared as a white solid. Purification was by flash chromatography eluting with $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (98:2 gradient to 95:5, with 5% NH_3 in the MeOH).

25

Step D: - Synthesis of 3-[N'-(*t*-Butoxycarbonyl)-L-alaninyl]-amino-2,4-dioxo-1,5-bis-phenyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine

30

Following General Procedure III-I above using N-Boc-L-alanine (Novabiochem) and the product from Step C, 3-[N'-(*t*-butoxycarbonyl)-L-alaninyl]-amino-2,4-dioxo-1,5-bis-phenyl-2,3,4,5-tetrahydro-1H-1,5-

Following General Procedure 8-C and using 3-[N'-(*tert*-butylcarbamate)-L-alaninyl]-amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepine-2-one, the title compound was prepared as a white foam.

$C_{21}H_{23}N_4O_2$ (MW 363.48); mass spectroscopy (M+H) 364.2.

5

Example 8-Z

Synthesis of

3-(L-*tert*-Leucinyl)-amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

10 Step A - Synthesis of 3-[N'-(*tert*-Butylcarbamate)-L-*tert*-leucinyl]-amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

(S)-3-amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one, (1S)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptane-1-methanesulfonate (Example 8-B, 15 Step A) was free based by partitioning between methylene chloride and 1M potassium carbonate. The free amine was then coupled with N-Boc-*tert*-leucine following General Procedure III-D to give the title compound.

$C_{27}H_{35}N_4O_4$ (MW 479.66); mass spectroscopy 479.

20 Step B - Synthesis of 3-(L-*tert*-Leucinyl)-amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepin-2-one

Following General Procedure 8-C and using 3-[N'-(*tert*-butylcarbamate)-L-*tert*-leucinyl]-amino-2,3-dihydro-1-methyl-5-phenyl-1H-1,4-benzodiazepine-2-one, the title compound was prepared as a white foam.

25 Anal. Calcd for $C_{22}H_{25}N_4O_2 \cdot 0.5H_2O$: C, 68.19; H, 7.02; N, 14.40.
Found: C, 68.24; H, 7.00; N, 14.00.

Example 8-AA

Synthesis of

30 3-(L-Alaninyl)-amino-2,3-dihydro-1,5-dimethyl-1H-1,4-benzodiazepine

2,3-Dihydro-1,5-dimethyl-1H-1,4-benzodiazepine was prepared following General Procedures 8-I (using methyl iodide), 8-D and 8-F. Coupling of this intermediate with Boc-L-alanine (Novo) using General Procedure III-D, followed

-- 314 --

by deprotection using General Procedure 5-B afforded the title compound which was used without further purification.

Example 8-AB

5

Synthesis of 3-(L-3-Thienylglyciny)amino-2,4-dioxo- 1,5-bis-(2,2-dimethylpropyl)-2,3,4,5-tetrahydro- 1H-1,5-benzodiazepine

Step A: - Synthesis of N-(*t*-Butoxycarbonyl)-L-3-thienylglycine

10

N-(*t*-Butoxycarbonyl)-L-3-thienylglycine was prepared from L- α -(3-thienyl)glycine (Sigma) by the procedure described in Bodansky, M. et al; *The Practice of Peptide Synthesis*; Springer Verlag; 1994, p. 17.

15

Step B: - Synthesis of 3-[N'-(*t*-Butoxycarbonyl)-L-3-thienylglyciny]amino-2,4-dioxo-1,5-bis-(2,2-dimethylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine

20

Following General Procedure III-D above using the product from Example 8-V, Step C and the product from Step A above, 3-[N'-(*t*-butoxycarbonyl)-L-3-thienylglyciny]amino-2,4-dioxo-1,5-bis-(2,2-dimethylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine was prepared.

25

Step C: - Synthesis of 3-(L-3-Thienylglyciny)amino-2,4-dioxo-1,5-bis-(2,2-dimethylpropyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine

Following General Procedure 8-N above using the product from Step B, the title compound was prepared.

Example Bio-1

30

Cellular Screen for the Detection of Inhibitors of β -Amyloid Production

Numerous compounds of formula I above were assayed for their ability to inhibit β -amyloid production in a cell line possessing the Swedish mutation. This screening assay employed cells (K293 = human kidney cell line) which were stably transfected with the gene for amyloid precursor protein 751

-- 315 --

(APP751) containing the double mutation Lys₆₅₁Met₆₅₂ to Asn₆₅₁Leu₆₅₂ (APP751 numbering) in the manner described in International Patent Application Publication No. 94/10569⁸ and Citron et al.¹². This mutation is commonly called the Swedish mutation and the cells, designated as "293 751 SWE", were plated
5 in Corning 96-well plates at $2-4 \times 10^4$ cells per well in Dulbecco's minimal essential media (Sigma, St. Louis, MO) plus 10% fetal bovine serum. Cell number is important in order to achieve β -amyloid ELISA results within the linear range of the assay (~ 0.2 to 2.5 ng per mL).

10 Following overnight incubation at 37°C in an incubator equilibrated with 10% carbon dioxide, media were removed and replaced with $200 \mu\text{L}$ of a compound of formula I (drug) containing media per well for a two hour pretreatment period and cells were incubated as above. Drug stocks were prepared in 100% dimethyl sulfoxide such that at the final drug concentration
15 used in the treatment, the concentration of dimethyl sulfoxide did not exceed 0.5% and, in fact, usually equaled 0.1%.

At the end of the pretreatment period, the media were again removed and replaced with fresh drug containing media as above and cells were incubated for
20 an additional two hours. After treatment, plates were centrifuged in a Beckman GPR at 1200 rpm for five minutes at room temperature to pellet cellular debris from the conditioned media. From each well, $100 \mu\text{L}$ of conditioned media or appropriate dilutions thereof were transferred into an ELISA plate precoated with antibody 266 [P. Seubert, *Nature* (1992) 359:325-327] against amino acids
25 13-28 of β -amyloid peptide as described in International Patent Application Publication No. 94/10569⁸ and stored at 4°C overnight. An ELISA assay employing labelled antibody 3D6 [P. Seubert, *Nature* (1992) 359:325-327] against amino acids 1-5 of β -amyloid peptide was run the next day to measure the amount of β -amyloid peptide produced.

30

-- 316 --

Cytotoxic effects of the compounds were measured by a modification of the method of Hansen, et al.¹³. To the cells remaining in the tissue culture plate was added 25 μ L of a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) (Sigma, St. Louis, MO) stock solution (5 mg/mL) to a final concentration of 1 mg/mL. Cells were incubated at 37°C for one hour, and cellular activity was stopped by the addition of an equal volume of MTT lysis buffer (20% w/v sodium dodecylsulfate in 50% dimethylformamide, pH 4.7). Complete extraction was achieved by overnight shaking at room temperature. The difference in the OD_{562nm} and the OD_{650nm} was measured in a Molecular Device's UV_{max} microplate reader as an indicator of the cellular viability.

The results of the β -amyloid peptide ELISA were fit to a standard curve and expressed as ng/mL β -amyloid peptide. In order to normalize for cytotoxicity, these results were divided by the MTT results and expressed as a percentage of the results from a drug free control. All results are the mean and standard deviation of at least six replicate assays.

The test compounds were assayed for β -amyloid peptide production inhibition activity in cells using this assay. The results of this assay demonstrate that the compounds of formula I inhibit β -amyloid peptide production by at least 30% as compared to control.

Example Bio-2

***In Vivo* Suppression of β -Amyloid Release and/or Synthesis**

This example illustrates how the compounds of this invention could be tested for *in vivo* suppression of β -amyloid release and/or synthesis. For these experiments, 3 to 4 month old PDAPP mice are used [Games et al., (1995) *Nature* 373:523-527]. Depending upon which compound is being tested, the compound is usually formulated at between 1 and 10 mg/mL. Because of the low solubility factors of the compounds, they may be formulated with various vehicles, such as corn oil (Safeway, South San Francisco, CA); 10% ethanol in

-- 317 --

corn oil; 2-hydroxypropyl- β -cyclodextrin (Research Biochemicals International, Natick MA); and carboxy-methyl-cellulose (Sigma Chemical Co., St. Louis MO).

5 The mice are dosed subcutaneously with a 26 gauge needle and 3 hours later the animals are euthanized via CO₂ narcosis and blood is taken by cardiac puncture using a 1 cc 25G 5/8" tuberculin syringe/needle coated with solution of 0.5 M EDTA, pH 8.0. The blood is placed in a Becton-Dickinson vacutainer tube containing EDTA and spun down for 15 minutes at 1500 xg at 5°C. The
10 brains of the mice are then removed and the cortex and hippocampus are dissected out and placed on ice.

1. Brain Assay

 To prepare hippocampal and cortical tissue for enzyme-linked
15 immunosorbent assays (ELISAs) each brain region is homogenized in 10 volumes of ice cold guanidine buffer (5.0 M guanidine-HCl, 50 mM Tris-HCl, pH 8.0) using a Kontes motorized pestle (Fisher, Pittsburgh PA). The homogenates are gently rocked on a rotating platform for three to four hours at room temperature and stored at -20°C prior to quantitation of β -amyloid.

20 The brain homogenates are diluted 1:10 with ice-cold casein buffer [0.25% casein, phosphate buffered saline (PBS), 0.05% sodium azide, 20 μ g/ml aprotinin, 5 mM EDTA, pH 8.0, 10 μ g/ml leupeptin], thereby reducing the final concentration of guanidine to 0.5 M, before centrifugation at 16,000 xg for 20
25 minutes at 4°C. Samples are further diluted, if necessary, to achieve an optimal range for the ELISA measurements by the addition of casein buffer with 0.5 M guanidine hydrochloride added. The β -amyloid standards (1-40 or 1-42 amino acids) were prepared such that the final composition equaled 0.5 M guanidine in the presence of 0.1% bovine serum albumin (BSA).

30

-- 318 --

The total β -amyloid sandwich ELISA; quantitating both β -amyloid (aa 1-40) and β -amyloid (aa 1-42) consists of two monoclonal antibodies (mAb) to β -amyloid. The capture antibody, 266 [P. Seubert, *Nature* (1992) 359:325-327], is specific to amino acids 13 - 28 of β -amyloid. The antibody 3D6 [Johnson-
5 Wood et al., *PNAS USA* (1997) 94:1550-1555], which is specific to amino acids 1 - 5 of β -amyloid, is biotinylated and served as the reporter antibody in the assay. The 3D6 biotinylation procedure employs the manufacturer's (Pierce, Rockford IL) protocol for NHS-biotin labeling of immunoglobulins except that 100 mM sodium bicarbonate, pH 8.5 buffer is used. The 3D6 antibody does not
10 recognize secreted amyloid precursor protein (APP) or full-length APP but detects only β -amyloid species with an amino terminal aspartic acid. The assay has a lower limit of sensitivity of ~50 pg/ml (11 pM) and shows no cross-reactivity to the endogenous murine β -amyloid peptide at concentrations up to 1 ng/ml.

15

The configuration of the sandwich ELISA quantitating the level of β -amyloid (aa 1-42) employs the mAb 21F12 [Johnson-Wood et al., *PNAS USA* (1997) 94:1550-1555] (which recognizes amino acids 33-42 of β -amyloid) as the capture antibody. Biotinylated 3D6 is also the reporter antibody in this assay
20 which has a lower limit of sensitivity of ~125 pg/ml (28 pM).

The 266 and 21F12 capture mAbs are coated at 10 μ g/ml into 96 well immunoassay plates (Costar, Cambridge MA) overnight at room temperature. The plates are then aspirated and blocked with 0.25% human serum albumin in
25 PBS buffer for at least 1 hour at room temperature, then stored desiccated at 4°C until use. The plates are rehydrated with wash buffer (Tris-buffered saline, 0.05% Tween 20) prior to use. The samples and standards are added to the plates and incubated overnight at 4°C. The plates are washed ≥ 3 times with wash buffer between each step of the assay. The biotinylated 3D6, diluted to
30 0.5 μ g/ml in casein incubation buffer (0.25% casein, PBS, 0.05% Tween 20, pH 7.4) is incubated in the well for 1 hour at room temperature. Avidin-HRP

-- 319 --

(Vector, Burlingame CA) diluted 1:4000 in casein incubation buffer is added to the wells for 1 hour at room temperature. The colorimetric substrate, Slow TMB-ELISA (Pierce, Cambridge MA), is added and allowed to react for 15 minutes, after which the enzymatic reaction is stopped with addition of 2 N H₂SO₄. Reaction product is quantified using a Molecular Devices Vmax (Molecular Devices, Menlo Park CA) measuring the difference in absorbance at 450 nm and 650 nm.

2. Blood Assay

The EDTA plasma is diluted 1:1 in specimen diluent (0.2 gm/l sodium phosphate•H₂O (monobasic), 2.16 gm/l sodium phosphate•7H₂O (dibasic), 0.5gm/l thimerosal, 8.5 gm/l sodium chloride, 0.5 ml Triton X-405, 6.0 g/l globulin-free bovine serum albumin; and water). The samples and standards in specimen diluent are assayed using the total β-amyloid assay (266 capture/3D6 reporter) described above for the brain assay except the specimen diluent was used instead of the casein diluents described.

Formulations other than those described above can also be used for oral delivery and intravenous delivery to a mammal. For oral delivery, the compound can be mixed with either 100% corn oil or, alternatively, in a solution containing 80% corn oil, 19.5% oleic acid and 0.5% labrafil. The compound can be mixed with the above solutions in concentrations ranging from 1 mg/mL to 10 mg/mL. The compound in solution is preferably administered orally to the mammal at a dose volume of 5 mL/kg of body weight. For IV delivery, the compound is preferably mixed with a solution of 3% ethanol, 3% solutol HS-15 and 94% saline. The compound is preferably mixed with the above solution in concentrations ranging from 0.25 mg/mL to 5 mg/mL. The compound in solution is preferably administered by IV to the mammal at a dose volume of 2 mL/kg of body weight.

30

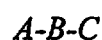
-- 320 --

From the foregoing description, various modifications and changes in the composition and method will occur to those skilled in the art. All such modifications coming within the scope of the appended claims are intended to be included therein.

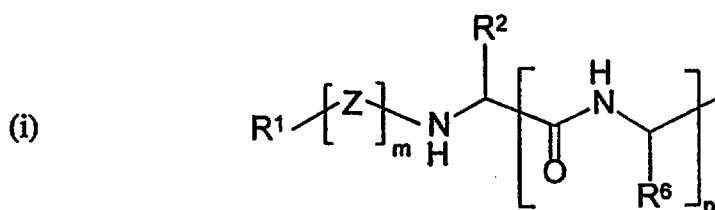


WHAT IS CLAIMED IS:

1. A method for inhibiting β -amyloid peptide release and/or its synthesis in a cell which method comprises administering to such a cell an amount of a compound or a mixture of compounds effective in inhibiting the cellular release and/or synthesis of β -amyloid peptide wherein said compounds are represented by formula I:



wherein *A* is selected from the group consisting of:



where R^1 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted cycloalkyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic;

Z is selected from the group consisting of

- (a) a group having the formula $-CX'X''C(O)-$ where X' is hydrogen, hydroxy or fluoro; X'' is hydrogen, hydroxy or fluoro, or X' and X'' together form an oxo group;
- (b) a group having the formula $-T-CX'X''C(O)-$ where *T* is selected from the group consisting of oxygen, sulfur and $-NR^3$ where R^3 is hydrogen, acyl, alkyl, aryl or heteroaryl group; X' is hydrogen or fluoro, X'' is hydrogen, hydroxy or fluoro, or X' and X'' together form an oxo group; and
- (c) a group having the formula $-CX'X''-T-C(O)-$ where *T* is selected from the group consisting of oxygen, sulfur and $-NR^3$ where R^3 is



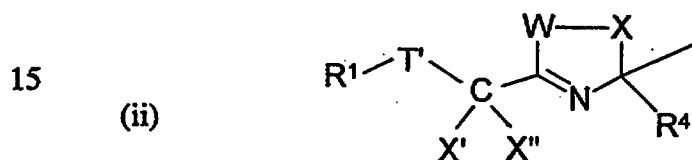
hydrogen, acyl, alkyl, aryl or heteroaryl group; X' is hydrogen or fluoro, X'' is hydrogen, hydroxy or fluoro, or X' and X'' together form an oxo group;

R² is selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclic;

R⁶ is selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclic;

m is an integer equal to 0 or 1; and

p is an integer equal to 0 or 1;



where R¹ is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted cycloalkyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic;

T' is selected from the group consisting of a bond covalently linking R¹ to -CX'X'', oxygen, sulfur and -NR³ where R³ is hydrogen, acyl, alkyl, aryl or heteroaryl group;

W and X are independently selected from the group consisting of -(CR⁷R⁷)_q-, oxygen, sulfur and -NR⁸ where *q* is an integer equal to one or two, and each R⁷ and R⁸ is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl, acyl, acyloxy, carboxyl, carboxyl esters and heterocyclic and further, when *q* is 2, an R⁷ group on each of the carbon atoms can optionally be fused to form an aryl, heteroaryl, heterocyclic or cycloalkyl group with the ethylene group with the



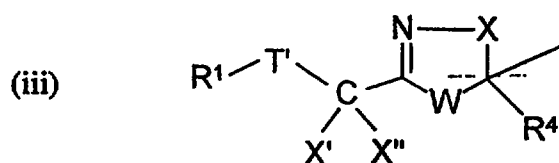
proviso that when unsaturated, the remaining R^7 group on each carbon atom participates in the unsaturation;

and with the further proviso that when W is oxygen, then X is not also oxygen;

5 X' is hydrogen, hydroxy or fluoro, X'' is hydrogen, hydroxy or fluoro, or X' and X'' together form an oxo group;

R^4 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, heteroaryl and heterocyclic; and

10



where R^1 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted cycloalkyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic;

20

T' is selected from the group consisting of a bond covalently linking R^1 to $-CX'X''-$, oxygen, sulfur and $-NR^3$ where R^3 is hydrogen, acyl, alkyl, aryl or heteroaryl group;

W and X are independently selected from the group consisting of $-(CR^7R^q)_q-$, oxygen, sulfur and $-NR^8$ where q is an integer equal to one or two and each R^7 and R^8 is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl, acyl, acyloxy, carboxyl, carboxyl esters, and heterocyclic and further, when q is 2, an R^7 group on each of the carbon atoms can optionally be fused to form an aryl, heteroaryl, heterocyclic or cycloalkyl group with the ethylene group with the proviso that when unsaturated, the remaining R^7 group on each carbon atom participates in the unsaturation;

25

30

X' is hydrogen, hydroxy or fluoro, X'' is hydrogen, hydroxy or fluoro, or X' and X'' together form an oxo group;



-- 324 --

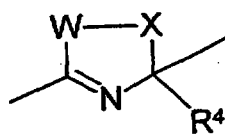
R^4 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, heteroaryl and heterocyclic;

5 B is selected from the group consisting of:



10 where R^5 is selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, heteroaryl and heterocyclic;

15 (ii)



20 W and X are independently selected from the group consisting of $-(CR^7R^7)_q-$, oxygen, sulfur and $-NR^8$ where q is an integer equal to one or two, and each R^7 and R^8 is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl, acyl, acyloxy, carboxyl, carboxyl esters, and heterocyclic and further, when q is 2, an R^7
25 group on each of the carbon atoms can optionally be fused to form an aryl, heteroaryl, heterocyclic or cycloalkyl group with the ethylene group with the proviso that when unsaturated, the remaining R^7 group on each carbon atom participates in the unsaturation;

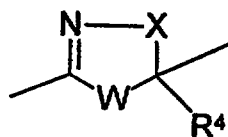
30 and with the further proviso that when W is oxygen, then X is not also oxygen;

R^4 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, heteroaryl and heterocyclic;

35



(iii)



5

W and X are independently selected from the group consisting of $-(CR^7R^7)_q-$, oxygen, sulfur and $-NR^8$ where q is an integer equal to 1 or 2 and each R^7 and R^8 is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl, acyl, acyloxy, and heterocyclic and further, when q is 2, an R^7 group on each of the carbon atoms can optionally be fused to form an aryl, heteroaryl, heterocyclic or cycloalkyl group with the proviso that when unsaturated, the remaining R^7 group on each carbon atom participates in the unsaturation;

15

R^4 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, heteroaryl and heterocyclic; and

(iv) when A is either formula (ii) or (iii) as defined above, then B can also be a covalent bond linking A to C ;

20

C is selected from the group consisting of:

(i) $-C(O)Y$ or $-C(S)Y$

where Y is selected from the group consisting of:

25

(a) alkyl or cycloalkyl,

(b) substituted alkyl with the proviso that the substitution on said substituted alkyl do not include α -haloalkyl, α -diazoalkyl, α -OC(O)alkyl, or α -OC(O)aryl groups,

30

(c) alkoxy or thioalkoxy,

(d) substituted alkoxy or substituted thioalkoxy,

(e) hydroxy,

(f) aryl,

(g) heteroaryl,



(h) heterocyclic,

(i) $-NR'R''$ where R' and R'' are independently selected from hydrogen, alkyl, alkenyl, alkynyl, substituted alkyl, substituted alkenyl, substituted alkenyl, cycloalkyl, aryl, heteroaryl, heterocyclic, where one of R' or R'' is hydroxy or alkoxy, and where R' and R'' are joined to form a cyclic group having from 2 to 8 carbon atoms optionally containing 1 to 2 additional heteroatoms selected from oxygen, sulfur and nitrogen and optionally substituted with one or more alkyl, alkoxy or carboxylalkyl groups,

(j) $-NHSO_2-R^8$ where R^8 is selected from alkyl, substituted alkyl, alkenyl, substituted alkenyl, cycloalkyl, aryl, heteroaryl and heterocyclic,

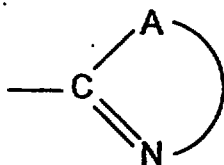
(k) $-NR^9NR^{10}R^{10}$ where R^9 is hydrogen or alkyl, and each R^{10} is independently selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, cycloalkyl, aryl, heteroaryl, heterocyclic, and

(l) $-ONR^9[C(O)O]_zR^{10}$ where z is zero or one, R^9 and R^{10} are as defined above;

(ii) $-CR^{11}R^{11}Y'$

where each R^{11} is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, heteroaryl and heterocyclic and Y' is selected from the group consisting of hydroxyl, alkoxy, amino, thiol, substituted alkoxy, thioalkoxy, substituted thioalkoxy, $-OC(O)R^9$, $-SSR^9$, and $-SSC(O)R^9$ where R^9 is selected from the group consisting of alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl and heterocyclic; and

(iii)



where A, together with $-C=N-$, forms a heterocyclic group which is optionally fused to form a bi- or multi-fused ring system (preferably no more than 5 fused



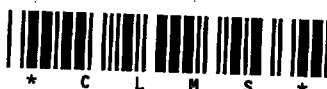
rings) with one or more ring structures selected from the group consisting of cycloalkyl, cycloalkenyl, heterocyclic, aryl and heteroaryl group which, in turn, each of such ring structures is optionally substituted with 1 to 4 substituents selected from the group consisting of hydroxyl, halo, alkoxy, substituted alkoxy, thioalkoxy, substituted thioalkoxy, nitro, cyano, carboxyl, carboxyl esters, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, heteroaryl, heterocyclic, $-\text{NHC}(\text{O})\text{R}^{10}$, $-\text{NHSO}_2\text{R}^{10}$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{NHR}^{10}$, $-\text{C}(\text{O})\text{NR}^{10}\text{R}^{10}$, $-\text{S}(\text{O})\text{R}^{10}$, $-\text{S}(\text{O})_2\text{R}^{10}$, $-\text{S}(\text{O})_2\text{NHR}^{10}$ and $-\text{S}(\text{O})_2\text{NR}^{10}\text{R}^{10}$ where each R^{10} is independently selected from the group consisting of alkyl, substituted alkyl, or aryl, amino, N-alkylamino, N,N-dialkylamino, N-substituted alkylamino, N,N-disubstituted alkylamino, N-alkenylamino, N,N-dialkenylamino, N-substituted alkenylamino, N,N-disubstituted alkenylamino, N-cycloalkylamino, N,N-dicycloalkylamino, N-substituted cycloalkylamino, N,N-disubstituted cycloalkylamino, N-arylamino, N,N-diarylamino, N-heteroarylamino, N,N-diheteroarylamino, N-heterocyclic amino, N,N-diheterocyclic amino and mixed N,N-amino groups comprising a first and second substituent on said amino group which substituents are selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, cycloalkyl, substituted cycloalkyl, aryl, heteroaryl, and heterocyclic provided that said first and second substituents are not the same;

with the proviso that when *A* has structure (i) and *B* has structure (i), then *C* does not have structure (i) or (ii);

with the further provisos that

A. when *A* has structure (i) with R^1 being phenyl, *Z* being $-\text{CH}_2\text{OC}(\text{O})-$, R_2 being methyl and *p* being zero, *B* has structure (iii) with *W* being $-\text{NH}-$, *X* being $-\text{CH}_2-$, and R^4 being benzyl then *C* is not $-\text{C}(\text{O})\text{OCH}_3$;

B. when *A* has structure (i) with R^1 being 3,5-difluorophenyl, *Z* being $-\text{CH}_2\text{C}(\text{O})-$, R^2 being methyl, and *p* being zero, *B* has structure (ii) with *W* being $>\text{NC}(\text{O})\text{OC}(\text{CH}_3)_3$, *X* being $-\text{CH}_2-$, and R^4 being phenyl, then *C* is not $-\text{C}(\text{O})\text{OCH}_3$; and



C. when *A* has structure (ii) wherein R^1 is 3,5-difluorophenyl, T' is a bond linking R^1 to $-CX'X''-$, X' and X'' are hydrogen, W is sulfur, X is methylene and R^4 is methyl, and *B* is a covalent bond linking *A* to *C*, then *C* is not $-C(O)OCH_3$.

5

2. A method for preventing the onset of AD in a patient at risk for developing AD which method comprises administering to said patient a pharmaceutical composition comprising a pharmaceutically inert carrier and an effective amount of a compound or a mixture of compounds of formula I:

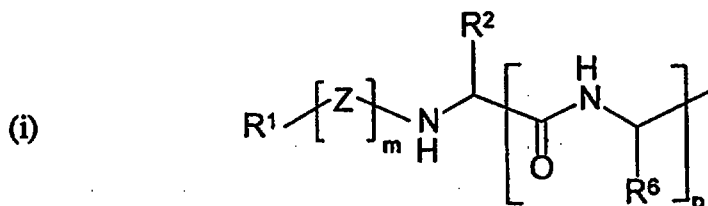
10

A-B-C

15

wherein *A* is selected from the group consisting of:

20



25

where R^1 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted cycloalkyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic;

Z is selected from the group consisting of

30

(a) a group having the formula $-CX'X''C(O)-$ where X' is hydrogen, hydroxy or fluoro; X'' is hydrogen, hydroxy or fluoro, or X' and X'' together form an oxo group;

(b) a group having the formula $-T-CX'X''C(O)-$ where *T* is selected from the group consisting of oxygen, sulfur and $-NR^3$ where R^3 is hydrogen, acyl, alkyl, aryl or heteroaryl group; X' is hydrogen or fluoro, X'' is hydrogen, hydroxy or fluoro, or X' and X'' together form an oxo group; and

35



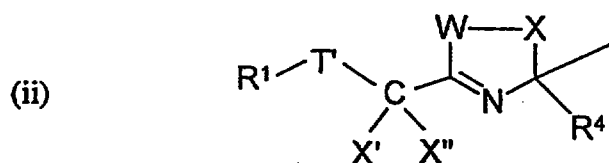
- (c) a group having the formula $-CX'X''-T-C(O)-$ where T is selected from the group consisting of oxygen, sulfur and $-NR^3$ where R^3 is hydrogen, acyl, alkyl, aryl or heteroaryl group; X' is hydrogen or fluoro, X'' is hydrogen, hydroxy or fluoro, or X' and X'' together form an oxo group;

R^2 is selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclic;

R^6 is selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclic;

m is an integer equal to 0 or 1; and

p is an integer equal to 0 or 1;



where R^1 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted cycloalkyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic;

T' is selected from the group consisting of a bond covalently linking R^1 to $-CX'X''-$, oxygen, sulfur and $-NR^3$ where R^3 is hydrogen, acyl, alkyl, aryl or heteroaryl group;

W and X are independently selected from the group consisting of $-(CR^7R^8)_q-$, oxygen, sulfur and $-NR^8$ where q is an integer equal to one or two, and each R^7 and R^8 is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl, acyl, acyloxy, carboxyl, carboxyl esters and heterocyclic and further, when q is 2, an R^7 group on each of the carbon atoms can optionally be fused to form an aryl,

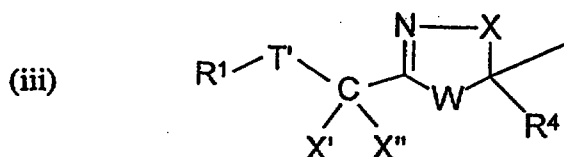


heteroaryl, heterocyclic or cycloalkyl group with the ethylene group with the proviso that when unsaturated, the remaining R^7 group on each carbon atom participates in the unsaturation;

and with the further proviso that when W is oxygen, then X is not also oxygen;

X' is hydrogen, hydroxy or fluoro, X'' is hydrogen, hydroxy or fluoro, or X' and X'' together form an oxo group;

R^4 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, heteroaryl and heterocyclic; and



where R^1 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted cycloalkyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic;

T' is selected from the group consisting of a bond covalently linking R^1 to $-CX'X''-$, oxygen, sulfur and $-NR^3$ where R^3 is hydrogen, acyl, alkyl, aryl or heteroaryl group;

W and X are independently selected from the group consisting of $-(CR^7R^7)_q-$, oxygen, sulfur and $-NR^8$ where q is an integer equal to one or two and each R^7 and R^8 is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl, acyl, acyloxy, carboxyl, carboxyl esters, and heterocyclic and further, when q is 2, an R^7 group on each of the carbon atoms can optionally be fused to form an aryl, heteroaryl, heterocyclic or cycloalkyl group with the ethylene group with the proviso that when unsaturated, the remaining R^7 group on each carbon atom participates in the unsaturation;



X' is hydrogen, hydroxy or fluoro, X'' is hydrogen, hydroxy or fluoro, or X' and X'' together form an oxo group;

R⁴ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, heteroaryl and heterocyclic;

B is selected from the group consisting of:



where R⁵ is selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, heteroaryl and heterocyclic;

15



20

W and X are independently selected from the group consisting of $-(CR^7R^7)_q-$, oxygen, sulfur and $-NR^8$ where q is an integer equal to one or two, and each R⁷ and R⁸ is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl, acyl, acyloxy, carboxyl, carboxyl esters, and heterocyclic and further, when q is 2, an R⁷ group on each of the carbon atoms can optionally be fused to form an aryl, heteroaryl, heterocyclic or cycloalkyl group with the ethylene group with the proviso that when unsaturated, the remaining R⁷ group on each carbon atom participates in the unsaturation;

30

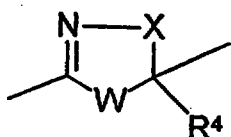
and with the further proviso that when W is oxygen, then X is not also oxygen;

R⁴ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, heteroaryl and heterocyclic;

35



(iii)



5

W and X are independently selected from the group consisting of $-(CR^7R^7)_q-$, oxygen, sulfur and $-NR^8$ where q is an integer equal to 1 or 2 and each R^7 and R^8 is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl, acyl, acyloxy, and heterocyclic and further, when q is 2, an R^7 group on each of the carbon atoms can optionally be fused to form an aryl, heteroaryl, heterocyclic or cycloalkyl group with the ethylene group with the proviso that when unsaturated, the remaining R^7 group on each carbon atom participates in the unsaturation;

15

R^4 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, heteroaryl and heterocyclic; and

(iv) when A is either formula (ii) or (iii) as defined above, then B can also be a covalent bond linking A to C ;

20

C is selected from the group consisting of:

(i) $-C(O)Y$ or $-C(S)Y$

where Y is selected from the group consisting of:

25

(a) alkyl or cycloalkyl,

(b) substituted alkyl with the proviso that the substitution on said substituted alkyl do not include α -haloalkyl, α -diazoalkyl, α -OC(O)alkyl, or α -OC(O)aryl groups,

(c) alkoxy or thioalkoxy,

30

(d) substituted alkoxy or substituted thioalkoxy,

(e) hydroxy,

(f) aryl,

(g) heteroaryl,



(h) heterocyclic,

(i) $-NR'R''$ where R' and R'' are independently selected from hydrogen, alkyl, alkenyl, alkynyl, substituted alkyl, substituted alkenyl, substituted alkenyl, cycloalkyl, aryl, heteroaryl, heterocyclic, where one of R' or R'' is hydroxy or alkoxy, and where R' and R'' are joined to form a cyclic group having from 2 to 8 carbon atoms optionally containing 1 to 2 additional heteroatoms selected from oxygen, sulfur and nitrogen and optionally substituted with one or more alkyl, alkoxy or carboxylalkyl groups,

(j) $-NHSO_2-R^8$ where R^8 is selected from alkyl, substituted alkyl, alkenyl, substituted alkenyl, cycloalkyl, aryl, heteroaryl and heterocyclic,

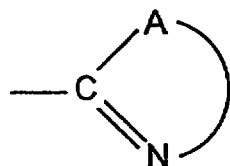
(k) $-NR^9NR^{10}R^{10}$ where R^9 is hydrogen or alkyl, and each R^{10} is independently selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, cycloalkyl, aryl, heteroaryl, heterocyclic, and

(l) $-ONR^9[C(O)O]_zR^{10}$ where z is zero or one, R^9 and R^{10} are as defined above;

(ii) $-CR^{11}R^{11}Y'$

where each R^{11} is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, heteroaryl and heterocyclic and Y' is selected from the group consisting of hydroxyl, alkoxy, amino, thiol, substituted alkoxy, thioalkoxy, substituted thioalkoxy, $-OC(O)R^9$, $-SSR^9$, and $-SSC(O)R^9$ where R^9 is selected from the group consisting of alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl and heterocyclic; and

(iii)



where A , together with $-C=N-$, forms a heterocyclic group which is optionally fused to form a bi- or multi-fused ring system (preferably no more than 5 fused



rings) with one or more ring structures selected from the group consisting of cycloalkyl, cycloalkenyl, heterocyclic, aryl and heteroaryl group which, in turn, each of such ring structures is optionally substituted with 1 to 4 substituents selected from the group consisting of hydroxyl, halo, alkoxy, substituted alkoxy, thioalkoxy, substituted thioalkoxy, nitro, cyano, carboxyl, carboxyl esters, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, heteroaryl, heterocyclic, -NHC(O)R^{10} , $\text{-NHSO}_2\text{R}^{10}$, -C(O)NH_2 , -C(O)NHR^{10} , $\text{-C(O)NR}^{10}\text{R}^{10}$, -S(O)R^{10} , $\text{-S(O)}_2\text{R}^{10}$, $\text{-S(O)}_2\text{NHR}^{10}$ and $\text{-S(O)}_2\text{NR}^{10}\text{R}^{10}$ where each R^{10} is independently selected from the group consisting of alkyl, substituted alkyl, or aryl, amino, N-alkylamino, N,N-dialkylamino, N-substituted alkylamino, N,N-disubstituted alkylamino, N-alkenylamino, N,N-dialkenylamino, N-substituted alkenylamino, N,N-disubstituted alkenylamino, N-cycloalkylamino, N,N-dicycloalkylamino, N-substituted cycloalkylamino, N,N-disubstituted cycloalkylamino, N-arylamino, N,N-diarylamino, N-heteroarylamino, N,N-diheteroarylamino, N-heterocyclic amino, N,N-diheterocyclic amino and mixed N,N-amino groups comprising a first and second substituent on said amino group which substituents are selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, cycloalkyl, substituted cycloalkyl, aryl, heteroaryl, and heterocyclic provided that said first and second substituents are not the same;

with the proviso that when *A* has structure (i) and *B* has structure (i), then *C* does not have structure (i) or (ii);

with the further provisos that

A. when *A* has structure (i) with R^1 being phenyl, *Z* being $\text{-CH}_2\text{OC(O)-}$, R_2 being methyl and *p* being zero, *B* has structure (iii) with *W* being -NH- , *X* being $\text{-CH}_2\text{-}$, and R^4 being benzyl then *C* is not -C(O)OCH_3 ;

B. when *A* has structure (i) with R^1 being 3,5-difluorophenyl, *Z* being $\text{-CH}_2\text{C(O)-}$, R^2 being methyl, and *p* being zero, *B* has structure (ii) with *W* being $\text{>NC(O)OC(CH}_3)_3$, *X* being $\text{-CH}_2\text{-}$, and R^4 being phenyl, then *C* is not -C(O)OCH_3 ; and



C. when *A* has structure (ii) wherein R^1 is 3,5-difluorophenyl, T' is a bond linking R^1 to $-CX'X''-$, X' and X'' are hydrogen, W is sulfur, X is methylene and R^4 is methyl, and *B* is a covalent bond linking *A* to *C*, then *C* is not $-C(O)OCH_3$.

5

3. A method for treating a patient with AD in order to inhibit further deterioration in the condition of that patient which method comprises administering to said patient a pharmaceutical composition comprising a pharmaceutically inert carrier and an effective amount of a compound or a mixture of compounds of formula I:

10

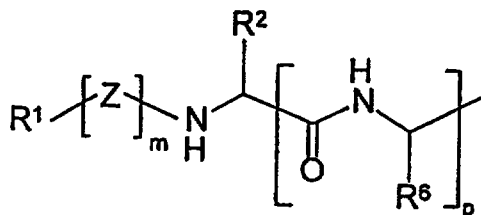
A-B-C

15

wherein *A* is selected from the group consisting of:

20

(i)



25

where R^1 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted cycloalkyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic;

Z is selected from the group consisting of

30

- (a) a group having the formula $-CX'X''C(O)-$ where X' is hydrogen, hydroxy or fluoro; X'' is hydrogen, hydroxy or fluoro, or X' and X'' together form an oxo group;
- (b) a group having the formula $-T-CX'X''C(O)-$ where *T* is selected from the group consisting of oxygen, sulfur and $-NR^3$ where R^3 is hydrogen, acyl, alkyl, aryl or heteroaryl group; X' is hydrogen



or fluoro, X'' is hydrogen, hydroxy or fluoro, or X' and X'' together form an oxo group; and

- (c) a group having the formula $-CX'X''-T-C(O)-$ where T is selected from the group consisting of oxygen, sulfur and $-NR^3$ where R^3 is hydrogen, acyl, alkyl, aryl or heteroaryl group; X' is hydrogen or fluoro, X'' is hydrogen, hydroxy or fluoro, or X' and X'' together form an oxo group;

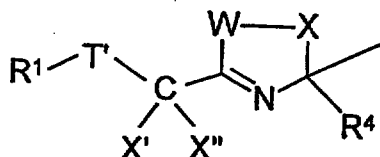
R^2 is selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclic;

R^6 is selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclic;

m is an integer equal to 0 or 1; and

p is an integer equal to 0 or 1;

20 (ii)



where R^1 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted cycloalkyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic;

T' is selected from the group consisting of a bond covalently linking R^1 to $-CX'X''-$, oxygen, sulfur and $-NR^3$ where R^3 is hydrogen, acyl, alkyl, aryl or heteroaryl group;

W and X are independently selected from the group consisting of $-(CR^7R^8)_q-$, oxygen, sulfur and $-NR^8$ where q is an integer equal to one or two, and each R^7 and R^8 is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl, acyl, acyloxy,



carboxyl, carboxyl esters and heterocyclic and further, when q is 2, an R^7 group on each of the carbon atoms can optionally be fused to form an aryl, heteroaryl, heterocyclic or cycloalkyl group with the ethylene group with the proviso that when unsaturated, the remaining R^7 group on each carbon atom participates in the unsaturation;

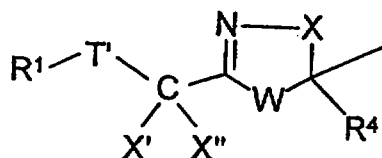
and with the further proviso that when W is oxygen, then X is not also oxygen;

X' is hydrogen, hydroxy or fluoro, X'' is hydrogen, hydroxy or fluoro, or X' and X'' together form an oxo group;

R^4 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, heteroaryl and heterocyclic; and

15

(iii)



20

where R^1 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted cycloalkyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic;

T' is selected from the group consisting of a bond covalently linking R^1 to $-CX'X''-$, oxygen, sulfur and $-NR^3$ where R^3 is hydrogen, acyl, alkyl, aryl or heteroaryl group;

W and X are independently selected from the group consisting of $-(CR^7R^7)_q-$, oxygen, sulfur and $-NR^8$ where q is an integer equal to one or two and each R^7 and R^8 is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl, acyl, acyloxy, carboxyl, carboxyl esters, and heterocyclic and further, when q is 2, an R^7 group on each of the carbon atoms can optionally be fused to form an aryl, heteroaryl, heterocyclic or cycloalkyl group with the ethylene group with the



proviso that when unsaturated, the remaining R^7 group on each carbon atom participates in the unsaturation;

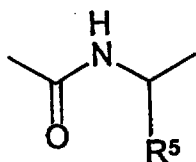
X' is hydrogen, hydroxy or fluoro, X'' is hydrogen, hydroxy or fluoro, or X' and X'' together form an oxo group;

- 5 R^4 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, heteroaryl and heterocyclic;

B is selected from the group consisting of:

10

(i)

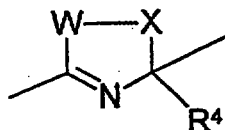


15

where R^5 is selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, heteroaryl and heterocyclic;

20

(ii)



25

W and X are independently selected from the group consisting of $-(CR^7R^7)_q$, oxygen, sulfur and $-NR^8$ where q is an integer equal to one or two, and each R^7 and R^8 is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl, acyl, acyloxy, carboxyl, carboxyl esters, and heterocyclic and further, when q is 2, an R^7 group on each of the carbon atoms can optionally be fused to form an aryl, heteroaryl, heterocyclic or cycloalkyl group with the ethylene group with the proviso that when unsaturated, the remaining R^7 group on each carbon atom participates in the unsaturation;

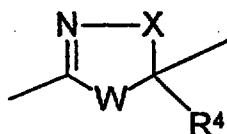
30

and with the further proviso that when W is oxygen, then X is not also oxygen;



R^4 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, heteroaryl and heterocyclic;

(iii)



W and X are independently selected from the group consisting of $-(CR^7R^8)_q-$, oxygen, sulfur and $-NR^8$ where q is an integer equal to 1 or 2 and each R^7 and R^8 is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl, acyl, acyloxy, and heterocyclic and further, when q is 2, an R^7 group on each of the carbon atoms can optionally be fused to form an aryl, heteroaryl, heterocyclic or cycloalkyl group with the proviso that when unsaturated, the remaining R^7 group on each carbon atom participates in the unsaturation;

R^4 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, heteroaryl and heterocyclic; and

(iv) when A is either formula (ii) or (iii) as defined above, then B can also be a covalent bond linking A to C ;

C is selected from the group consisting of:

(i) $-C(O)Y$ or $-C(S)Y$

where Y is selected from the group consisting of:

(a) alkyl or cycloalkyl,

(b) substituted alkyl with the proviso that the substitution on said substituted alkyl do not include α -haloalkyl, α -diazoalkyl, α -OC(O)alkyl, or α -OC(O)aryl groups,

(c) alkoxy or thioalkoxy,

(d) substituted alkoxy or substituted thioalkoxy,



- (e) hydroxy,
- (f) aryl,
- (g) heteroaryl,
- (h) heterocyclic,

5 (i) $-NR'R''$ where R' and R'' are independently selected from hydrogen, alkyl, alkenyl, alkynyl, substituted alkyl, substituted alkenyl, substituted alkenyl, cycloalkyl, aryl, heteroaryl, heterocyclic, where one of R' or R'' is hydroxy or alkoxy, and where R' and R'' are joined to form a cyclic group having from 2 to 8 carbon atoms optionally containing 1 to 2 additional
10 heteroatoms selected from oxygen, sulfur and nitrogen and optionally substituted with one or more alkyl, alkoxy or carboxylalkyl groups,

(j) $-NHSO_2-R^8$ where R^8 is selected from alkyl, substituted alkyl, alkenyl, substituted alkenyl, cycloalkyl, aryl, heteroaryl and heterocyclic,

(k) $-NR^9NR^{10}R^{10}$ where R^9 is hydrogen or alkyl, and each R^{10} is
15 independently selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, cycloalkyl, aryl, heteroaryl, heterocyclic, and

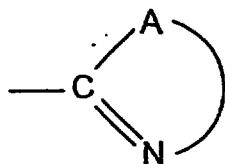
(l) $-ONR^9[C(O)O]_zR^{10}$ where z is zero or one, R^9 and R^{10} are as defined above;

20 (ii) $-CR^{11}R^{11}Y'$

where each R^{11} is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, heteroaryl and heterocyclic and Y' is selected from the group consisting of hydroxyl, alkoxy, amino, thiol, substituted alkoxy, thioalkoxy, substituted
25 thioalkoxy, $-OC(O)R^9$, $-SSR^9$, and $-SSC(O)R^9$ where R^9 is selected from the group consisting of alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl and heterocyclic; and

30

(iii)





where A, together with $-C=N-$, forms a heterocyclic group which is optionally fused to form a bi- or multi-fused ring system (preferably no more than 5 fused rings) with one or more ring structures selected from the group consisting of cycloalkyl, cycloalkenyl, heterocyclic, aryl and heteroaryl group which, in turn, each of such ring structures is optionally substituted with 1 to 4 substituents selected from the group consisting of hydroxyl, halo, alkoxy, substituted alkoxy, thioalkoxy, substituted thioalkoxy, nitro, cyano, carboxyl, carboxyl esters, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, heteroaryl, heterocyclic, $-NHC(O)R^{10}$, $-NHSO_2R^{10}$, $-C(O)NH_2$, $-C(O)NHR^{10}$, $-C(O)NR^{10}R^{10}$, $-S(O)R^{10}$, $-S(O)_2R^{10}$, $-S(O)_2NHR^{10}$ and $-S(O)_2NR^{10}R^{10}$ where each R^{10} is independently selected from the group consisting of alkyl, substituted alkyl, or aryl, amino, N-alkylamino, N,N-dialkylamino, N-substituted alkylamino, N,N-disubstituted alkylamino, N-alkenylamino, N,N-dialkenylamino, N-substituted alkenylamino, N,N-disubstituted alkenylamino, N-cycloalkylamino, N,N-dicycloalkylamino, N-substituted cycloalkylamino, N,N-disubstituted cycloalkylamino, N-arylamino, N,N-diarylamino, N-heteroarylamino, N,N-diheteroarylamino, N-heterocyclic amino, N,N-diheterocyclic amino and mixed N,N-amino groups comprising a first and second substituent on said amino group which substituents are selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, cycloalkyl, substituted cycloalkyl, aryl, heteroaryl, and heterocyclic provided that said first and second substituents are not the same;

with the proviso that when A has structure (i) and B has structure (i), then C does not have structure (i) or (ii);

with the further provisos that

A. when A has structure (i) with R^1 being phenyl, Z being $-CH_2OC(O)-$, R_2 being methyl and p being zero, B has structure (iii) with W being $-NH-$, X being $-CH_2-$, and R^4 being benzyl then C is not $-C(O)OCH_3$;

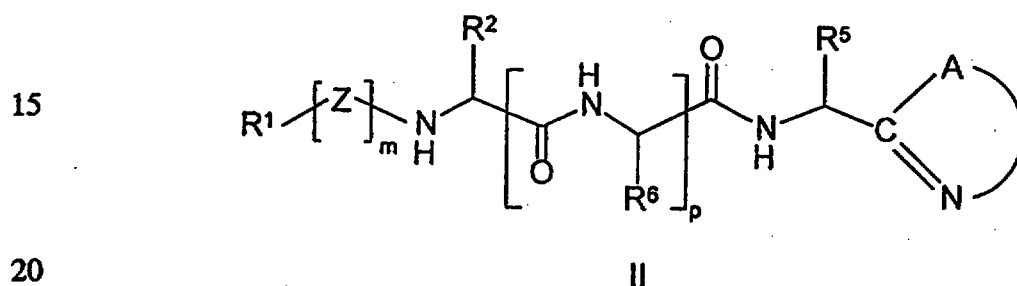
B. when A has structure (i) with R^1 being 3,5-difluorophenyl, Z being



-CH₂C(O)-, R² being methyl, and *p* being zero, *B* has structure (ii) with *W* being >NC(O)OC(CH₃)₃, *X* being -CH₂-, and R⁴ being phenyl, then *C* is not -C(O)OCH₃; and

C. when *A* has structure (ii) wherein R¹ is 3,5-difluorophenyl, T' is a
 5 bond linking R¹ to -CX'X"-, X' and X" are hydrogen, *W* is sulfur, *X* is methylene and R⁴ is methyl, and *B* is a covalent bond linking *A* to *C*, then *C* is not -C(O)OCH₃.

4. The method according to Claims 1, 2 or 3 wherein the compound of
 10 formula I is further characterized by formula II below:



wherein R¹, R², R⁵, R⁶, A, Z, *m* and *p* are as defined in Claim 1.

25 5. The method according to Claim 4 wherein *m* is one, Z is -CX'X"C(O)-, X" is hydrogen, X' is hydrogen or fluoro or X' and X" form an oxo group.

30 6. The method according to Claim 5 wherein R₁ is an unsubstituted aryl group selected from the group consisting of phenyl, 1-naphthyl and 2-naphthyl.

7. The method according to Claim 5 wherein R₁ is a substituted aryl group selected from the group consisting of monosubstituted phenyls, disubstituted phenyls, and trisubstituted phenyls.



8. The method according to Claim 7 wherein said substituted R_i phenyl group is selected from the group consisting of 2-chlorophenyl, 2-fluorophenyl, 2-bromophenyl, 2-hydroxyphenyl, 2-nitrophenyl, 2-methylphenyl, 2-methoxyphenyl, 2-phenoxyphenyl, 2-trifluoromethylphenyl, 4-fluorophenyl, 4-chlorophenyl, 4-bromophenyl, 4-nitrophenyl, 4-methylphenyl, 4-hydroxyphenyl, 4-methoxyphenyl, 4-ethoxyphenyl, 4-butoxyphenyl, 4-*iso*-propylphenyl, 4-phenoxyphenyl, 4-trifluoromethylphenyl, 4-hydroxymethylphenyl, 3-methoxyphenyl, 3-hydroxyphenyl, 3-nitrophenyl, 3-fluorophenyl, 3-chlorophenyl, 3-bromophenyl, 3-phenoxyphenyl, 3-thiomethoxyphenyl, 3-methylphenyl, 3-trifluoromethylphenyl, 2,3-dichlorophenyl, 2,3-difluorophenyl, 2,4-dichlorophenyl, 2,5-dimethoxyphenyl, 3,4-dichlorophenyl, 3,4-difluorophenyl, 3,4-methylenedioxyphenyl, 3,4-dimethoxyphenyl, 3,5-difluorophenyl, 3,5-dichlorophenyl, 3,5-di-(trifluoromethyl)phenyl, 3,5-dimethoxyphenyl, 2,4-dichlorophenyl, 2,4-difluorophenyl, 2,6-difluorophenyl, 3,4,5-trifluorophenyl, 3,4,5-trimethoxyphenyl, 3,4,5-tri-(trifluoromethyl)phenyl, 2,4,6-trifluorophenyl, 2,4,6-trimethylphenyl, 2,4,6-tri-(trifluoromethyl)phenyl, 2,3,5-trifluorophenyl, 2,4,5-trifluorophenyl, 2,5-difluorophenyl, 2-fluoro-3-trifluoromethylphenyl, 4-fluoro-2-trifluoromethylphenyl, 2-fluoro-4-trifluoromethylphenyl, 4-benzyloxyphenyl, 2-chloro-6-fluorophenyl, 2-fluoro-6-chlorophenyl, 2,3,4,5,6-pentafluorophenyl, 2,5-dimethylphenyl, 4-phenylphenyl and 2-fluoro-3-trifluoromethylphenyl.

9. The method according to Claim 4 wherein R¹ is an alkaryl group selected from the group consisting of benzyl, 2-phenylethyl and 3-phenyl-*n*-propyl.

10. The method according to Claim 4 wherein R¹ is selected from alkyl, substituted alkyl, alkenyl, cycloalkyl and cycloalkenyl groups.



11. The method according to Claim 10 wherein R¹ is selected from the group consisting of *iso*-propyl, *n*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *t*-butyl, -CH₂CH=CH₂, -CH₂CH=CH(CH₂)₄CH₃, cyclopropyl, cyclobutyl, cyclohexyl, cyclopentyl, cyclohex-1-enyl, -CH₂-cyclopropyl, -CH₂-cyclobutyl, -CH₂-
5 cyclohexyl, -CH₂-cyclopentyl, -CH₂CH₂-cyclopropyl, -CH₂CH₂-cyclobutyl, -CH₂CH₂-cyclohexyl, and -CH₂CH₂-cyclopentyl.

12. The method according to Claim 4 wherein R¹ is a heteroaryl or substituted heteroaryls selected from the group consisting of pyrid-2-yl, pyrid-3-
10 yl, pyrid-4-yl, fluoropyridyls (including 5-fluoropyrid-3-yl), chloropyridyls (including 5-chloropyrid-3-yl), thiophen-2-yl, thiophen-3-yl, benzothiazol-4-yl, 2-phenylbenzoxazol-5-yl, furan-2-yl, benzofuran-2-yl, thionaphthen-2-yl, 2-chlorothiophen-5-yl, 3-methylisoxazol-5-yl, 2-(thiophenyl)thiophen-5-yl, 6-methoxythionaphthen-2-yl, 3-phenyl-1,2,4-thioxadiazol-5-yl, and 2-
15 phenyloxazol-4-yl.

13. The method according to Claim 4 wherein R² is selected from the group consisting of methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, phenyl, benzyl, cyclohexyl, cyclopentyl, cycloheptyl, and
20 -CH₂CH₂SCH₃.

14. The method according to Claim 4 wherein R⁵ and R⁶ substituents are independently selected from the group consisting of hydrogen, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, -CH₂CH(CH₂CH₃)₂, 2-methyl-*n*-butyl, 6-fluoro-*n*-hexyl, phenyl, benzyl,
25 cyclohexyl, cyclopentyl, cycloheptyl, allyl, *iso*-but-2-enyl, 3-methylpentyl, -CH₂-cyclopropyl, -CH₂-cyclohexyl, -CH₂CH₂-cyclopropyl, -CH₂CH₂-cyclohexyl, -CH₂-indol-3-yl, *p*-(phenyl)phenyl, *o*-fluorophenyl, *m*-fluorophenyl, *p*-fluorophenyl, *m*-methoxyphenyl, *p*-methoxyphenyl,
30 phenethyl, benzyl, *m*-hydroxybenzyl, *p*-hydroxybenzyl, *p*-nitrobenzyl, *m*-trifluoromethylphenyl, *p*-(CH₃)₂NCH₂CH₂CH₂O-benzyl,



p -(CH₃)₃COC(O)CH₂O-benzyl, p -(HOOCCH₂O)-benzyl, 2-aminopyrid-6-yl, p -(N-morpholino-CH₂CH₂O)-benzyl, -CH₂CH₂C(O)NH₂, -CH₂-imidazol-4-yl, -CH₂-(3-tetrahydrofuranyl), -CH₂-thiophen-2-yl, -CH₂(1-methyl)cyclopropyl, -CH₂-thiophen-3-yl, thiophen-3-yl, thiophen-2-yl, -CH₂-C(O)O-*t*-butyl,

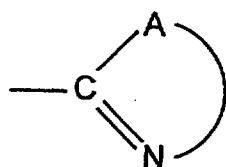
5 -CH₂-C(CH₃)₃, -CH₂CH(CH₂CH₃)₂, -2-methylcyclopentyl, -cyclohex-2-enyl, -CH[CH(CH₃)₂]COOCH₃, -CH₂CH₂N(CH₃)₂, -CH₂C(CH₃)=CH₂, -CH₂CH=CHCH₃ (cis and trans), -CH₂OH, -CH(OH)CH₃, -CH(O-*t*-butyl)CH₃, -CH₂OCH₃, -(CH₂)₄NH-Boc, -(CH₂)₄NH₂, -CH₂-pyridyl (e.g., 2-pyridyl, 3-pyridyl and 4-pyridyl), pyridyl (2-pyridyl, 3-pyridyl and 4-pyridyl), -CH₂-

10 naphthyl (e.g., 1-naphthyl and 2-naphthyl), -CH₂-(N-morpholino), p -(N-morpholino-CH₂CH₂O)-benzyl, benzo[b]thiophen-2-yl, 5-chlorobenzo[b]thiophen-2-yl, 4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl, benzo[b]thiophen-3-yl, 5-chlorobenzo[b]thiophen-3-yl, benzo[b]thiophen-5-yl, 6-methoxynaphth-2-yl, -CH₂CH₂SCH₃, thien-2-yl, thien-3-yl, and the like..

15

15. The method according to Claim 4 wherein the

20

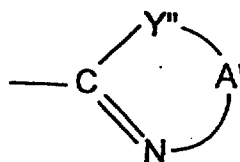


group is further characterized

25

by the following heterocyclic structure:

30



35

wherein Y'' is a heteroatom selected from oxygen, sulfur and >NR⁸ where R⁸ is as defined above and A', together with -Y''-C=N-, forms a heterocyclic group which is optionally fused to form a bi- or multi-fused ring system (preferably no more than 5 fused rings) with one or more ring structures



selected from the group consisting of cycloalkyl, cycloalkenyl, heterocyclic, aryl and heteroaryl group which, in turn, each of such ring structures are optionally substituted with 1 to 4 substituents selected from the group consisting of hydroxyl, halo, alkoxy, substituted alkoxy, thioalkoxy, substituted

5 thioalkoxy, nitro, cyano, carboxyl, carboxyl esters, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, amino, N-alkylamino, N,N-dialkylamino, N-substituted alkylamino, N-alkyl N-substituted alkylamino, N,N-disubstituted alkylamino, aryl, heteroaryl, heterocyclic, -NHC(O)R¹⁰, -NHSO₂R¹⁰, -C(O)NH₂, -C(O)NHR¹⁰, -C(O)NR¹⁰R¹⁰, -S(O)R¹⁰, -S(O)₂R¹⁰,

10 -S(O)₂NHR¹⁰ and -S(O)₂NR¹⁰R¹⁰ where each R¹⁰ is independently selected from the group consisting of alkyl, substituted alkyl, or aryl.

16. The method according to Claim 15 wherein the heterocyclic structure is selected from 3-methyl-1,2,4-oxadiazol-5-yl, thiazolin-2-yl, 3-

15 phenyl-1,2,4-oxadiazol-5-yl and 3-(*p*-methoxy-benzyl)-1,2,4-oxadiazol-5-yl.

17. The method according to Claim 4 wherein the compound of formula II is selected from the group consisting of:

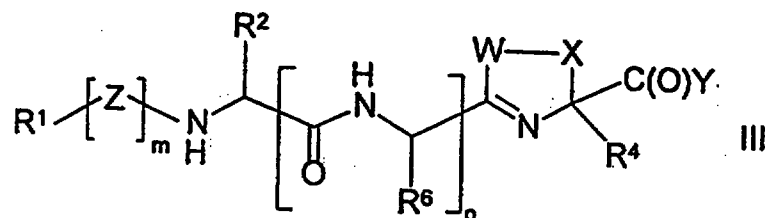
- 20 (S)-5-[1-*N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]amino]ethyl-3-ethyl-1,2,4-oxadiazole
- (S)-5-[1-*N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]amino-2-phenylethyl]-3-methyl-1,2,4-oxadiazole
- 25 2-[1-*N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]amino-1-phenyl]methyl-2-thiazoline
- (S)-5-[1-*N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]amino-1-phenyl]methyl-3-methyl-1,2,4-oxadiazole
- 30 (S)-5-[1-*N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]amino-1-phenyl]methyl-3-phenyl-1,2,4-oxadiazole; and
- 35 (S)-5-[1-*N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]amino-1-phenyl]methyl-3-(4-methoxyphenylmethyl)-1,2,4-oxadiazole.



18. The method according to Claims 1, 2 or 3 wherein the compound of formula I is further characterized by formula III and IV below:

5

10

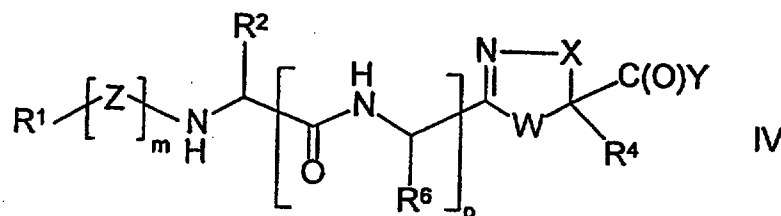


15

and

20

25



wherein R^1 , R^2 , R^4 , R^6 , W , X , Y , Z , m and p are as defined above.

30

19. The method according to Claim 18 wherein m is one, Z is $-\text{CX}'\text{X}''\text{C}(\text{O})-$, X'' is hydrogen, X' is hydrogen or fluoro and where X' and X'' form an oxo group.

35

20. The method according to Claim 19 wherein R^1 is an unsubstituted aryl group selected from the group consisting of phenyl, 1-naphthyl and 2-naphthyl.

40

21. The method according to Claim 19 wherein R^1 is a substituted aryl group selected from the group consisting of monosubstituted phenyls, disubstituted phenyls, and trisubstituted phenyls.



22. The method according to Claim 21 wherein said substituted R¹ phenyl group is selected from the group consisting of 2-chlorophenyl, 2-fluorophenyl, 2-bromophenyl, 2-hydroxyphenyl, 2-nitrophenyl, 2-methylphenyl, 2-methoxyphenyl, 2-phenoxyphenyl, 2-trifluoromethylphenyl; 4-fluorophenyl, 4-chlorophenyl, 4-bromophenyl, 4-nitrophenyl, 4-methylphenyl, 4-hydroxyphenyl, 4-methoxyphenyl, 4-ethoxyphenyl, 4-butoxyphenyl, 4-*iso*-propylphenyl, 4-phenoxyphenyl, 4-trifluoromethylphenyl, 4-hydroxymethylphenyl, 3-methoxyphenyl, 3-hydroxyphenyl, 3-nitrophenyl, 3-fluorophenyl, 3-chlorophenyl, 3-bromophenyl, 3-phenoxyphenyl, 3-thiomethoxyphenyl, 3-methylphenyl, 3-trifluoromethylphenyl, 2,3-dichlorophenyl, 2,3-difluorophenyl, 2,4-dichlorophenyl, 2,5-dimethoxyphenyl, 3,4-dichlorophenyl, 3,4-difluorophenyl, 3,4-methylenedioxyphenyl, 3,4-dimethoxyphenyl, 3,5-difluorophenyl, 3,5-dichlorophenyl, 3,5-di-(trifluoromethyl)phenyl, 3,5-dimethoxyphenyl, 2,4-dichlorophenyl, 2,4-difluorophenyl, 2,6-difluorophenyl, 3,4,5-trifluorophenyl, 3,4,5-trimethoxyphenyl, 3,4,5-tri-(trifluoromethyl)phenyl, 2,4,6-trifluorophenyl, 2,4,6-trimethylphenyl, 2,4,6-tri-(trifluoromethyl)phenyl, 2,3,5-trifluorophenyl, 2,4,5-trifluorophenyl, 2,5-difluorophenyl, 2-fluoro-3-trifluoromethylphenyl, 4-fluoro-2-trifluoromethylphenyl, 2-fluoro-4-trifluoromethylphenyl, 4-benzyloxyphenyl, 2-chloro-6-fluorophenyl, 2-fluoro-6-chlorophenyl, 2,3,4,5,6-pentafluorophenyl, 2,5-dimethylphenyl, 4-phenylphenyl and 2-fluoro-3-trifluoromethylphenyl.

23. The method according to Claim 18 wherein R¹ is an alkaryl group selected from the group consisting of benzyl, 2-phenylethyl and 3-phenyl-*n*-propyl.

24. The method according to Claim 18 wherein R¹ is selected from alkyl, substituted alkyl alkenyl, cycloalkyl and cycloalkenyl groups.



25. The method according to Claim 24 wherein R^1 is selected from the group consisting of *iso*-propyl, *n*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *t*-butyl, $-\text{CH}_2\text{CH}=\text{CH}_2$, $-\text{CH}_2\text{CH}=\text{CH}(\text{CH}_2)_4\text{CH}_3$, cyclopropyl, cyclobutyl, cyclohexyl, cyclopentyl, cyclohex-1-enyl, $-\text{CH}_2$ -cyclopropyl, $-\text{CH}_2$ -cyclobutyl,
5 $-\text{CH}_2$ -cyclohexyl, $-\text{CH}_2$ -cyclopentyl, $-\text{CH}_2\text{CH}_2$ -cyclopropyl, $-\text{CH}_2\text{CH}_2$ -cyclobutyl, $-\text{CH}_2\text{CH}_2$ -cyclohexyl and $-\text{CH}_2\text{CH}_2$ -cyclopentyl.

26. The method according to Claim 18 wherein R^1 is a heteroaryl or substituted heteroaryls selected from the group consisting of pyrid-2-yl, pyrid-3-
10 yl, pyrid-4-yl, fluoropyridyls (including 5-fluoropyrid-3-yl), chloropyridyls (including 5-chloropyrid-3-yl), thiophen-2-yl, thiophen-3-yl, benzothiazol-4-yl, 2-phenylbenzoxazol-5-yl, furan-2-yl, benzofuran-2-yl, thionaphthen-2-yl, 2-chlorothiophen-5-yl, 3-methylisoxazol-5-yl, 2-(thiophenyl)thiophen-5-yl, 6-methoxythionaphthen-2-yl, 3-phenyl-1,2,4-thioxadiazol-5-yl, and 2-
15 phenyloxazol-4-yl.

27. The method according to Claim 18 wherein R^2 is selected from the group consisting of methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, phenyl, benzyl, cyclohexyl, cyclopentyl, cycloheptyl, and $-\text{CH}_2\text{CH}_2\text{SCH}_3$.
20

28. The method according to Claim 18 wherein R^4 is selected from the group consisting of hydrogen, methyl, phenyl and benzyl.

29. The method according to Claim 18 wherein R^6 is selected from the group consisting of hydrogen, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, $-\text{CH}_2\text{CH}(\text{CH}_2\text{CH}_3)_2$, 2-methyl-*n*-butyl, 6-fluoro-*n*-hexyl, phenyl, benzyl, cyclohexyl, cyclopentyl, cycloheptyl, allyl, *iso*-but-2-enyl, 3-methylpentyl, $-\text{CH}_2$ -cyclopropyl, $-\text{CH}_2$ -cyclohexyl, $-\text{CH}_2\text{CH}_2$ -cyclopropyl, $-\text{CH}_2\text{CH}_2$ -cyclohexyl, $-\text{CH}_2$ -indol-3-yl, *p*-(phenyl)phenyl,
25 *o*-fluorophenyl, *m*-fluorophenyl, *p*-fluorophenyl, *m*-methoxyphenyl, *p*-methoxyphenyl, phenethyl, benzyl, *m*-hydroxybenzyl, *p*-hydroxybenzyl,
30



- p*-nitrobenzyl, *m*-trifluoromethylphenyl, *p*-(CH₃)₂NCH₂CH₂CH₂O-benzyl,
p-(CH₃)₃COC(O)CH₂O-benzyl, *p*-(HOOCCH₂O)-benzyl, 2-aminopyrid-6-yl,
p-(N-morpholino-CH₂CH₂O)-benzyl, -CH₂CH₂C(O)NH₂, -CH₂-imidazol-4-yl,
 -CH₂-(3-tetrahydrofuranyl), -CH₂-thiophen-2-yl, -CH₂-(1-methyl)cyclopropyl,
 5 -CH₂-thiophen-3-yl, thiophen-3-yl, thiophen-2-yl, -CH₂-C(O)O-*t*-butyl,
 -CH₂-C(CH₃)₃, -CH₂CH(CH₂CH₃)₂, -2-methylcyclopentyl, -cyclohex-2-enyl,
 -CH[CH(CH₃)₂]COOCH₃, -CH₂CH₂N(CH₃)₂, -CH₂C(CH₃)=CH₂,
 -CH₂CH=CHCH₃ (cis and trans), -CH₂OH, -CH(OH)CH₃, -CH(O-*t*-butyl)CH₃,
 -CH₂OCH₃, -(CH₂)₄NH-Boc, -(CH₂)₄NH₂, -CH₂-pyridyl (e.g., 2-pyridyl,
 10 3-pyridyl and 4-pyridyl), pyridyl (2-pyridyl, 3-pyridyl and 4-pyridyl),
 -CH₂-naphthyl (e.g., 1-naphthyl and 2-naphthyl), -CH₂-(N-morpholino),
p-(N-morpholino-CH₂CH₂O)-benzyl, benzo[b]thiophen-2-yl,
 5-chlorobenzo[b]thiophen-2-yl, 4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl,
 benzo[b]thiophen-3-yl, 5-chlorobenzo[b]thiophen-3-yl, benzo[b]thiophen-5-yl,
 15 6-methoxynaphth-2-yl, -CH₂CH₂SCH₃, thien-2-yl and thien-3-yl.

30. The method according to Claim 18 wherein Y is hydroxy, alkoxy, substituted alkoxy and -NR'R''.

- 20 31. The method according to Claim 30 wherein Y is selected from the group consisting of methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *iso*-butoxy, *t*-butoxy, *neo*-pentoxy, benzyloxy, 2-phenylethoxy, 3-phenyl-*n*-propoxy, 3-iodo-*n*-propoxy, 4-bromo-*n*-butoxy, amino (-NH₂), -NH(*iso*-butyl),
 -NH(*sec*-butyl), N-methylamino, N,N-dimethylamino, N-benzylamino, N-
 25 morpholino, azetidino, N-thiomorpholino, N-piperidinyl, N-hexamethyleneimino, N-heptamethylene-imino, N-pyrrolidinyl, -NH-methallyl,
 -NHCH₂-(furan-2-yl), -NHCH₂-cyclopropyl, -NH(*t*-butyl), -NH(*p*-methylphenyl), -NHCH₃, -NHCH₂(*p*-fluorophenyl), -NHCH₂CH₂OCH₃, -NH-cyclohexyl, -NHCH₂CH₂N(CH₃)₂, -NHCH₂C(CH₃)₃, -NHCH₂-(pyrid-2-yl),
 30 -NHCH₂-(pyrid-3-yl), -NHCH₂-(pyrid-4-yl), N-thiazolindinyl,



- N(CH₂CH₂CH₃)₂, -NHOH, -NH(*p*-NO₂-φ), -NHCH₂(*p*-NO₂-φ), -NHCH₂(*m*-NO₂-φ), -N(CH₃)OCH₃, -N(CH₃)CH₂-φ, -NHCH₂-(3,5-di-fluorophenyl),
 -NHCH₂CH₂F, -NHCH₂(*p*-CH₃O-φ), -NHCH₂(*m*-CH₃O-φ), -NHCH₂(*p*-CF₃-φ),
 -N(CH₃)CH₂CH₂OCH₃, -NHCH₂CH₂φ, -NHCH(CH₃)φ, -NHCH₂-(*p*-F-φ),
 5 -N(CH₃)CH₂CH₂N(CH₃)₂, -NHCH₂-(tetrahydrofuran-2-yl), and
 -CH₂CH₂CH(CH₃)₂.

32. The method according to Claim 18 wherein the heterocyclic
 structures defined by W and X are selected from the group consisting of 4,5-
 10 dihydrothiazoles, 3,4-dihydro-1,3-isodiazoles, 3,4-dihydro-3-N-t-butoxy-3-
 isodiazoles, and 4,5-dihydrooxazoles.

33. The method according to Claim 18 wherein the compound of
 formula II is selected from the group consisting of:

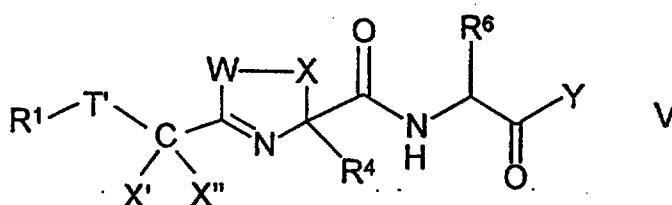
- 15 (S)-2-[1-(3,5-difluorophenylacetamido)ethyl]-4-ethoxycarbonyl-2-
 thiazoline
 1-*tert*-butoxycarbonyl-2-[1-(*N*-carbobenzyloxy)aminoethyl]-4-
 20 methoxycarbonyl-4-phenylmethyl-2-imidazoline
 1-*tert*-butoxycarbonyl-2-[1-(3,5-difluorophenylacetamido)ethyl]-4-
 methoxycarbonyl-4-phenylmethyl-2-imidazoline
 25 2-[1-(3,5-difluorophenylacetamido)ethyl]-4-methoxycarbonyl-4-
 phenylmethyl-2-imidazoline
 2-[1-(3,5-difluorophenylacetamido)ethyl]-4-methoxycarbonyl-4-phenyl-2-
 30 imidazoline
 2-[1-(3,5-difluorophenylacetamido)-1-phenyl]methyl-4-ethoxycarbonyl-2-
 thiazoline
 1-*tert*-butoxycarbonyl-2-[1-(*N*-carbobenzyloxy)aminoethyl]-4-
 35 methoxycarbonyl-4-phenyl-2-imidazoline
 2-[(S)-1-(3,5-dichloroanilino)ethyl]-(S)-4-methoxycarbonyl-2-oxazolidine
 (S)-2-[1-(3,5-difluorophenylacetamido)ethyl]-5(R,S)-ethoxycarbonyl-2-
 40 oxazoline



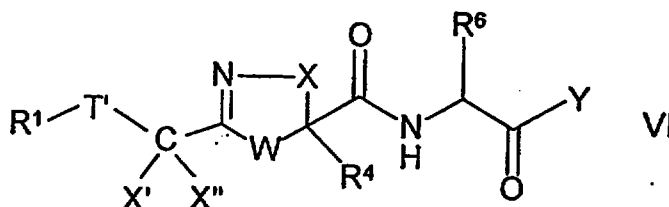
2-[1-(3,5-difluorophenylacetamido)-1-phenyl]methyl-4-methoxycarbonyl-2-thiazoline; and

[1-(*N*-carbobenzyloxy)aminoethyl]-4-methoxycarbonyl-4-phenyl-2-imidazoline.

34. The method according to Claims 1, 2 or 3 wherein the compound of formula I is further characterized by formula V and VI below:



and



where R^1 , R^4 , R^6 , T' , X' , X'' , W , X , and Y are as defined above.

35. The method according to Claim 34 wherein m is one, Z is $-CX'X''C(O)-$, X'' is hydrogen, X' is hydrogen or fluoro and X' and X'' form an oxo group.

36. The method according to Claim 35 wherein R^1 is an unsubstituted aryl group selected from the group consisting of phenyl, 1-naphthyl and 2-naphthyl.



37. The method according to Claim 35 wherein R^1 is a substituted aryl group selected from the group consisting of monosubstituted phenyls, disubstituted phenyls, and trisubstituted phenyls.

5 38. The method according to Claim 37 wherein said substituted R^1 phenyl group is selected from the group consisting of 2-chlorophenyl, 2-fluorophenyl, 2-bromophenyl, 2-hydroxyphenyl, 2-nitrophenyl, 2-methylphenyl, 2-methoxyphenyl, 2-phenoxyphenyl, 2-trifluoromethylphenyl, 4-fluorophenyl, 4-chlorophenyl, 4-bromophenyl, 4-nitrophenyl, 4-methylphenyl,
10 4-hydroxyphenyl, 4-methoxyphenyl, 4-ethoxyphenyl, 4-butoxyphenyl, 4-*iso*-propylphenyl, 4-phenoxyphenyl, 4-trifluoromethylphenyl, 4-hydroxymethylphenyl, 3-methoxyphenyl, 3-hydroxyphenyl, 3-nitrophenyl, 3-fluorophenyl, 3-chlorophenyl, 3-bromophenyl, 3-phenoxyphenyl, 3-thiomethoxyphenyl, 3-methylphenyl, 3-trifluoromethylphenyl, 2,3-
15 dichlorophenyl, 2,3-difluorophenyl, 2,4-dichlorophenyl, 2,5-dimethoxyphenyl, 3,4-dichlorophenyl, 3,4-difluorophenyl, 3,4-methylenedioxyphenyl, 3,4-dimethoxyphenyl, 3,5-difluorophenyl, 3,5-dichlorophenyl, 3,5-di-(trifluoromethyl)phenyl, 3,5-dimethoxyphenyl, 2,4-dichlorophenyl, 2,4-difluorophenyl, 2,6-difluorophenyl, 3,4,5-trifluorophenyl,
20 3,4,5-trimethoxyphenyl, 3,4,5-tri-(trifluoromethyl)phenyl, 2,4,6-trifluorophenyl, 2,4,6-trimethylphenyl, 2,4,6-tri-(trifluoromethyl)phenyl, 2,3,5-trifluorophenyl, 2,4,5-trifluorophenyl, 2,5-difluorophenyl, 2-fluoro-3-trifluoromethylphenyl, 4-fluoro-2-trifluoromethylphenyl, 2-fluoro-4-trifluoromethylphenyl, 4-benzyloxyphenyl, 2-chloro-6-fluorophenyl, 2-fluoro-6-chlorophenyl,
25 2,3,4,5,6-pentafluorophenyl, 2,5-dimethylphenyl, 4-phenylphenyl and 2-fluoro-3-trifluoromethylphenyl.

39. The method according to Claim 34 wherein R^1 is an alkaryl group selected from the group consisting of benzyl, 2-phenylethyl and 3-phenyl-*n*-
30 propyl.



40. The method according to Claim 34 wherein R¹ is selected from alkyl, substituted alkyl, alkenyl, cycloalkyl and cycloalkenyl groups.

41. The method according to Claim 40 wherein R¹ is selected from the group consisting of *iso*-propyl, *n*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *t*-butyl, -CH₂CH=CH₂, -CH₂CH=CH(CH₂)₄CH₃, cyclopropyl, cyclobutyl, cyclohexyl, cyclopentyl, cyclohex-1-enyl, -CH₂-cyclopropyl, -CH₂-cyclobutyl, -CH₂-cyclohexyl, -CH₂-cyclopentyl, -CH₂CH₂-cyclopropyl, -CH₂CH₂-cyclobutyl, -CH₂CH₂-cyclohexyl and -CH₂CH₂-cyclopentyl.

10

42. The method according to Claim 34 wherein R¹ is a heteroaryl or substituted heteroaryls selected from the group consisting of pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, fluoropyridyls (including 5-fluoropyrid-3-yl), chloropyridyls (including 5-chloropyrid-3-yl), thiophen-2-yl, thiophen-3-yl, benzothiazol-4-yl, 2-phenylbenzoxazol-5-yl, furan-2-yl, benzofuran-2-yl, thionaphthen-2-yl, 2-chlorothiophen-5-yl, 3-methylisoxazol-5-yl, 2-(thiophenyl)thiophen-5-yl, 6-methoxythionaphthen-2-yl, 3-phenyl-1,2,4-thioxadiazol-5-yl, and 2-phenyloxazol-4-yl.

15

43. The method according to Claim 34 wherein R⁴ is selected from the group consisting of hydrogen, methyl, phenyl and benzyl.

20

44. The method according to Claim 34 wherein R⁶ is selected from the group consisting of hydrogen, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, -CH₂CH(CH₂CH₃)₂, 2-methyl-*n*-butyl, 6-fluoro-*n*-hexyl, phenyl, benzyl, cyclohexyl, cyclopentyl, cycloheptyl, allyl, *iso*-but-2-enyl, 3-methylpentyl, -CH₂-cyclopropyl, -CH₂-cyclohexyl, -CH₂CH₂-cyclopropyl, -CH₂CH₂-cyclohexyl, -CH₂-indol-3-yl, *p*-(phenyl)phenyl, *o*-fluorophenyl, *m*-fluorophenyl, *p*-fluorophenyl, *m*-methoxyphenyl, *p*-methoxyphenyl, phenethyl, benzyl, *m*-hydroxybenzyl, *p*-hydroxybenzyl, *p*-nitrobenzyl, *m*-trifluoromethylphenyl, *p*-(CH₃)₂NCH₂CH₂CH₂O-benzyl,

25

30



p -(CH₃)₃COC(O)CH₂O-benzyl, p -(HOOCCH₂O)-benzyl, 2-aminopyrid-6-yl,
 p -(N-morpholino-CH₂CH₂O)-benzyl, -CH₂CH₂C(O)NH₂, -CH₂-imidazol-4-yl,
 -CH₂-(3-tetrahydrofuranyl), -CH₂-thiophen-2-yl, -CH₂-(1-methyl)cyclopropyl,
 -CH₂-thiophen-3-yl, thiophen-3-yl, thiophen-2-yl, -CH₂-C(O)O-*t*-butyl,
 5 -CH₂-C(CH₃)₃, -CH₂CH(CH₂CH₃)₂, -2-methylcyclopentyl, -cyclohex-2-enyl,
 -CH[CH(CH₃)₂]COOCH₃, -CH₂CH₂N(CH₃)₂, -CH₂C(CH₃)=CH₂,
 -CH₂CH=CHCH₃ (cis and trans), -CH₂OH, -CH(OH)CH₃, -CH(O-*t*-butyl)CH₃,
 -CH₂OCH₃, -(CH₂)₄NH-Boc, -(CH₂)₄NH₂, -CH₂-pyridyl (e.g., 2-pyridyl,
 3-pyridyl and 4-pyridyl), pyridyl (2-pyridyl, 3-pyridyl and 4-pyridyl),
 10 -CH₂-naphthyl (e.g., 1-naphthyl and 2-naphthyl), -CH₂-(N-morpholino),
 p -(N-morpholino-CH₂CH₂O)-benzyl, benzo[b]thiophen-2-yl,
 5-chlorobenzo[b]thiophen-2-yl, 4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl,
 benzo[b]thiophen-3-yl, 5-chlorobenzo[b]thiophen-3-yl, benzo[b]thiophen-5-yl,
 6-methoxynaphth-2-yl, -CH₂CH₂SCH₃, thien-2-yl and thien-3-yl.

15

45. The method according to Claim 34 wherein Y is hydroxy, alkoxy, substituted alkoxy and -NR'R".

46. The method according to Claim 45 wherein Y is selected from the
 20 group consisting of methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy,
iso-butoxy, *t*-butoxy, *neo*-pentoxy, benzyloxy, 2-phenylethoxy, 3-phenyl-*n*-
 propoxy, 3-iodo-*n*-propoxy, 4-bromo-*n*-butoxy, amino (-NH₂),
 -NH(*iso*-butyl), -NH(*sec*-butyl), N-methylamino, N,N-dimethylamino,
 N-benzylamino, N-morpholino, azetidino, N-thiomorpholino, N-piperidinyl,
 25 N-hexamethyleneimino, N-heptamethylene-imino, N-pyrrolidinyl,
 -NH-methallyl, -NHCH₂-(furan-2-yl), -NHCH₂-cyclopropyl, -NH(*t*-butyl),
 -NH(*p*-methylphenyl), -NHCH₂CH₂OCH₃, -NHCH₂(*p*-fluorophenyl), -NHCH₂CH₂OCH₃,
 -NH-cyclohexyl, -NHCH₂CH₂N(CH₃)₂, -NHCH₂C(CH₃)₃, -NHCH₂-(pyrid-2-yl),
 -NHCH₂-(pyrid-3-yl), -NHCH₂-(pyrid-4-yl), N-thiazolidinyl,
 30 -N(CH₂CH₂CH₃)₂, -NHOH, -NH(*p*-NO₂-φ), -NHCH₂(*p*-NO₂-φ),



-NHCH₂(*m*-NO₂-φ), -N(CH₃)OCH₃, -N(CH₃)CH₂-φ, -NHCH₂-(3,5-di-fluorophenyl), -NHCH₂CH₂F, -NHCH₂(*p*-CH₃O-φ), -NHCH₂(*m*-CH₃O-φ), -NHCH₂(*p*-CF₃-φ), -N(CH₃)CH₂CH₂OCH₃, -NHCH₂CH₂φ, -NHCH(CH₃)φ, -NHCH₂-(*p*-F-φ), -N(CH₃)CH₂CH₂N(CH₃)₂ and -NHCH₂-(tetrahydrofuran-2-yl).

5

47. The method according to Claim 34 wherein the heterocyclic structures defined by W and X are selected from the group consisting of 4,5-dihydrothiazoles, 3,4-dihydro-1,3-isodiazoles, 3,4-dihydro-3-N-t-butoxy-3-isodiazoles, and 4,5-dihydrooxazoles.

10

48. The method according to Claim 34 wherein said compound of formula V and VI are selected from the group consisting of

(4R)-4-[N-(1S)-(1-methoxycarbonyl-1-phenyl)methyl]carbamoyl-2-(3,5-difluorophenylmethyl)-4-methyl-2-thiazoline

15

4-[N-(S)-(1-methoxycarbonyl-1-phenyl)methyl]carbamoyl-2-(3,5-difluorophenylmethyl)-2-thiazoline; and

20

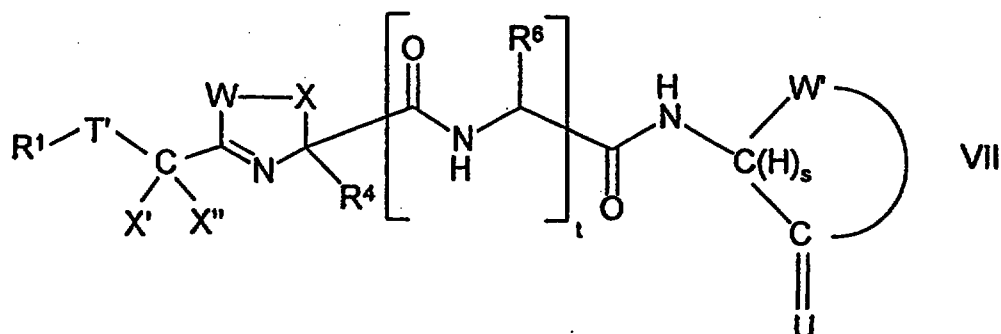
4-[N-(S)-(1-methoxycarbonyl-1-phenyl)methyl]carbamoyl-2-(3,5-difluorophenylmethyl)-4-methyl-2-imidazoline.

25

48. A method for inhibiting β-amyloid peptide release and/or its synthesis in a cell which method comprises administering to such a cell an amount of a compound or a mixture of compounds effective in inhibiting the cellular release and/or synthesis of β-amyloid peptide wherein said compounds are represented by formula VII and VIII:

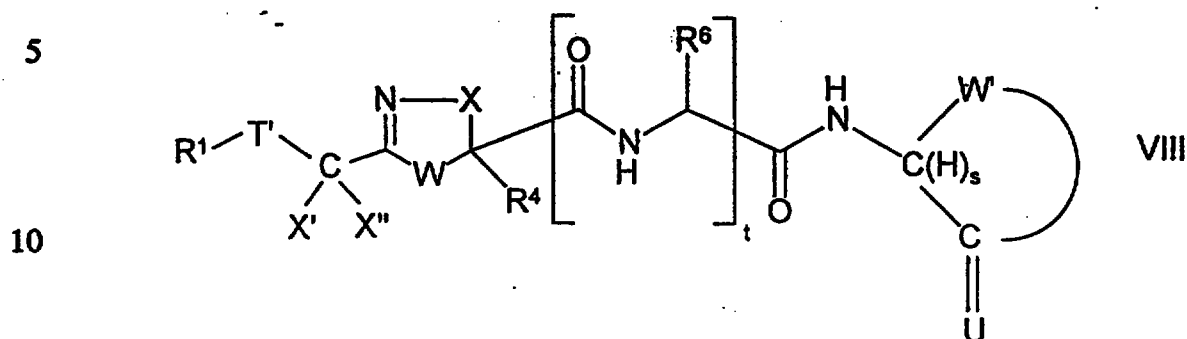
30

35





and



15 wherein R^1 , R^4 , R^6 , T' , X' , X'' , W and X are as defined above;

W' , together with $-C(H)_sC(=U)-$, forms a cycloalkyl, cycloalkenyl, heterocyclic, substituted cycloalkyl, or substituted cycloalkenyl group wherein each of said cycloalkyl, cycloalkenyl, heterocyclic, substituted cycloalkyl or substituted cycloalkenyl group is optionally fused to form a bi- or multi-fused ring system (preferably no more than 5 fused rings) with one or more ring structures selected from the group consisting of cycloalkyl, cycloalkenyl, heterocyclic, aryl and heteroaryl group which, in turn, each of such ring structures is optionally substituted with 1 to 4 substituents selected from the group consisting of hydroxyl, halo, alkoxy, substituted alkoxy, thioalkoxy, substituted thioalkoxy, aryl, heteroaryl, heterocyclic, nitro, cyano, carboxyl, carboxyl esters, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, amino, N-alkylamino, N,N-dialkylamino, N-substituted alkylamino, N-alkyl N-substituted alkylamino, N,N-disubstituted alkylamino, $-NHC(O)R^{10}$, $-NH SO_2 R^{10}$, $-C(O)NH_2$, $-C(O)NHR^{10}$, $-C(O)NR^{10}R^{10}$, $-S(O)R^{10}$, $-S(O)_2R^{10}$, $-S(O)_2NHR^{10}$ and $-S(O)_2NR^{10}R^{10}$ where each R^{10} is independently selected from the group consisting of alkyl, substituted alkyl, or aryl;

20

25

30

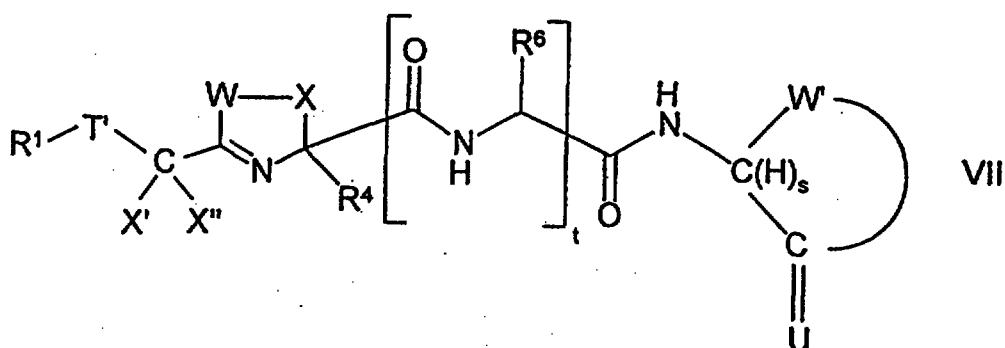
U is selected from the group consisting of oxo ($=O$), thiooxo ($=S$), hydroxyl ($-H$, $-OH$), thiol (H , $-SH$) and hydro (H , H);

s is an integer equal to 0 or 1; and

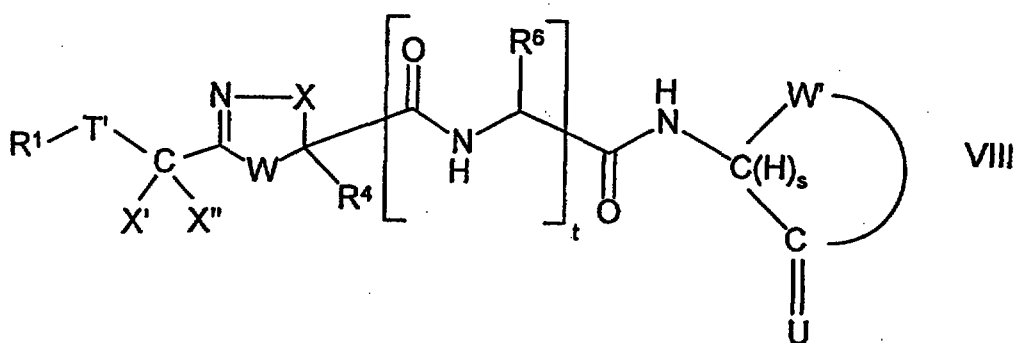
35 t is an integer equal to 0 or 1.



49. A method for preventing the onset of AD in a patient at risk for developing AD which method comprises administering to said patient a pharmaceutical composition comprising a pharmaceutically inert carrier and an effective amount of a compound or a mixture of compounds of formula VII and VIII:



and



wherein R^1 , R^4 , R^6 , T' , X' , X'' , W and X are as defined above;

W' , together with $-C(H)_sC(=U)-$, forms a cycloalkyl, cycloalkenyl, heterocyclic, substituted cycloalkyl, or substituted cycloalkenyl group wherein each of said cycloalkyl, cycloalkenyl, heterocyclic, substituted cycloalkyl or substituted cycloalkenyl group is optionally fused to form a bi- or multi-fused ring system (preferably no more than 5 fused rings) with one or more ring structures selected from the group consisting of cycloalkyl, cycloalkenyl, heterocyclic, aryl and heteroaryl group which, in turn, each of such ring structures is optionally substituted with 1 to 4 substituents selected from the



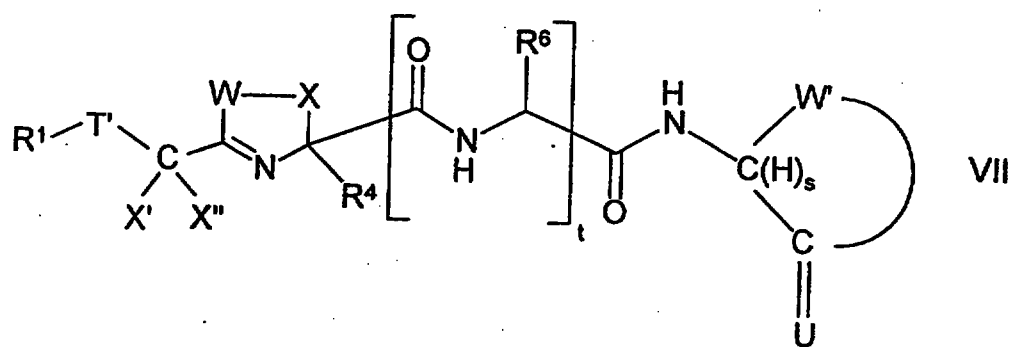
group consisting of hydroxyl, halo, alkoxy, substituted alkoxy, thioalkoxy, substituted thioalkoxy, aryl, heteroaryl, heterocyclic, nitro, cyano, carboxyl, carboxyl esters, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, amino, N-alkylamino, N,N-dialkylamino, N-substituted alkylamino, N-alkyl N-substituted alkylamino, N,N-disubstituted alkylamino, -NHC(O)R¹⁰, -NHSO₂R¹⁰, -C(O)NH₂, -C(O)NHR¹⁰, -C(O)NR¹⁰R¹⁰, -S(O)R¹⁰, -S(O)₂R¹⁰, -S(O)₂NHR¹⁰ and -S(O)₂NR¹⁰R¹⁰ where each R¹⁰ is independently selected from the group consisting of alkyl, substituted alkyl, or aryl;

U is selected from the group consisting of oxo (=O), thiooxo (=S), hydroxyl (-H, -OH), thiol (H, -SH) and hydro (H, H);

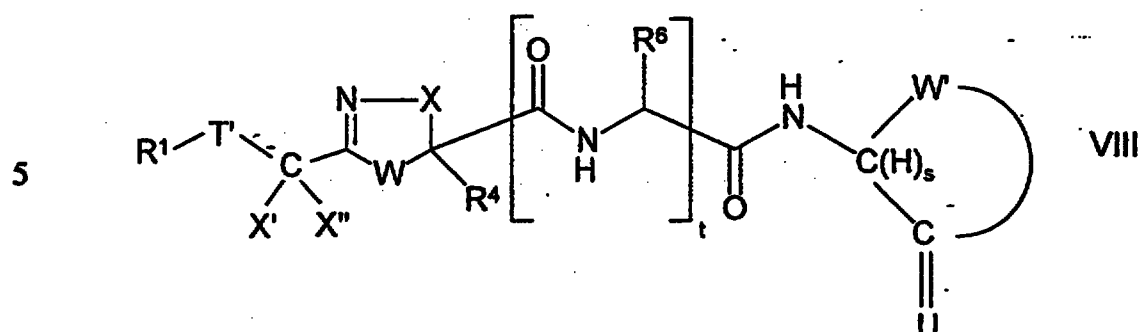
s is an integer equal to 0 or 1; and

t is an integer equal to 0 or 1.

50. A method for treating a patient with AD in order to inhibit further deterioration in the condition of that patient which method comprises administering to said patient a pharmaceutical composition comprising a pharmaceutically inert carrier and an effective amount of a compound or a mixture of compounds of formula VII and VIII:



and



wherein R^1 , R^4 , R^6 , T' , X' , X'' , W and X are as defined above;

W' , together with $-C(H)_sC(=U)-$, forms a cycloalkyl, cycloalkenyl, heterocyclic, substituted cycloalkyl, or substituted cycloalkenyl group wherein each of said cycloalkyl, cycloalkenyl, heterocyclic, substituted cycloalkyl or substituted cycloalkenyl group is optionally fused to form a bi- or multi-fused ring system (preferably no more than 5 fused rings) with one or more ring structures selected from the group consisting of cycloalkyl, cycloalkenyl, heterocyclic, aryl and heteroaryl group which, in turn, each of such ring structures is optionally substituted with 1 to 4 substituents selected from the group consisting of hydroxyl, halo, alkoxy, substituted alkoxy, thioalkoxy, substituted thioalkoxy, aryl, heteroaryl, heterocyclic, nitro, cyano, carboxyl, carboxyl esters, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, amino, N-alkylamino, N,N-dialkylamino, N-substituted alkylamino, N-alkyl N-substituted alkylamino, N,N-disubstituted alkylamino, $-NHC(O)R^{10}$, $-NHSO_2R^{10}$, $-C(O)NH_2$, $-C(O)NHR^{10}$, $-C(O)NR^{10}R^{10}$, $-S(O)R^{10}$, $-S(O)_2R^{10}$, $-S(O)_2NHR^{10}$ and $-S(O)_2NR^{10}R^{10}$ where each R^{10} is independently selected from the group consisting of alkyl, substituted alkyl, or aryl;

15

20

25

U is selected from the group consisting of oxo ($=O$), thiooxo ($=S$), hydroxyl ($-H$, $-OH$), thiol (H , $-SH$) and hydro (H , H);

30

s is an integer equal to 0 or 1; and

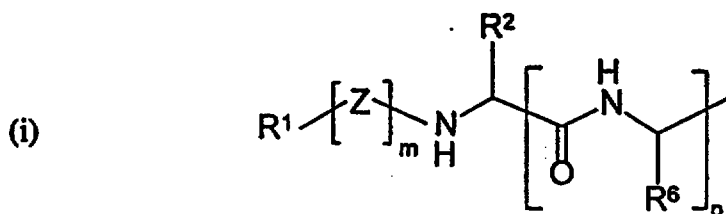
t is an integer equal to 0 or 1.

51. A compound of formula I:



A-B-C

wherein A is selected from the group consisting of:



where R¹ is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted cycloalkyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic;

Z is selected from the group consisting of

- (a) a group having the formula -CX'X"C(O)- where X' is hydrogen, hydroxy or fluoro; X" is hydrogen, hydroxy or fluoro, or X' and X" together form an oxo group;
- (b) a group having the formula -T-CX'X"C(O)- where T is selected from the group consisting of oxygen, sulfur and -NR³ where R³ is hydrogen, acyl, alkyl, aryl or heteroaryl group; X' is hydrogen or fluoro, X" is hydrogen, hydroxy or fluoro, or X' and X" together form an oxo group; and
- (c) a group having the formula -CX'X"-T-C(O)- where T is selected from the group consisting of oxygen, sulfur and -NR³ where R³ is hydrogen, acyl, alkyl, aryl or heteroaryl group; X' is hydrogen or fluoro, X" is hydrogen, hydroxy or fluoro, or X' and X" together form an oxo group;

R² is selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclic;

R⁶ is selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclic;

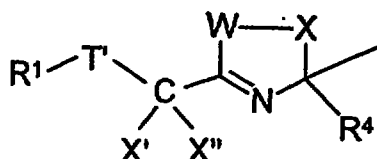
m is an integer equal to 0 or 1; and

p is an integer equal to 0 or 1;



5

(ii)



10

where R^1 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted cycloalkyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic;

15

T' is selected from the group consisting of a bond covalently linking R^1 to $-CX'X''-$, oxygen, sulfur and $-NR^3$ where R^3 is hydrogen, acyl, alkyl, aryl or heteroaryl group;

20

W and X are independently selected from the group consisting of $-(CR^7R^8)_q-$, oxygen, sulfur and $-NR^8$ where q is an integer equal to one or two, and each R^7 and R^8 is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl, acyl, acyloxy, carboxyl, carboxyl esters and heterocyclic and further, when q is 2, an R^7 group on each of the carbon atoms can optionally be fused to form an aryl, heteroaryl, heterocyclic or cycloalkyl group with the ethylene group with the proviso that when unsaturated, the remaining R^7 group on each carbon atom participates in the unsaturation;

25

and with the further proviso that when W is oxygen, then X is not also oxygen;

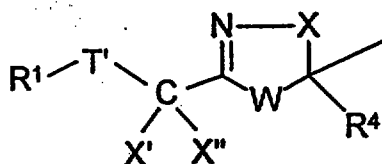
30

X' is hydrogen, hydroxy or fluoro, X'' is hydrogen, hydroxy or fluoro, or X' and X'' together form an oxo group;

R^4 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, heteroaryl and heterocyclic; and



(iii)



5

where R^1 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkenyl, substituted alkynyl, substituted cycloalkyl, substituted cycloalkenyl, aryl, heteroaryl and heterocyclic;

10

T' is selected from the group consisting of a bond covalently linking R^1 to $-CX'X''-$, oxygen, sulfur and $-NR^3$ where R^3 is hydrogen, acyl, alkyl, aryl or heteroaryl group;

15

W and X are independently selected from the group consisting of $-(CR^7R^q)_q-$, oxygen, sulfur and $-NR^8$ where q is an integer equal to one or two and each R^7 and R^8 is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl, acyl, acyloxy, carboxyl, carboxyl esters, and heterocyclic and further, when q is 2, an R^7 group on each of the carbon atoms can optionally be fused to form an aryl, heteroaryl, heterocyclic or cycloalkyl group with the proviso that when unsaturated, the remaining R^7 group on each carbon atom participates in the unsaturation;

20

X' is hydrogen, hydroxy or fluoro, X'' is hydrogen, hydroxy or fluoro, or X' and X'' together form an oxo group;

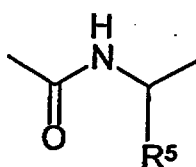
25

R^4 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, heteroaryl and heterocyclic;

B is selected from the group consisting of:

30

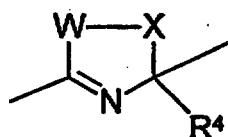
(i)





where R^5 is selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, heteroaryl and heterocyclic;

(ii)

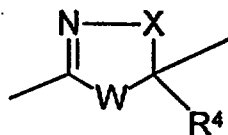


W and X are independently selected from the group consisting of $-(CR^7R^7)_q-$, oxygen, sulfur and $-NR^8$ where q is an integer equal to one or two, and each R^7 and R^8 is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl, acyl, acyloxy, carboxyl, carboxyl esters, and heterocyclic and further, when q is 2, an R^7 group on each of the carbon atoms can optionally be fused to form an aryl, heteroaryl, heterocyclic or cycloalkyl group with the ethylene group with the proviso that when unsaturated, the remaining R^7 group on each carbon atom participates in the unsaturation;

and with the further proviso that when W is oxygen, then X is not also oxygen;

R^4 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, heteroaryl and heterocyclic;

(iii)



W and X are independently selected from the group consisting of $-(CR^7R^7)_q-$, oxygen, sulfur and $-NR^8$ where q is an integer equal to 1 or 2 and each R^7 and R^8 is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl, acyl, acyloxy, and heterocyclic and further, when q is 2, an R^7 group on each of the carbon



atoms can optionally be fused to form an aryl, heteroaryl, heterocyclic or cycloalkyl group with the ethylene group with the proviso that when unsaturated, the remaining R⁷ group on each carbon atom participates in the unsaturation;

- 5 R⁴ is selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, heteroaryl and heterocyclic; and

(iv) when A is either formula (ii) or (iii) as defined above, then B can also be a covalent bond linking A to C;

- 10 C is selected from the group consisting of:

(i) -C(O)Y or -C(S)Y

where Y is selected from the group consisting of:

- (a) alkyl or cycloalkyl,
- 15 (b) substituted alkyl with the proviso that the substitution on said substituted alkyl do not include α -haloalkyl, α -diazoalkyl, α -OC(O)alkyl, or α -OC(O)aryl groups,
- (c) alkoxy or thioalkoxy,
- (d) substituted alkoxy or substituted thioalkoxy,
- 20 (e) hydroxy,
- (f) aryl,
- (g) heteroaryl,
- (h) heterocyclic,
- (i) -NR'R'' where R' and R'' are independently selected from hydrogen,
- 25 alkyl, alkenyl, alkynyl, substituted alkyl, substituted alkenyl, substituted alkenyl, cycloalkyl, aryl, heteroaryl, heterocyclic, where one of R' or R'' is hydroxy or alkoxy, and where R' and R'' are joined to form a cyclic group having from 2 to 8 carbon atoms optionally containing 1 to 2 additional heteroatoms selected from oxygen, sulfur and nitrogen and optionally
- 30 substituted with one or more alkyl, alkoxy or carboxylalkyl groups,



(j) $-\text{NHSO}_2\text{-R}^8$ where R^8 is selected from alkyl, substituted alkyl, alkenyl, substituted alkenyl, cycloalkyl, aryl, heteroaryl and heterocyclic,

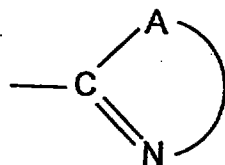
(k) $-\text{NR}^9\text{NR}^{10}\text{R}^{10}$ where R^9 is hydrogen or alkyl, and each R^{10} is independently selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, cycloalkyl, aryl, heteroaryl, heterocyclic, and

(l) $-\text{ONR}^9[\text{C}(\text{O})\text{O}]_z\text{R}^{10}$ where z is zero or one, R^9 and R^{10} are as defined above;

(ii) $-\text{CR}^{11}\text{R}^{11}\text{Y}'$

where each R^{11} is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, heteroaryl and heterocyclic and Y' is selected from the group consisting of hydroxyl, alkoxy, amino, thiol, substituted alkoxy, thioalkoxy, substituted thioalkoxy, $-\text{OC}(\text{O})\text{R}^9$, $-\text{SSR}^9$, and $-\text{SSC}(\text{O})\text{R}^9$ where R^9 is selected from the group consisting of alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl and heterocyclic; and

(iii)



where A, together with $-\text{C}=\text{N}-$, forms a heterocyclic group which is optionally fused to form a bi- or multi-fused ring system (preferably no more than 5 fused rings) with one or more ring structures selected from the group consisting of cycloalkyl, cycloalkenyl, heterocyclic, aryl and heteroaryl group which, in turn, each of such ring structures is optionally substituted with 1 to 4 substituents selected from the group consisting of hydroxyl, halo, alkoxy, substituted alkoxy, thioalkoxy, substituted thioalkoxy, nitro, cyano, carboxyl, carboxyl esters, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, heteroaryl, heterocyclic, $-\text{NHC}(\text{O})\text{R}^{10}$, $-\text{NHSO}_2\text{R}^{10}$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{NHR}^{10}$, $-\text{C}(\text{O})\text{NR}^{10}\text{R}^{10}$, $-\text{S}(\text{O})\text{R}^{10}$, $-\text{S}(\text{O})_2\text{R}^{10}$, $-\text{S}(\text{O})_2\text{NHR}^{10}$ and



-S(O)₂NR¹⁰R¹⁰ where each R¹⁰ is independently selected from the group consisting of alkyl, substituted alkyl, or aryl, amino, N-alkylamino, N,N-dialkylamino, N-substituted alkylamino, N,N-disubstituted alkylamino, N-alkenylamino, N,N-dialkenylamino, N-substituted alkenylamino, N,N-disubstituted alkenylamino, N-cycloalkylamino, N,N-dicycloalkylamino, N-substituted cycloalkylamino, N,N-disubstituted cycloalkylamino, N-arylamino, N,N-diarylamino, N-heteroarylamino, N,N-diheteroarylamino, N-heterocyclic amino, N,N-diheterocyclic amino and mixed N,N-amino groups comprising a first and second substituent on said amino group which substituents are selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, cycloalkyl, substituted cycloalkyl, aryl, heteroaryl, and heterocyclic provided that said first and second substituents are not the same;

with the proviso that when *A* has structure (i) and *B* has structure (i), then *C* does not have structure (i) or (ii);

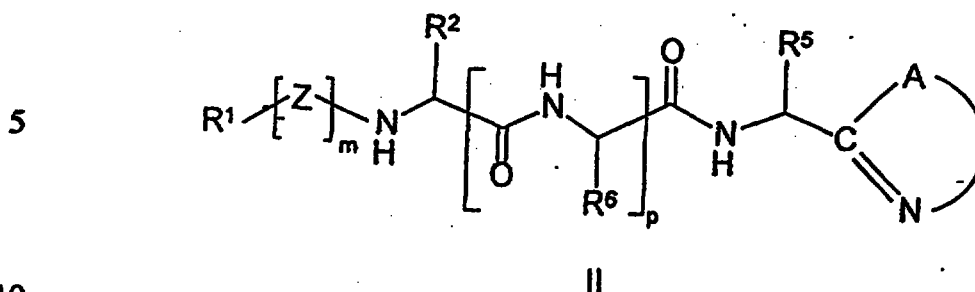
with the further provisos that

A. when *A* has structure (i) with R¹ being phenyl, Z being -CH₂OC(O)-, R₂ being methyl and *p* being zero, *B* has structure (iii) with W being -NH-, X being -CH₂-, and R⁴ being benzyl then *C* is not -C(O)OCH₃;

B. when *A* has structure (i) with R¹ being 3,5-difluorophenyl, Z being -CH₂C(O)-, R² being methyl, and *p* being zero, *B* has structure (ii) with W being >NC(O)OC(CH₃)₃, X being -CH₂-, and R⁴ being phenyl, then *C* is not -C(O)OCH₃; and

C. when *A* has structure (ii) wherein R¹ is 3,5-difluorophenyl, T' is a bond linking R¹ to -CX'X"-, X' and X" are hydrogen, W is sulfur, X is methylene and R⁴ is methyl, and *B* is a covalent bond linking *A* to *C*, then *C* is not -C(O)OCH₃.

52. The compound according to Claim 51 wherein the compound of formula I is further characterized by formula II below:



wherein R^1 , R^2 , R^5 , R^6 , A, Z, m and p are as defined in Claim 51.

53. The compound according to Claim 52 wherein m is one, Z is
 15 -CX'X"C(O)-, X" is hydrogen, X' is hydrogen or fluoro or X' and X" form an
 oxo group.

54. The compound according to Claim 52 wherein R_1 is an
 20 unsubstituted aryl group selected from the group consisting of phenyl, 1-
 naphthyl and 2-naphthyl.

55. The compound according to Claim 52 wherein R_1 is a substituted
 aryl group selected from the group consisting of monosubstituted phenyls,
 disubstituted phenyls, and trisubstituted phenyls.

25

56. The compound according to Claim 55 wherein said substituted R_1
 phenyl group is selected from the group consisting of 2-chlorophenyl, 2-
 fluorophenyl, 2-bromophenyl, 2-hydroxyphenyl, 2-nitrophenyl, 2-methylphenyl,
 2-methoxyphenyl, 2-phenoxyphenyl, 2-trifluoromethylphenyl, 4-fluorophenyl,
 30 4-chlorophenyl, 4-bromophenyl, 4-nitrophenyl, 4-methylphenyl,
 4-hydroxyphenyl, 4-methoxyphenyl, 4-ethoxyphenyl, 4-butoxyphenyl,
 4-*iso*-propylphenyl, 4-phenoxyphenyl, 4-trifluoromethylphenyl,
 4-hydroxymethylphenyl, 3-methoxyphenyl, 3-hydroxyphenyl, 3-nitrophenyl,
 3-fluorophenyl, 3-chlorophenyl, 3-bromophenyl, 3-phenoxyphenyl,
 35 3-thiomethoxyphenyl, 3-methylphenyl, 3-trifluoromethylphenyl,
 2,3-dichlorophenyl, 2,3-difluorophenyl, 2,4-dichlorophenyl,



2,5-dimethoxyphenyl, 3,4-dichlorophenyl, 3,4-difluorophenyl,
3,4-methylenedioxyphenyl, 3,4-dimethoxyphenyl, 3,5-difluorophenyl,
3,5-dichlorophenyl, 3,5-di-(trifluoromethyl)phenyl, 3,5-dimethoxyphenyl,
2,4-dichlorophenyl, 2,4-difluorophenyl, 2,6-difluorophenyl, 3,4,5-
5 trifluorophenyl, 3,4,5-trimethoxyphenyl, 3,4,5-tri-(trifluoromethyl)phenyl,
2,4,6-trifluorophenyl, 2,4,6-trimethylphenyl, 2,4,6-tri-(trifluoromethyl)phenyl,
2,3,5-trifluorophenyl, 2,4,5-trifluorophenyl, 2,5-difluorophenyl, 2-fluoro-3-
trifluoromethylphenyl, 4-fluoro-2-trifluoromethylphenyl, 2-fluoro-4-
trifluoromethylphenyl, 4-benzyloxyphenyl, 2-chloro-6-fluorophenyl, 2-fluoro-6-
10 chlorophenyl, 2,3,4,5,6-pentafluorophenyl, 2,5-dimethylphenyl, 4-phenylphenyl
and 2-fluoro-3-trifluoromethylphenyl.

57. The compound according to Claim 52 wherein R¹ is an alkaryl
group selected from the group consisting of benzyl, 2-phenylethyl and 3-phenyl-
15 *n*-propyl.

58. The compound according to Claim 52 wherein R¹ is selected from
alkyl, substituted alkyl, alkenyl, cycloalkyl and cycloalkenyl groups.

59. The compound according to Claim 58 wherein R¹ is selected from
the group consisting of *iso*-propyl, *n*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *t*-
butyl, -CH₂CH=CH₂, -CH₂CH=CH(CH₂)₄CH₃, cyclopropyl, cyclobutyl,
cyclohexyl, cyclopentyl, cyclohex-1-enyl, -CH₂-cyclopropyl, -CH₂-cyclobutyl,
-CH₂-cyclohexyl, -CH₂-cyclopentyl, -CH₂CH₂-cyclopropyl, -CH₂CH₂-
25 cyclobutyl, -CH₂CH₂-cyclohexyl, and -CH₂CH₂-cyclopentyl.

60. The compound according to Claim 52 wherein R¹ is a heteroaryl or
substituted heteroaryls selected from the group consisting of pyrid-2-yl, pyrid-3-
yl, pyrid-4-yl, fluoropyridyls (including 5-fluoropyrid-3-yl), chloropyridyls
30 (including 5-chloropyrid-3-yl), thiophen-2-yl, thiophen-3-yl, benzothiazol-4-yl,
2-phenylbenzoxazol-5-yl, furan-2-yl, benzofuran-2-yl, thionaphthen-2-yl, 2-



chlorothiophen-5-yl, 3-methylisoxazol-5-yl, 2-(thiophenyl)thiophen-5-yl, 6-methoxythionaphthen-2-yl, 3-phenyl-1,2,4-thioxadiazol-5-yl, and 2-phenyloxazol-4-yl.

5 61. The compound according to Claim 52 wherein R² is selected from the group consisting of methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, phenyl, benzyl, cyclohexyl, cyclopentyl, cycloheptyl, and -CH₂CH₂SCH₃.

62. The compound according to Claim 52 wherein R⁵ and R⁶

10 substituents are independently selected from the group consisting of hydrogen, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, -CH₂CH(CH₂CH₃)₂, 2-methyl-*n*-butyl, 6-fluoro-*n*-hexyl, phenyl, benzyl, cyclohexyl, cyclopentyl, cycloheptyl, allyl, *iso*-but-2-enyl, 3-methylpentyl, -CH₂-cyclopropyl, -CH₂-cyclohexyl, -CH₂CH₂-cyclopropyl, -CH₂CH₂-cyclohexyl, -CH₂-indol-3-yl, *p*-(phenyl)phenyl, *o*-fluorophenyl,

15 *m*-fluorophenyl, *p*-fluorophenyl, *m*-methoxyphenyl, *p*-methoxyphenyl, phenethyl, benzyl, *m*-hydroxybenzyl, *p*-hydroxybenzyl, *p*-nitrobenzyl, *m*-trifluoromethylphenyl, *p*-(CH₃)₂NCH₂CH₂CH₂O-benzyl, *p*-(CH₃)₃COC(O)CH₂O-benzyl, *p*-(HOOCCH₂O)-benzyl, 2-aminopyrid-6-yl, *p*-(N-morpholino-CH₂CH₂O)-benzyl, -CH₂CH₂C(O)NH₂, -CH₂-imidazol-4-yl,

20 -CH₂-(3-tetrahydrofuranyl), -CH₂-thiophen-2-yl, -CH₂-(1-methyl)cyclopropyl, -CH₂-thiophen-3-yl, thiophen-3-yl, thiophen-2-yl, -CH₂-C(O)O-*t*-butyl, -CH₂-C(CH₃)₃, -CH₂CH(CH₂CH₃)₂, 2-methylcyclopentyl, -cyclohex-2-enyl, -CH[CH(CH₃)₂]COOCH₃, -CH₂CH₂N(CH₃)₂, -CH₂C(CH₃)=CH₂,

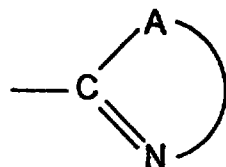
25 -CH₂CH=CHCH₃ (*cis* and *trans*), -CH₂OH, -CH(OH)CH₃, -CH(O-*t*-butyl)CH₃, -CH₂OCH₃, -(CH₂)₄NH-Boc, -(CH₂)₄NH₂, -CH₂-pyridyl (e.g., 2-pyridyl, 3-pyridyl and 4-pyridyl), pyridyl (2-pyridyl, 3-pyridyl and 4-pyridyl), -CH₂-naphthyl (e.g., 1-naphthyl and 2-naphthyl), -CH₂-(N-morpholino), *p*-(N-morpholino-CH₂CH₂O)-benzyl, benzo[b]thiophen-2-yl,

30 5-chlorobenzo[b]thiophen-2-yl, 4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl, benzo[b]thiophen-3-yl, 5-chlorobenzo[b]thiophen-3-yl, benzo[b]thiophen-5-yl,



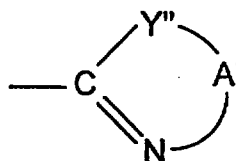
6-methoxynaphth-2-yl, $-\text{CH}_2\text{CH}_2\text{SCH}_3$, thien-2-yl, thien-3-yl, and the like..

63. The compound according to Claim 52 wherein the



group is further characterized

by the following heterocyclic structure:



wherein Y'' is a heteroatom selected from oxygen, sulfur and $>\text{NR}^8$ where R^8 is as defined above and A' , together with $-\text{Y}''-\text{C}=\text{N}-$, forms a heterocyclic group which is optionally fused to form a bi- or multi-fused ring system (preferably no more than 5 fused rings) with one or more ring structures selected from the group consisting of cycloalkyl, cycloalkenyl, heterocyclic, aryl and heteroaryl group which, in turn, each of such ring structures are optionally substituted with 1 to 4 substituents selected from the group consisting of hydroxyl, halo, alkoxy, substituted alkoxy, thioalkoxy, substituted thioalkoxy, nitro, cyano, carboxyl, carboxyl esters, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, amino, N-alkylamino, N,N-dialkylamino, N-substituted alkylamino, N-alkyl N-substituted alkylamino, N,N-disubstituted alkylamino, aryl, heteroaryl, heterocyclic, $-\text{NHC}(\text{O})\text{R}^{10}$, $-\text{NHSO}_2\text{R}^{10}$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{NHR}^{10}$, $-\text{C}(\text{O})\text{NR}^{10}\text{R}^{10}$, $-\text{S}(\text{O})\text{R}^{10}$, $-\text{S}(\text{O})_2\text{R}^{10}$, $-\text{S}(\text{O})_2\text{NHR}^{10}$ and $-\text{S}(\text{O})_2\text{NR}^{10}\text{R}^{10}$ where each R^{10} is independently selected from the group consisting of alkyl, substituted alkyl, or aryl.



64. The compound according to Claim 63 wherein the heterocyclic structure is selected from 3-methyl-1,2,4-oxadiazol-5-yl, thiazolin-2-yl, 3-phenyl-1,2,4-oxadiazol-5-yl and 3-(*p*-methoxy-benzyl)-1,2,4-oxadiazol-5-yl.

65. The compound according to Claim 52 wherein the compound of formula II is selected from the group consisting of:

(S)-5-[1-*N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]amino]ethyl-3-ethyl-1,2,4-oxadiazole

(S)-5-[1-*N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]amino-2-phenylethyl]-3-methyl-1,2,4-oxadiazole

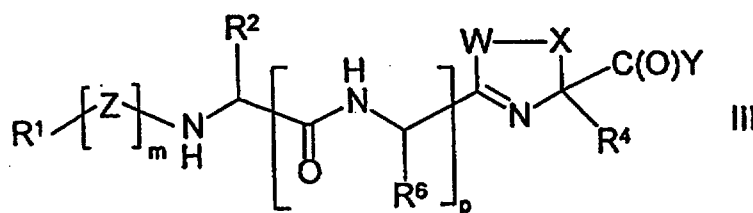
2-[1-*N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]amino-1-phenyl]methyl-2-thiazoline

(S)-5-[1-*N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]amino-1-phenyl]methyl-3-methyl-1,2,4-oxadiazole

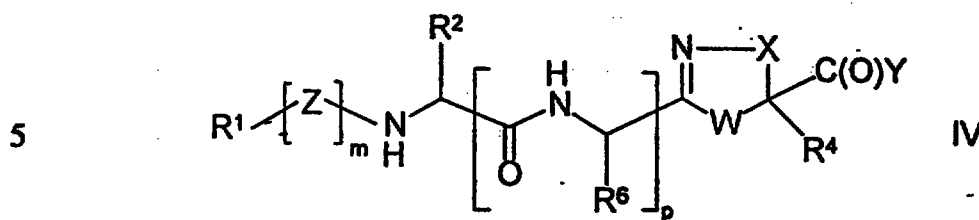
(S)-5-[1-*N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]amino-1-phenyl]methyl-3-phenyl-1,2,4-oxadiazole; and

(S)-5-[1-*N*-[*N*-(3,5-difluorophenylacetyl)-L-alaninyl]amino-1-phenyl]methyl-3-(4-methoxyphenylmethyl)-1,2,4-oxadiazole.

66. The compound according to Claim 51 wherein the compound of formula I is further characterized by formula III and IV below:



and



10

wherein R^1 , R^2 , R^4 , R^6 , W , X , Y , Z , m and p are as defined in Claim 51.

15

67. The compound according to Claim 66 wherein m is one, Z is $-\text{CX}'\text{X}''\text{C}(\text{O})-$, X'' is hydrogen, X' is hydrogen or fluoro and where X' and X'' form an oxo group.

20

68. The compound according to Claim 66 wherein R^1 is an unsubstituted aryl group selected from the group consisting of phenyl, 1-naphthyl and 2-naphthyl.

25

69. The compound according to Claim 66 wherein R^1 is a substituted aryl group selected from the group consisting of monosubstituted phenyls, disubstituted phenyls, and trisubstituted phenyls.

30

70. The compound according to Claim 69 wherein said substituted R^1 phenyl group is selected from the group consisting of 2-chlorophenyl, 2-fluorophenyl, 2-bromophenyl, 2-hydroxyphenyl, 2-nitrophenyl, 2-methylphenyl, 2-methoxyphenyl, 2-phenoxyphenyl, 2-trifluoromethylphenyl, 4-fluorophenyl, 4-chlorophenyl, 4-bromophenyl, 4-nitrophenyl, 4-methylphenyl, 4-hydroxyphenyl, 4-methoxyphenyl, 4-ethoxyphenyl, 4-butoxyphenyl, 4-*iso*-propylphenyl, 4-phenoxyphenyl, 4-trifluoromethylphenyl, 4-hydroxymethylphenyl, 3-methoxyphenyl, 3-hydroxyphenyl, 3-nitrophenyl, 3-fluorophenyl, 3-chlorophenyl, 3-bromophenyl, 3-phenoxyphenyl, 3-thiomethoxyphenyl, 3-methylphenyl, 3-trifluoromethylphenyl, 2,3-dichlorophenyl, 2,3-difluorophenyl, 2,4-dichlorophenyl,

35



2,5-dimethoxyphenyl, 3,4-dichlorophenyl, 3,4-difluorophenyl,
3,4-methylenedioxyphenyl, 3,4-dimethoxyphenyl, 3,5-difluorophenyl,
3,5-dichlorophenyl, 3,5-di-(trifluoromethyl)phenyl, 3,5-dimethoxyphenyl,
2,4-dichlorophenyl, 2,4-difluorophenyl, 2,6-difluorophenyl, 3,4,5-
5 trifluorophenyl, 3,4,5-trimethoxyphenyl, 3,4,5-tri-(trifluoromethyl)phenyl,
2,4,6-trifluorophenyl, 2,4,6-trimethylphenyl, 2,4,6-tri-(trifluoromethyl)phenyl,
2,3,5-trifluorophenyl, 2,4,5-trifluorophenyl, 2,5-difluorophenyl, 2-fluoro-3-
trifluoromethylphenyl, 4-fluoro-2-trifluoromethylphenyl, 2-fluoro-4-
trifluoromethylphenyl, 4-benzyloxyphenyl, 2-chloro-6-fluorophenyl, 2-fluoro-6-
10 chlorophenyl, 2,3,4,5,6-pentafluorophenyl, 2,5-dimethylphenyl, 4-phenylphenyl
and 2-fluoro-3-trifluoromethylphenyl.

71. The compound according to Claim 66 wherein R¹ is an alkaryl
group selected from the group consisting of benzyl, 2-phenylethyl and 3-phenyl-
15 *n*-propyl.

72. The compound according to Claim 66 wherein R¹ is selected from
alkyl, substituted alkyl alkenyl, cycloalkyl and cycloalkenyl groups.

20 73. The compound according to Claim 72 wherein R¹ is selected from
the group consisting of *iso*-propyl, *n*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl,
t-butyl, -CH₂CH=CH₂, -CH₂CH=CH(CH₂)₄CH₃, cyclopropyl, cyclobutyl,
cyclohexyl, cyclopentyl, cyclohex-1-enyl, -CH₂-cyclopropyl, -CH₂-cyclobutyl,
-CH₂-cyclohexyl, -CH₂-cyclopentyl, -CH₂CH₂-cyclopropyl, -CH₂CH₂-
25 cyclobutyl, -CH₂CH₂-cyclohexyl and -CH₂CH₂-cyclopentyl.

74. The compound according to Claim 66 wherein R¹ is a heteroaryl or
substituted heteroaryls selected from the group consisting of pyrid-2-yl, pyrid-3-
yl, pyrid-4-yl, fluoropyridyls (including 5-fluoropyrid-3-yl), chloropyridyls
30 (including 5-chloropyrid-3-yl), thiophen-2-yl, thiophen-3-yl, benzothiazol-4-yl,
2-phenylbenzoxazol-5-yl, furan-2-yl, benzofuran-2-yl, thionaphthen-2-yl, 2-



chlorothiophen-5-yl, 3-methylisoxazol-5-yl, 2-(thiophenyl)thiophen-5-yl, 6-methoxythionaphthen-2-yl, 3-phenyl-1,2,4-thioxadiazol-5-yl, and 2-phenyloxazol-4-yl.

- 5 75. The compound according to Claim 66 wherein R² is selected from the group consisting of methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, phenyl, benzyl, cyclohexyl, cyclopentyl, cycloheptyl, and -CH₂CH₂SCH₃.
- 10 76. The compound according to Claim 66 wherein R⁴ is selected from the group consisting of hydrogen, methyl, phenyl and benzyl.
- 15 77. The compound according to Claim 66 wherein R⁶ is selected from the group consisting of hydrogen, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, -CH₂CH(CH₂CH₃)₂, 2-methyl-*n*-butyl, 6-fluoro-*n*-hexyl, phenyl, benzyl, cyclohexyl, cyclopentyl, cycloheptyl, allyl, *iso*-but-2-enyl, 3-methylpentyl, -CH₂-cyclopropyl, -CH₂-cyclohexyl, -CH₂CH₂-cyclopropyl, -CH₂CH₂-cyclohexyl, -CH₂-indol-3-yl, *p*-(phenyl)phenyl, *o*-fluorophenyl, *m*-fluorophenyl, *p*-fluorophenyl, *m*-methoxyphenyl, *p*-methoxyphenyl, phenethyl, benzyl, *m*-hydroxybenzyl, *p*-hydroxybenzyl, *p*-nitrobenzyl, *m*-trifluoromethylphenyl, *p*-(CH₃)₂NCH₂CH₂CH₂O-benzyl, *p*-(CH₃)₃COC(O)CH₂O-benzyl, *p*-(HOOCCH₂O)-benzyl, 2-aminopyrid-6-yl, *p*-(*N*-morpholino-CH₂CH₂O)-benzyl, -CH₂CH₂C(O)NH₂, -CH₂-imidazol-4-yl, -CH₂-(3-tetrahydrofuranyl), -CH₂-thiophen-2-yl, -CH₂-(1-methyl)cyclopropyl, -CH₂-thiophen-3-yl, thiophen-3-yl, thiophen-2-yl, -CH₂-C(O)O-*t*-butyl, -CH₂-C(CH₃)₃, -CH₂CH(CH₂CH₃)₂, -2-methylcyclopentyl, -cyclohex-2-enyl, -CH[CH(CH₃)₂]COOCH₃, -CH₂CH₂N(CH₃)₂, -CH₂C(CH₃)=CH₂, -CH₂CH=CHCH₃ (*cis* and *trans*), -CH₂OH, -CH(OH)CH₃, -CH(O-*t*-butyl)CH₃, -CH₂OCH₃, -(CH₂)₄NH-Boc, -(CH₂)₄NH₂, -CH₂-pyridyl (e.g., 2-pyridyl, 3-pyridyl and 4-pyridyl), pyridyl (2-pyridyl, 3-pyridyl and 4-pyridyl), -CH₂-naphthyl (e.g., 1-naphthyl and 2-naphthyl), -CH₂-(*N*-morpholino),
- 20
- 25
- 30



p-(N-morpholino-CH₂CH₂O)-benzyl, benzo[b]thiophen-2-yl, 5-chlorobenzo[b]thiophen-2-yl, 4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl, benzo[b]thiophen-3-yl, 5-chlorobenzo[b]thiophen-3-yl, benzo[b]thiophen-5-yl, 6-methoxynaphth-2-yl, -CH₂CH₂SCH₃, thien-2-yl and thien-3-yl.

5

78. The compound according to Claim 66 wherein Y is hydroxy, alkoxy, substituted alkoxy and -NR'R".

79. The compound according to Claim 78 wherein Y is selected from the group consisting of methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *iso*-butoxy, *t*-butoxy, *neo*-pentoxy, benzyloxy, 2-phenylethoxy, 3-phenyl-*n*-propoxy, 3-iodo-*n*-propoxy, 4-bromo-*n*-butoxy, amino (-NH₂), -NH(*iso*-butyl), -NH(*sec*-butyl), N-methylamino, N,N-dimethylamino, N-benzylamino, N-morpholino, azetidino, N-thiomorpholino, N-piperidinyl, N-hexamethyleneimino, N-heptamethylene-imino, N-pyrrolidinyl, -NH-methallyl, -NHCH₂-(furan-2-yl), -NHCH₂-cyclopropyl, -NH(*t*-butyl), -NH(*p*-methylphenyl), -NHCH₂-(*p*-fluorophenyl), -NHCH₂CH₂OCH₃, -NH-cyclohexyl, -NHCH₂CH₂N(CH₃)₂, -NHCH₂C(CH₃)₃, -NHCH₂-(pyrid-2-yl), -NHCH₂-(pyrid-3-yl), -NHCH₂-(pyrid-4-yl), N-thiazolindinyl, -N(CH₂CH₂CH₃)₂, -NHOH, -NH(*p*-NO₂-φ), -NHCH₂(*p*-NO₂-φ), -NHCH₂(*m*-NO₂-φ), -N(CH₃)OCH₃, -N(CH₃)CH₂-φ, -NHCH₂-(3,5-di-fluorophenyl), -NHCH₂CH₂F, -NHCH₂(*p*-CH₃O-φ), -NHCH₂(*m*-CH₃O-φ), -NHCH₂(*p*-CF₃-φ), -N(CH₃)CH₂CH₂OCH₃, -NHCH₂CH₂φ, -NHCH(CH₃)φ, -NHCH₂-(*p*-F-φ), -N(CH₃)CH₂CH₂N(CH₃)₂, -NHCH₂-(tetrahydrofuran-2-yl), and -CH₂CH₂CH(CH₃)₂.

25

80. The compound according to Claim 66 wherein the heterocyclic structures defined by W and X are selected from the group consisting of 4,5-dihydrothiazoles, 3,4-dihydro-1,3-isodiazoles, 3,4-dihydro-3-N-*t*-butoxy-3-isodiazoles, and 4,5-dihydrooxazoles.

30



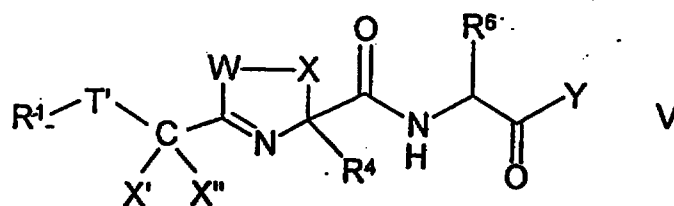
81. The compound according to Claim 66 wherein the compound of formula II is selected from the group consisting of:

- 5 (S)-2-[1-(3,5-difluorophenylacetamido)ethyl]-4-ethoxycarbonyl-2-thiazoline
- 1-*tert*-butoxycarbonyl-2-[1-(*N*-carbobenzyloxy)aminoethyl]-4-methoxycarbonyl-4-phenylmethyl-2-imidazoline
- 10 1-*tert*-butoxycarbonyl-2-[1-(3,5-difluorophenylacetamido)ethyl]-4-methoxycarbonyl-4-phenylmethyl-2-imidazoline
- 15 2-[1-(3,5-difluorophenylacetamido)ethyl]-4-methoxycarbonyl-4-phenylmethyl-2-imidazoline
- 20 2-[1-(3,5-difluorophenylacetamido)ethyl]-4-methoxycarbonyl-4-phenyl-2-imidazoline
- 2-[1-(3,5-difluorophenylacetamido)-1-phenyl]methyl-4-ethoxycarbonyl-2-thiazoline
- 1-*tert*-butoxycarbonyl-2-[1-(*N*-carbobenzyloxy)aminoethyl]-4-methoxycarbonyl-4-phenyl-2-imidazoline
- 25 2-[(S)-1-(3,5-dichloroanilino)ethyl]-(S)-4-methoxycarbonyl-2-oxazolidine
- (S)-2-[1-(3,5-difluorophenylacetamido)ethyl]-5(R,S)-ethoxycarbonyl-2-oxazoline
- 30 2-[1-(3,5-difluorophenylacetamido)-1-phenyl]methyl-4-methoxycarbonyl-2-thiazoline; and
- 35 [1-(*N*-carbobenzyloxy)aminoethyl]-4-methoxycarbonyl-4-phenyl-2-imidazoline.

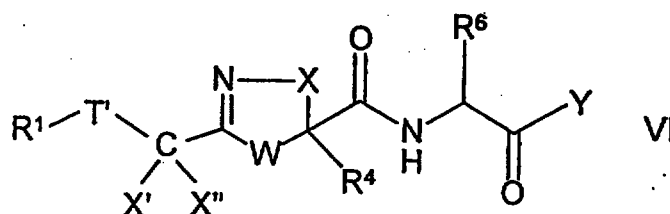
82. The compound according to Claim 51 wherein the compound of formula I is further characterized by formula V and VI below:

40

45



and



where R^1 , R^4 , R^6 , T' , X' , X'' , W , X , and Y are as defined in Claim 51.

83. The compound according to Claim 82 wherein m is one, Z is $-\text{CX}'\text{X}''\text{C}(\text{O})-$, X'' is hydrogen, X' is hydrogen or fluoro and X' and X'' form an oxo group.

84. The compound according to Claim 82 wherein R^1 is an unsubstituted aryl group selected from the group consisting of phenyl, 1-naphthyl and 2-naphthyl.

85. The compound according to Claim 82 wherein R^1 is a substituted aryl group selected from the group consisting of monosubstituted phenyls, disubstituted phenyls, and trisubstituted phenyls.

86. The compound according to Claim 85 wherein said substituted R^1 phenyl group is selected from the group consisting of 2-chlorophenyl, 2-fluorophenyl, 2-bromophenyl, 2-hydroxyphenyl, 2-nitrophenyl, 2-methylphenyl, 2-methoxyphenyl, 2-phenoxyphenyl, 2-trifluoromethylphenyl, 4-fluorophenyl, 4-chlorophenyl, 4-bromophenyl, 4-nitrophenyl, 4-methylphenyl,



- 4-hydroxyphenyl, 4-methoxyphenyl, 4-ethoxyphenyl, 4-butoxyphenyl, 4-*iso*-propylphenyl, 4-phenoxyphenyl, 4-trifluoromethylphenyl,
4-hydroxymethylphenyl, 3-methoxyphenyl, 3-hydroxyphenyl, 3-nitrophenyl,
3-fluorophenyl, 3-chlorophenyl, 3-bromophenyl, 3-phenoxyphenyl,
5 3-thiomethoxyphenyl, 3-methylphenyl, 3-trifluoromethylphenyl, 2,3-dichlorophenyl, 2,3-difluorophenyl, 2,4-dichlorophenyl, 2,5-dimethoxyphenyl, 3,4-dichlorophenyl, 3,4-difluorophenyl, 3,4-methylenedioxyphenyl, 3,4-dimethoxyphenyl, 3,5-difluorophenyl, 3,5-dichlorophenyl, 3,5-di-(trifluoromethyl)phenyl, 3,5-dimethoxyphenyl, 2,4-dichlorophenyl,
10 2,4-difluorophenyl, 2,6-difluorophenyl, 3,4,5-trifluorophenyl, 3,4,5-trimethoxyphenyl, 3,4,5-tri-(trifluoromethyl)phenyl, 2,4,6-trifluorophenyl, 2,4,6-trimethylphenyl, 2,4,6-tri-(trifluoromethyl)phenyl, 2,3,5-trifluorophenyl, 2,4,5-trifluorophenyl, 2,5-difluorophenyl, 2-fluoro-3-trifluoromethylphenyl, 4-fluoro-2-trifluoromethylphenyl, 2-fluoro-4-trifluoromethylphenyl,
15 4-benzyloxyphenyl, 2-chloro-6-fluorophenyl, 2-fluoro-6-chlorophenyl, 2,3,4,5,6-pentafluorophenyl, 2,5-dimethylphenyl, 4-phenylphenyl and 2-fluoro-3-trifluoromethylphenyl.

87. The compound according to Claim 82 wherein R¹ is an alkaryl
20 group selected from the group consisting of benzyl, 2-phenylethyl and 3-phenyl-*n*-propyl.

88. The compound according to Claim 82 wherein R¹ is selected from
alkyl, substituted alkyl, alkenyl, cycloalkyl and cycloalkenyl groups.

25

89. The compound according to Claim 88 wherein R¹ is selected from
the group consisting of *iso*-propyl, *n*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl,
t-butyl, -CH₂CH=CH₂, -CH₂CH=CH(CH₂)₄CH₃, cyclopropyl, cyclobutyl,
cyclohexyl, cyclopentyl, cyclohex-1-enyl, -CH₂-cyclopropyl, -CH₂-cyclobutyl,
30 -CH₂-cyclohexyl, -CH₂-cyclopentyl, -CH₂CH₂-cyclopropyl, -CH₂CH₂-
cyclobutyl, -CH₂CH₂-cyclohexyl and -CH₂CH₂-cyclopentyl.



90. The compound according to Claim 82 wherein R¹ is a heteroaryl or substituted heteroaryls selected from the group consisting of pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, fluoropyridyls (including 5-fluoropyrid-3-yl), chloropyridyls (including 5-chloropyrid-3-yl), thiophen-2-yl, thiophen-3-yl, benzothiazol-4-yl, 2-phenylbenzoxazol-5-yl, furan-2-yl, benzofuran-2-yl, thionaphthen-2-yl, 2-chlorothiophen-5-yl, 3-methylisoxazol-5-yl, 2-(thiophenyl)thiophen-5-yl, 6-methoxythionaphthen-2-yl, 3-phenyl-1,2,4-thioxadiazol-5-yl, and 2-phenyloxazol-4-yl.

91. The compound according to Claim 82 wherein R⁴ is selected from the group consisting of hydrogen, methyl, phenyl and benzyl.

92. The compound according to Claim 82 wherein R⁶ is selected from the group consisting of hydrogen, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, -CH₂CH(CH₂CH₃)₂, 2-methyl-*n*-butyl, 6-fluoro-*n*-hexyl, phenyl, benzyl, cyclohexyl, cyclopentyl, cycloheptyl, allyl, *iso*-but-2-enyl, 3-methylpentyl, -CH₂-cyclopropyl, -CH₂-cyclohexyl, -CH₂CH₂-cyclopropyl, -CH₂CH₂-cyclohexyl, -CH₂-indol-3-yl, *p*-(phenyl)phenyl, *o*-fluorophenyl, *m*-fluorophenyl, *p*-fluorophenyl, *m*-methoxyphenyl, *p*-methoxyphenyl, phenethyl, benzyl, *m*-hydroxybenzyl, *p*-hydroxybenzyl, *p*-nitrobenzyl, *m*-trifluoromethylphenyl, *p*-(CH₃)₂NCH₂CH₂CH₂O-benzyl, *p*-(CH₃)₃COC(O)CH₂O-benzyl, *p*-(HOOCCH₂O)-benzyl, 2-aminopyrid-6-yl, *p*-(*N*-morpholino-CH₂CH₂O)-benzyl, -CH₂CH₂C(O)NH₂, -CH₂-imidazol-4-yl, -CH₂-(3-tetrahydrofuranyl), -CH₂-thiophen-2-yl, -CH₂-(1-methyl)cyclopropyl, -CH₂-thiophen-3-yl, thiophen-3-yl, thiophen-2-yl, -CH₂-C(O)O-*t*-butyl, -CH₂-C(CH₃)₃, -CH₂CH(CH₂CH₃)₂, 2-methylcyclopentyl, -cyclohex-2-enyl, -CH[CH(CH₃)₂]COOCH₃, -CH₂CH₂N(CH₃)₂, -CH₂C(CH₃)=CH₂, -CH₂CH=CHCH₃ (cis and trans), -CH₂OH, -CH(OH)CH₃, -CH(O-*t*-butyl)CH₃, -CH₂OCH₃, -(CH₂)₄NH-Boc, -(CH₂)₄NH₂, -CH₂-pyridyl (e.g., 2-pyridyl, 3-pyridyl and 4-pyridyl), pyridyl (2-pyridyl, 3-pyridyl and 4-pyridyl), -CH₂-naphthyl (e.g., 1-naphthyl and 2-naphthyl), -CH₂-(*N*-morpholino),



p-(N-morpholino-CH₂CH₂O)-benzyl, benzo[b]thiophen-2-yl, 5-chlorobenzo[b]thiophen-2-yl, 4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl, benzo[b]thiophen-3-yl, 5-chlorobenzo[b]thiophen-3-yl, benzo[b]thiophen-5-yl, 6-methoxynaphth-2-yl, -CH₂CH₂SCH₃, thien-2-yl and thien-3-yl.

5

93. The compound according to Claim 82 wherein Y is hydroxy, alkoxy, substituted alkoxy and -NR'R".

94. The compound according to Claim 93 wherein Y is selected from the group consisting of methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *iso*-butoxy, *t*-butoxy, *neo*-pentoxy, benzyloxy, 2-phenylethoxy, 3-phenyl-*n*-propoxy, 3-iodo-*n*-propoxy, 4-bromo-*n*-butoxy, amino (-NH₂), -NH(*iso*-butyl), -NH(*sec*-butyl), N-methylamino, N,N-dimethylamino, N-benzylamino, N-morpholino, azetidino, N-thiomorpholino, N-piperidinyl, N-hexamethyleneimino, N-heptamethylene-imino, N-pyrrolidinyl, -NH-methallyl, -NHCH₂-(furan-2-yl), -NHCH₂-cyclopropyl, -NH(*t*-butyl), -NH(*p*-methylphenyl), -NHCH₃, -NHCH₂(*p*-fluorophenyl), -NHCH₂CH₂OCH₃, -NH-cyclohexyl, -NHCH₂CH₂N(CH₃)₂, -NHCH₂C(CH₃)₃, -NHCH₂-(pyrid-2-yl), -NHCH₂-(pyrid-3-yl), -NHCH₂-(pyrid-4-yl), N-thiazolindinyl, -N(CH₂CH₂CH₃)₂, -NHOH, -NH(*p*-NO₂-φ), -NHCH₂(*p*-NO₂-φ), -NHCH₂(*m*-NO₂-φ), -N(CH₃)OCH₃, -N(CH₃)CH₂-φ, -NHCH₂-(3,5-di-fluorophenyl), -NHCH₂CH₂F, -NHCH₂(*p*-CH₃O-φ), -NHCH₂(*m*-CH₃O-φ), -NHCH₂(*p*-CF₃-φ), -N(CH₃)CH₂CH₂OCH₃, -NHCH₂CH₂φ, -NHCH(CH₃)φ, -NHCH₂-(*p*-F-φ), -N(CH₃)CH₂CH₂N(CH₃)₂ and -NHCH₂-(tetrahydrofuran-2-yl).

25

95. The method according to Claim 82 wherein the heterocyclic structures defined by W and X are selected from the group consisting of 4,5-dihydrothiazoles, 3,4-dihydro-1,3-isodiazoles, 3,4-dihydro-3-N-*t*-butoxy-3-isodiazoles, and 4,5-dihydrooxazoles.

30



96. The method according to Claim 82 wherein said compound of formula V and VI are selected from the group consisting of

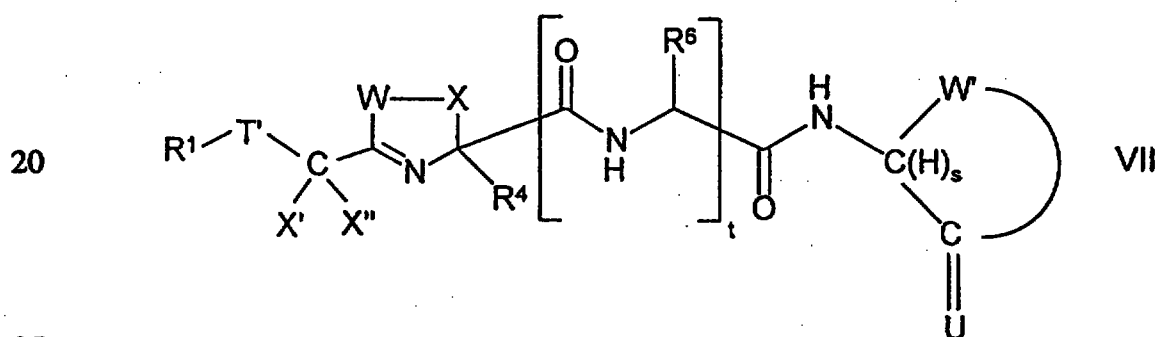
5 (4R)-4-[N-(1S)-(1-methoxycarbonyl-1-phenyl)methyl]carbamoyl-2-(3,5-difluorophenylmethyl)-4-methyl-2-thiazoline

4-[N-(S)-(1-methoxycarbonyl-1-phenyl)methyl]carbamoyl-2-(3,5-difluorophenylmethyl)-2-thiazoline; and

10 4-[N-(S)-(1-methoxycarbonyl-1-phenyl)methyl]carbamoyl-2-(3,5-difluorophenylmethyl)-4-methyl-2-imidazoline.

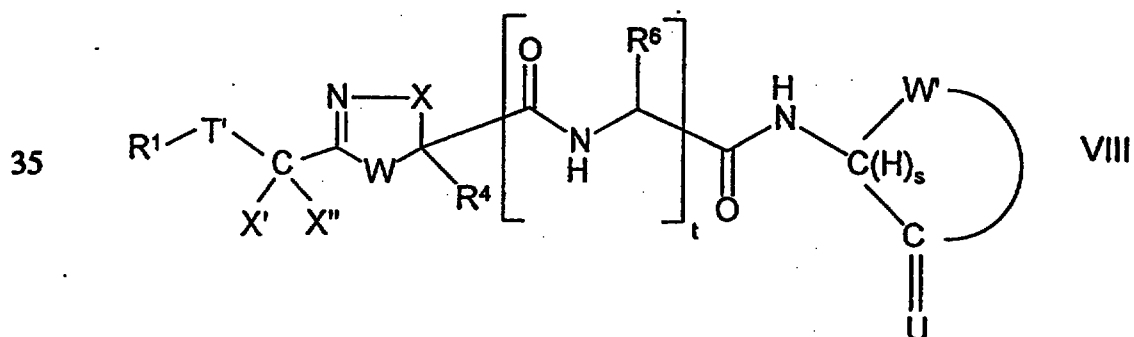
97. A compound of formula VII and VIII

15



and

30



wherein R¹, R⁴, R⁶, T', X', X'', W and X are as defined above;

W', together with -C(H)_sC(=U)-, forms a cycloalkyl, cycloalkenyl, heterocyclic, substituted cycloalkyl, or substituted cycloalkenyl group wherein



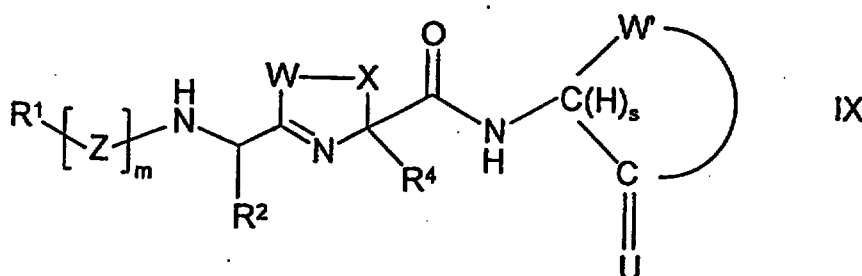
each of said cycloalkyl, cycloalkenyl, heterocyclic, substituted cycloalkyl or substituted cycloalkenyl group is optionally fused to form a bi- or multi-fused ring system (preferably no more than 5 fused rings) with one or more ring structures selected from the group consisting of cycloalkyl, cycloalkenyl, heterocyclic, aryl and heteroaryl group which, in turn, each of such ring structures is optionally substituted with 1 to 4 substituents selected from the group consisting of hydroxyl, halo, alkoxy, substituted alkoxy, thioalkoxy, substituted thioalkoxy, aryl, heteroaryl, heterocyclic, nitro, cyano, carboxyl, carboxyl esters, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, amino, N-alkylamino, N,N-dialkylamino, N-substituted alkylamino, N-alkyl N-substituted alkylamino, N,N-disubstituted alkylamino, -NHC(O)R¹⁰, -NHSO₂R¹⁰, -C(O)NH₂, -C(O)NHR¹⁰, -C(O)NR¹⁰R¹⁰, -S(O)R¹⁰, -S(O)₂R¹⁰, -S(O)₂NHR¹⁰ and -S(O)₂NR¹⁰R¹⁰ where each R¹⁰ is independently selected from the group consisting of alkyl, substituted alkyl, or aryl;

U is selected from the group consisting of oxo (=O), thiooxo (=S), hydroxyl (-H, -OH), thiol (H, -SH) and hydro (H,H);

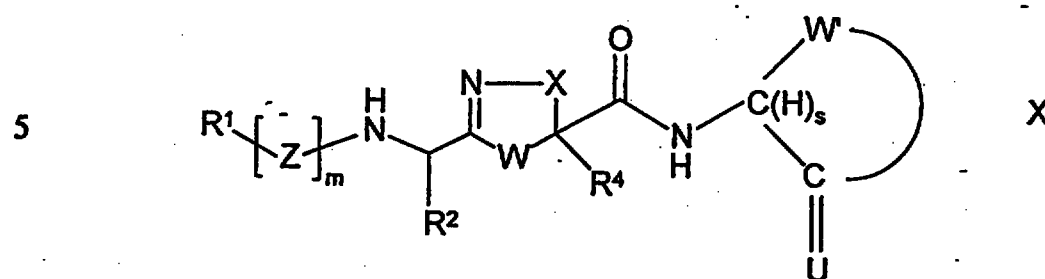
s is an integer equal to 0 or 1; and

t is an integer equal to 0 or 1.

98. A compound of formula IX and X:



and



wherein R¹, R⁴, R⁶, T', X', X'', W and X are as defined above;

W', together with -C(H)₃C(=U)-, forms a cycloalkyl, cycloalkenyl, heterocyclic, substituted cycloalkyl, or substituted cycloalkenyl group wherein each of said cycloalkyl, cycloalkenyl, heterocyclic, substituted cycloalkyl or substituted cycloalkenyl group is optionally fused to form a bi- or multi-fused ring system (preferably no more than 5 fused rings) with one or more ring structures selected from the group consisting of cycloalkyl, cycloalkenyl, heterocyclic, aryl and heteroaryl group which, in turn, each of such ring structures is optionally substituted with 1 to 4 substituents selected from the group consisting of hydroxyl, halo, alkoxy, substituted alkoxy, thioalkoxy, substituted thioalkoxy, aryl, heteroaryl, heterocyclic, nitro, cyano, carboxyl, carboxyl esters, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, amino, N-alkylamino, N,N-dialkylamino, N-substituted alkylamino, N-alkyl N-substituted alkylamino, N,N-disubstituted alkylamino, -NHC(O)R¹⁰, -NHSO₂R¹⁰, -C(O)NH₂, -C(O)NHR¹⁰, -C(O)NR¹⁰R¹⁰, -S(O)R¹⁰, -S(O)₂R¹⁰, -S(O)₂NHR¹⁰ and -S(O)₂NR¹⁰R¹⁰ where each R¹⁰ is independently selected from the group consisting of alkyl, substituted alkyl, or aryl;

U is selected from the group consisting of oxo (=O), thiooxo (=S), hydroxyl (-H, -OH), thiol (H, -SH) and hydro (H, H);

s is an integer equal to 0 or 1; and

t is an integer equal to 0 or 1..

99. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective amount of a compound according to any of Claims 51-98.

