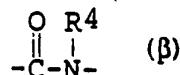
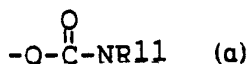
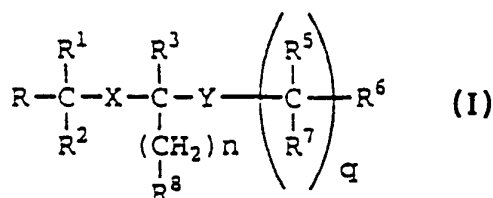




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : C07D 209/20, C07C 271/22 A61K 31/40, C07D 401/12 C07D 409/12, 405/12, 231/56 C07D 333/60, 417/12	A1	(11) International Publication Number: WO 94/04494 (43) International Publication Date: 3 March 1994 (03.03.94)
(21) International Application Number: PCT/US93/07552 (22) International Filing Date: 12 August 1993 (12.08.93) (30) Priority data: 930,252 13 August 1992 (13.08.92) US 097,264 23 July 1993 (23.07.93) US (71) Applicant: WARNER-LAMBERT COMPANY [US/US]; 2800 Plymouth Road, Ann Arbor, MI 48105 (US). (72) Inventors: HORWELL, David, Christopher ; 8 West Hill, Foxton, Cambridge CB2 6SZ (GB). HOWSON, William ; Brook Cottage, 46 Chapel Road, Weston Green, Weston Colville, Cambridgeshire SG1 2NX (GB). REES, David, Charles ; 25E Hughenden Lane, Glasgow G12 9XU (GB). ROBERTS, Edward ; Willow Tree Cottage, High Street, Ditton Green, Wood Ditton, Newmarket CB8 9SQ (GB). PRITCHARD, Martyn, Clive ; 11A Thistle Green, Swavesey, Cambridge CB4 5RJ (GB).		(74) Agents: ANDERSON, Elizabeth, M.; Warner-Lambert Company, 2800 Plymouth Road, Ann Arbor, MI 48105 (US) et al. (81) Designated States: AU, CA, CZ, FI, HU, JP, KR, NO, NZ, RU, SK, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>

(54) Title: TACHYKININ ANTAGONISTS



(57) Abstract

Compounds of formula (I) wherein R, R⁸ and R⁶ are possibly substituted phenyl, pyridine, thiophene, furan, naphthalene, etc.; R¹ and R² are each independently hydrogen or alkyl of from 1 to 4 atoms; R and R², when joined by a bond, can form a ring; X is α wherein R¹¹ is hydrogen or alkyl of from 1 to 3 carbon atoms; R³ is hydrogen or (CH₂)_mR¹³ where m is an integer of from 1 to 6 and R¹³ is H, CN, NH₂, N(CH₃)₂, or NHCOCH₃; n is an integer of from 1 to 2; Y is β wherein R⁴ is hydrogen or alkyl of from 1 to 3 carbon atoms, -CO₂-, etc.; R⁵ and R⁷ are each independently hydrogen or alkyl of from 1 to 4 carbon atoms; q is an integer of from 0 to 1. The compounds are nonpeptide tachykinin antagonists and are expected to be especially useful in asthma and rheumatoid arthritis.

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TACHYKININ ANTAGONISTS

BACKGROUND OF THE INVENTION

5

Over the last decade, major advances have been made in the understanding of the biology of the mammalian tachykinin neuropeptides. It is now well established that substance-P (1), neurokinin A (NKA) (2), and neurokinin B (NKB) (3), all of which share a common C-terminal sequence Phe-X-Gly-Leu-Met-NH₂, (Nakanishi S, Physiol Rev 1987;67:117), are widely distributed throughout the periphery and central nervous system (CNS) where they appear to interact with at least three receptor types referred to as NK₁, NK₂, and NK₃, (Guard S, et al., Neurosci Int 1991;18:149). Substance-P displays highest affinity for NK₁ receptors, whereas NKA and NKB bind preferentially to NK₂ and NK₃ receptors, respectively. Recently, all three receptors have been cloned and sequenced and shown to be members of the G-protein-linked "super family" of receptors (Nakanishi S, Annu Rev Neurosci 1991;14:123). A wealth of evidence supports the involvement of tachykinin neuropeptides in a variety of biological activities including pain transmission, vasodilation, smooth muscle contraction, bronchoconstriction, activation of the immune system (inflammatory pain), and neurogenic inflammation (Pernow B, Pharmacol Rev 1983;35:85). However, to date, a detailed understanding of the physiological roles of tachykinin neuropeptides has been severely hampered by a lack of selective, high affinity, metabolically stable tachykinin receptor antagonists that possess both good bioavailability and CNS penetration. Although several tachykinin receptor antagonists have been described (Tomczuk BE, et al.,

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Current Opinions in Therapeutic Patents 1991;1:197), most have been developed through the modification and/or deletion of one or more of the amino acids that comprise the endogenous mammalian tachykinins such that the resulting molecules are still peptides that possess poor pharmacokinetic properties and limited in vivo activities.

However, since 1991, a number of high-affinity nonpeptide antagonists have been reported. Snider RM, et al, (Science 1991;251:435), and Garret C, et al, (Proc Natl Acad Sci 1991;88:10208), described CP-96,345 and RP 67580, respectively, as antagonists at the NK₁ receptor, while Advenier C, et al., (Brit J Pharmacol 1992;105:78), presented data on SR 48969 showing its high affinity and selectivity for NK₂ receptors. It is of interest that most of the nonpeptide tachykinin receptor antagonists described to date arose, either directly or indirectly, out of the screening of large compound collections using a robust radioligand binding assay as the primary screen. Recently, FK 888, a "dipeptide" with high affinity for the NK₁ receptor was described (Fujii J, et al., Neuropeptide 1992;22:24).

International Publication Numbers WO 93/01169, WO 93/01165, and WO 93/001160 cover certain nonpeptide tachykinin receptor antagonists.

Substance-P is widely distributed throughout the periphery and central nervous system. It is believed to mediate a variety of biological actions, via an interaction with three receptor types referred to as NK₁, NK₂, and NK₃, including smooth muscle contraction, pain transmission, neuronal excitation, secretion of saliva, angiogenesis, broncho-constriction, activation of the immune system and neurogenic inflammation.

Accordingly, compounds capable of antagonizing the effects of substance-P at NK₁ receptors will be useful in treating or preventing a variety of brain disorders

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including pain, anxiety, panic, depression,
 schizophrenia, neuralgia, and addiction disorders;
 inflammatory diseases such as arthritis, asthma, and
 psoriasis; gastrointestinal disorders including
 5 colitis, Crohn's disease, irritable bowel syndrome, and
 satiety; allergic responses such as eczema and
 rhinitis; vascular disorders such as angina and
 migraine; neuropathological disorders including
 Parkinson's disease, multiple sclerosis, and
 10 Alzheimer's disease; and ophthalmic diseases including
 scleroderma.

The compounds of the invention, NK₁ receptor
 antagonists, are useful as anti-angiogenic agents for
 the treatment of conditions associated with aberrant
 15 neovascularization such as rheumatoid arthritis,
 atherosclerosis, and tumor cell growth. They will also
 be useful as agents for imaging NK₁ receptors in vivo
 in conditions such as ulcerative colitis and Crohn's
 disease.

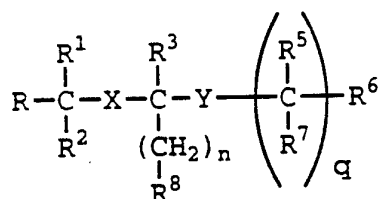
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SUMMARY OF THE INVENTION

The invention covers tachykinin antagonists. The
 25 compounds are nonpeptides which have proved to be
 highly selective and functional tachykinin antagonists.
 These compounds are unique in the alkylation/
 substitution pattern along their back bone.

Compounds of the invention are those of formula
 30

35



I

or a pharmaceutically acceptable salt thereof wherein

-4-

- R is phenyl,
pyridine,
thiophene,
furan,
5 naphthalene,
indole,
benzofuran, or
benzothiophene each unsubstituted,
mono-, di-, or trisubstituted by
10 alkyl,
hydroxy,
alkoxy,
NO₂,
halogen,
15 NH₂, or
CF₃;
- R¹ and R² are each independently hydrogen or alkyl
of from 1 to 4 atoms;
- R and R², when joined by a bond, can form a ring;
- 20
$$\text{X is } -\text{O}-\overset{\text{O}}{\parallel}{\text{C}}-\text{NR}^{11}$$
 wherein R¹¹ is hydrogen or alkyl of
from 1 to 3 carbon atoms;
- R³ is hydrogen or (CH₂)_mR¹³ where m is an integer
25 of from 1 to 6 and R¹³ is H, CN, NH₂, N(CH₃)₂, or
NHCOCH₃;
- n is an integer of from 1 to 2;
- R⁸ is phenyl,
pyridine,
30 thiophene,
furan,
naphthalene,
indole,
benzofuran, or
35 benzothiophene each unsubstituted, or

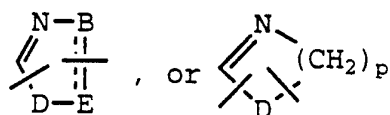
-5-

mono-, di-, or trisubstituted by
 alkyl,
 hydroxy,
 alkoxy,
 5 NO₂,
 halogen,
 NH₂, or
 CF₃;

10 Y is $\begin{array}{c} \text{O} \quad \text{R}^4 \\ \parallel \quad | \\ -\text{C}-\text{N}- \end{array}$ wherein R⁴ is hydrogen or alkyl of from
 1 to 3 carbon atoms,

-CO₂-,
 -COCH₂-,
 15 -CH₂O-,
 -CH₂NH-,
 -CH=CH-,
 -CH₂CH₂-,
 -CHOHCH₂-,

20



25 wherein B is nitrogen,
 CH, CH₂, oxygen, or sulfur, D is
 nitrogen, oxygen, or sulfur, E is
 nitrogen or CH, CH₂, p is an integer of
 from 3 to 4, and the dotted line
 indicates a double or single bond;

30 R⁵ and R⁷ are each independently hydrogen or alkyl
 of from 1 to 4 carbon atoms;

q is an integer of from 0 to 1; and

R⁶ is phenyl,

pyridine,
 35 thiophene,
 furan,
 naphthalene,

-6-

indole,
benzofuran, or
benzothiophene each unsubstituted, or
mono-, di-, or trisubstituted by

5 alkyl,
 hydroxy,
 alkoxy,
 NO₂,
 halogen,
10 NH₂, or
 CF₃;

straight alkyl of from 1 to 8 carbons, branched
alkyl of from 3 to 8 carbons, cycloalkyl of from
5 to 8 carbons, or heterocycloalkyl.

15 Other cyclic derivatives of Formula I are
contemplated such as would occur to one skilled in the
art.

Prodrugs of the above are also contemplated such
as would occur to one skilled in the art, see
20 Bundgaard, et al., Acta Pharm Suec, 1987;24:233-246.
For example, where a suitable moiety has been attached
to the linker X or Y or the indole N.

Preferred compounds of the invention are those of
Formula I above wherein

25 R is pyridine,
 thiophene,
 furan,
 naphthalene,
 indole,
30 benzofuran, or
 benzothiophene each unsubstituted,
 mono-, di-, or trisubstituted by
 alkyl,
 hydroxy,
35 alkoxy,
 NO₂,

-7-

halogen,

NH₂, orCF₃;

5 R¹ and R² are each independently hydrogen or alkyl
of from 1 to 4 atoms;

R and R², when joined by a bond, can form a ring;

10 X is $\begin{array}{c} \text{O} \\ \parallel \\ -\text{O}-\text{C}-\text{NR}^{11} \end{array}$ wherein R¹¹ is hydrogen or alkyl of
from 1 to 3 carbon atoms;

R³ is hydrogen or (CH₂)_mR¹³ where m is an integer
of from 1 to 6 and R¹³ is H, CN, NH₂, N(CH₃)₂, or
NHCOCH₃;

n is an integer of from 1 to 2;

15 R⁸ is phenyl,

pyridine,

thiophene,

furan,

naphthalene,

20 indole,

benzofuran, or

benzothiophene each unsubstituted, or

mono-, di-, or trisubstituted by

alkyl,

25 hydroxy,

alkoxy,

NO₂,

halogen,

NH₂, or

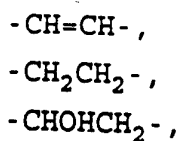
30 CF₃;

Y is $\begin{array}{c} \text{O} \quad \text{R}^4 \\ \parallel \quad | \\ -\text{C}-\text{N}- \end{array}$ wherein R⁴ is hydrogen or alkyl of from
1 to 3 carbon atoms,

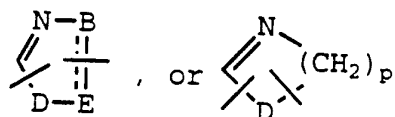
35 -CO₂-,

-COCH₂-,-CH₂O-,-CH₂NH-,

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5



10

wherein B is nitrogen,
 CH, CH₂, oxygen, or sulfur, D is nitrogen,
 oxygen, or sulfur, E is nitrogen, CH, CH₂,
 p is an integer of from 3 to 4, and the
 dotted line indicates a double or single
 bond;

15 R⁵ and R⁷ are each independently hydrogen or alkyl
 of from 1 to 4 carbon atoms;

q is an integer of from 0 to 1; and

R⁶ is phenyl,

20

pyridine,
 thiophene,
 furan,
 naphthalene,
 indole,
 benzofuran, or
 benzothiophene each unsubstituted, or
 25 mono-, di-, or trisubstituted by
 alkyl,
 hydroxy,
 alkoxy,
 NO₂,
 30 halogen,
 NH₂, or
 CF₃;

35

straight alkyl of from 1 to 8 carbons, branched
 alkyl of from 3 to 8 carbons, cycloalkyl of from
 5 to 8 carbons, or heterocycloalkyl;

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More preferred compounds of the invention are those of Formula I above wherein

R is phenyl

pyridyl,

5 thiophene,

furan,

naphthalene,

indole each unsubstituted, or

10 mono- or disubstituted by alkyl of 1 to 3 carbons, methoxy, ethoxy, chlorine,

fluorine, NH_2 , or CF_3 ;

R^1 and R^2 are each independently selected from hydrogen and methyl;

15 X is -OC(=O)-NR^{11} wherein R^{11} is hydrogen or methyl;

R^3 is hydrogen or $(\text{CH}_2)_m\text{R}^{13}$ where m is an integer of from 1 to 6 and R^{13} is H, CN, NH_2 , $\text{N}(\text{CH}_3)_2$,
20 or NHCOCH_3 ;

n is 1;

R^8 is phenyl,

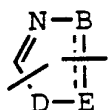
naphthyl,

indole, or

25 benzothiophene;

Y is $\text{-C(=O)-N(R}^4\text{)-CO}_2\text{-}$ wherein R^4 is hydrogen or methyl

30



wherein B is CH, CH_2 , D is sulfur, and E is CH, CH_2 ;

35 R^5 and R^7 are each independently hydrogen or methyl;

q is an integer of from 0 to 1, and

-10-

R⁶ is phenyl,
substituted phenyl, or
cyclohexyl.

5 Still more preferred compounds of the invention
are those of Formula I wherein

R is phenyl
thiophene,
furan,
each unsubstituted, or mono- or disubstituted
10 by alkyl of 1 to 3 carbons, methoxy, ethoxy,
chlorine, fluorine, NH₂, or CF₃;

R¹ and R² are each independently hydrogen or
methyl;

15 X is -O-C(=O)-NH- ;

R³ is hydrogen or methyl;

n is 1;

20 R⁸ is indole;

Y is -C(=O)-NH- or $\text{-C(=O)-NCH}_3\text{-}$;

25 R⁵ and R⁷ are each independently hydrogen or
methyl;

q is 1;

R⁶ is phenyl,
substituted phenyl, or
30 cyclohexyl.

Still more especially preferred compounds of the
invention are:

phenylmethyl (S)-[1-(1H-indol-3-ylmethyl)-
2-[methyl(phenylmethyl)amino]-2-oxoethyl]carbamate;
35 phenylmethyl [R-(R*S*)]-[1-(1H-indol-3-ylmethyl)-
2-oxo-2-[(1-phenylethyl)amino]ethyl]carbamate;
phenylmethyl [S-R*,R*]-[1-(1H-indol-3-ylmethyl)-
2-oxo-2-[(1-phenylethyl)amino]-ethyl]carbamate;

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- phenylmethyl [R- (R*, S*)] - [1- (1H-indol-3-ylmethyl) -
1-methyl-2-oxo-2- [(1-phenylethyl) amino] ethyl] carbamate;
phenylmethyl [S- (R*, R*)] - [1- (1H-indol-3-ylmethyl) -
2-oxo-2- [(1-phenylethyl) amino] ethyl] methyl carbamate;
5 phenylmethyl [S- (R*, S*)] - [1- (1H-indol-3-ylmethyl) -
2-oxo-2- [(1-phenylethyl) amino] ethyl] methyl carbamate;
(4-chlorophenyl) methyl (S) - [1- (1H-indole-
3-ylmethyl) -2-oxo-2- [(phenylmethyl) amino] ethyl] methyl -
carbamate;
10 (4-methoxyphenyl) methyl [R- (R*, S*)] - [1- (1H-indol-
3-ylmethyl) -1-methyl-2-oxo-2- [(1-phenylethyl) amino] -
ethyl] carbamate;
(4-chlorophenyl) methyl [R- (R*, S*)] - [1- (1H-indol-
ethyl] carbamate;
15 (4-methylphenyl) methyl [R- (R*, S*)] - [1- (1H-indol-
3-ylmethyl) -1-methyl-2-oxo-2- [(1-phenylethyl) amino] -
ethyl] carbamate;
phenylmethyl (S) - [1- (1H-indol-3-ylmethyl) -
2- [methyl (phenylmethyl) amino] -2-oxoethyl] carbamate;
20 phenylmethyl (S) - [2- [[(4-chlorophenyl) methyl] -
amino] 1- (1H-indol-3-ylmethyl) -2-oxoethyl] -
methyl carbamate;
phenylmethyl (S) - [1- (1H-indol-3-ylmethyl) -2-oxo-
2- [[[4- (trifluoromethyl) phenyl] methyl] amino] ethyl] -
25 methyl carbamate;
methyl N- [(phenylmethoxy) carbonyl] -,
[3,5-bis (trifluoromethyl) phenyl] -L-tryptophan;
phenylmethyl [1- (1H-indol-3-ylmethyl) -1-methyl-
2- [[1- (4-methylphenyl) ethyl] amino] -2-oxoethyl] -
30 carbamate;
phenylmethyl [R- (R*, R*)] - [2- [(1-cyclohexylethyl) -
amino] -1- (1H-indol-3-ylmethyl) -1-methyl-2-oxoethyl] -
carbamate;
phenylmethyl [2- [[1- [3,5-bis (trifluoromethyl) -
35 phenyl] ethyl] amino] -1- (1H-indol-3-ylmethyl) -1-methyl-
2-oxoethyl] carbamate;

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- phenylmethyl (R,RS) - [1-(1H-indol-3-ylmethyl) -
2-[[1-(4-methoxyphenyl)ethyl]amino] -1-methyl -
2-oxoethyl] carbamate;
- 4-pyridinylmethyl [R-(R*,S*)] - [1-(1H-indol-
3-ylmethyl) -1-methyl-2-oxo-2-[(1-phenylethyl)amino] -
carbamate;
- 3-thienylmethyl [R-(R*,S*)] - [1-(1H-indol-
3-ylmethyl) -1-methyl-2-oxo-2-[(1-phenylethyl)amino] -
ethyl] carbamate;
- 2-thienylmethyl [R-(R*,S*)] - [1-(1H-indol-
3-ylmethyl) -1-methyl-2-oxo-2-[(1-phenylethyl)amino] -
ethyl] carbamate;
- 2,3-dihydro-1H-inden-3-yl [R-(R*,S*)] -
[1-(1H-indol-3-ylmethyl) -1-methyl-2-oxo-
2-[(phenylethyl)amino]ethyl] carbamate;
- 1-naphthalenylmethyl [R-(R*,S*)] - [1-(1H-indol-
3-ylmethyl) -1-methyl-2-oxo-2-[(phenylethyl)amino] -
ethyl] carbamate;
- 2,3-dihydro-1H-inden-2-yl [1-(1H-indol-
3-ylmethyl) -1-methyl-2-oxo-2-[(phenylethyl)amino] -
ethyl] carbamate;
- (2-fluorophenyl)methyl [R-(R*,S*)] - [1-(1H-indol-
3-ylmethyl) -1-methyl-2-oxo-2-[(phenylethyl)amino] -
ethyl] carbamate;
- 3-furanylmethyl [R-(R*,S*)] - [1-(1H-indol-
3-ylmethyl) -1-methyl-2-oxo-2-[(phenylethyl)amino] -
ethyl] carbamate;
- 2-furanylmethyl [R-(R*,S*)] - [1-(1H-indol-
3-ylmethyl) -1-methyl-2-oxo-2-[(phenylethyl)amino] -
ethyl] carbamate;
- (3-fluorophenyl)methyl [R-(R*,S*)] - [1-(1H-indol-
3-ylmethyl) -1-methyl-2-oxo-2-[(phenylethyl)amino] -
ethyl] carbamate;
- (2,3-difluorophenyl)methyl [R-(R*,S*)] -
[1-(1H-indol-3-ylmethyl) -1-methyl-2-oxo-
2-[(phenylethyl)amino]ethyl] carbamate;

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(4-fluorophenyl)methyl [R-(R*,S*)] - [1-(1H-indol-3-ylmethyl)-1-methyl-2-oxo-2-[(phenylethyl)amino]ethyl] carbamate;

5 (2,4-difluorophenyl)methyl [R-(R*,S*)] - [1-(1H-indol-3-ylmethyl)-1-methyl-2-oxo-2-[(phenylethyl)amino]ethyl] carbamate;

(2,5-difluorophenyl)methyl [R-(R*,S*)] - [1-(1H-indol-3-ylmethyl)-1-methyl-2-oxo-2-[(phenylethyl)amino]ethyl] carbamate;

10 phenylmethyl [R-(R*,S*)] and [S-(R*,R*)] - [1-(1H-indazol-3-ylmethyl)-2-oxo-2-[(1-phenylethyl)amino]ethyl] carbamate;

phenylmethyl [R-(R*,S*)] and [S-(R*,R*)] - [1-[(5-fluoro-1H-indol-3-yl)methyl]-2-oxo-2-[(1-phenylethyl)amino]ethyl] carbamate;

15

phenylmethyl [1-(1-methyl-1H-indol-3-ylmethyl)-2-oxo-2-[(1-phenylethyl)amino]ethyl] carbamate;

phenylmethyl [R-(R*,S*)] - [1-(2-naphthalenylmethyl)-2-oxo-2-[(1-phenylmethyl)amino]ethyl] carbamate;

20 1-phenylethyl (S)-N-[(phenylmethoxy)carbonyl]-DL-tryptophan, (S)-;

phenylmethyl [1-(benzo[b]thien-3-ylmethyl)-1-methyl-2-oxo-2-[(1-phenylethyl)amino]ethyl] carbamate.

Another aspect of the invention is a pharmaceutical composition comprising an amount of a compound according to Formula I effective to treat respiratory disorders in a mammal suffering therefrom, and a pharmaceutically acceptable carrier.

25

Another aspect of the invention is a method for treating respiratory disorders in a mammal such as a human comprising administering a therapeutically effective amount of a compound according to Formula I.

30

Another aspect of the invention is a pharmaceutical composition comprising an amount of a compound according to Formula I effective to treat

35

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inflammation in a mammal suffering therefrom, and a pharmaceutically acceptable carrier.

Another aspect of the invention is a method for treating inflammation in a mammal such as a human comprising administering a therapeutically effective amount of a compound according to Formula I.

Another aspect of the invention is a pharmaceutical composition comprising an amount of a compound according to Formula I effective to treat gastrointestinal disorders in a mammal suffering therefrom, and a pharmaceutically acceptable carrier.

Another aspect of the invention is a method for treating gastrointestinal disorders in a mammal such as a human comprising administering a therapeutically effective amount of a compound according to Formula I.

Another aspect of the invention is a pharmaceutical composition comprising an amount of a compound according to Formula I effective to treat eye diseases such as dry eye and conjunctivitis in a mammal suffering therefrom, and a pharmaceutically acceptable carrier.

Another aspect of the invention is a method for treating eye diseases in a mammal such as a human comprising administering a therapeutically effective amount of a compound according to Formula I.

Another aspect of the invention is a pharmaceutical composition comprising an amount of a compound according to Formula I effective to treat allergies in a mammal suffering therefrom, and a pharmaceutically acceptable carrier.

Another aspect of the invention is a method for treating allergies in a mammal such as a human comprising administering a therapeutically effective amount of a compound according to Formula I.

Another aspect of the invention is a pharmaceutical composition comprising an amount of a

-15-

compound according to Formula I effective to treat diseases of the central nervous system in a mammal suffering therefrom, and a pharmaceutically acceptable carrier.

5 Another aspect of the invention is a method for treating diseases of the central nervous system in a mammal such as a human comprising administering a therapeutically effective amount of a compound according to Formula I.

10 Another aspect of the invention is a pharmaceutical composition comprising an amount of a compound according to Formula I effective to treat migraine in a mammal suffering therefrom, and a pharmaceutically acceptable carrier.

15 Another aspect of the invention is a method for treating migraine in a mammal such as a human comprising administering a therapeutically effective amount of a compound according to Formula I.

20 Another aspect of the invention is a pharmaceutical composition comprising an amount of compound according to Formula I effective to treat pain arising from neurogenic inflammation or inflammatory pain.

25 Another aspect of the invention is a method for treating pain such as pain arising from neurogenic inflammation in inflammatory pain status.

30 Another aspect of the invention is a pharmaceutical composition comprising an amount of a compound according to Formula I effective in treating conditions associated with aberrant neovascularization: rheumatoid arthritis, atherosclerosis, and tumor cell growth.

35 Another aspect of the invention is a method of treating conditions associated with aberrant neovascularization: rheumatoid arthritis, atherosclerosis, and tumor cell growth.

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Another aspect of the invention is using the compounds as imaging agents for imaging NK₁ receptors in vivo.

Processes for preparing the compounds and novel intermediates are included in the invention.

DETAILED DESCRIPTION OF THE INVENTION

The following terms are descriptive of the compounds of the instant invention.

The alkyl groups contemplated by the invention include straight, branched, or cyclic carbon chains of from 1 to 8 carbon atoms except where specifically stated otherwise. Representative groups are methyl ethyl, propyl, isopropyl, n-propyl, n-butyl, iso-butyl, sec-butyl, 2-methylhexyl, n-pentyl, 1-methylbutyl, 2,2-dimethylbutyl, 2-methylpentyl, 2,2-dimethylpropyl, n-hexyl, and the like.

The cycloalkyl groups contemplated by the invention comprise those having 3 to 6 carbon atoms.

The alkoxy groups contemplated by the invention comprise both straight and branched carbon chains of from 1 to 6 carbon atoms unless otherwise stated. Representative groups are methoxyl, ethoxy, propoxy, i-propoxy, t-butoxy, and hexoxy.

The term halogen is intended to include fluorine, chlorine, bromine, and iodine.

The term aryl is intended to include substituted or unsubstituted phenyl, naphthyl, biphenyl, and indanyl. The substituents include one or more substituents such as halogens, nitro, alkyl, alkoxy, alkylthio, hydroxy, trifluoromethyl, and others as specified or as would occur to one skilled in the art.

The term arylalkyl is as described above for the two terms individually.

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The term heterocyclic comprises substituted or unsubstituted pyridyl, 2- or 3-indolyl, thienyl, quinolyl, furanyl, isoquinolyl, benzofuranyl, and benzothiophenyl.

The term amide/ester replacement refers to such moieties as ketomethylene, methyleneoxy, tetrazole, 1,2,4-oxadiazole, and thiazole, etc. See for example Fincham, et al, J Med Chem, 1992;35:1472-1482 or Saunders, et al., J Med Chem, 1990;33:1128-1138.

The compounds of the instant invention are highly selective antagonists of the tachykinin receptor.

One such compound (Ex. 15) is an antagonist of the NK₁ receptor in contrast to substance-P methyl ester which is a known selective NK₁ receptor agonist. See Table I below.

TABLE I

Example	NK ₁ Antagonist Activity	
	pK _B /pA ₂	
	Guinea Pig Trachea ^a	Guinea Pig Ileum ^b
15	7.4	7.8
20	7.0	7.7
22	7.0	7.8
45	7.2	8.0
47	7.3	8.4
53	8.1	8.6
54	7.9	8.3

^a Ireland SJ, et al., Regulatory Peptides 1988;22:93.

^b McKnight AT, et al., Br J Pharmacol 1991;104:355-60.

As can be seen from the data in Table I above, the compounds of the invention (for example, Ex. 15), is a tachykinin NK₁ receptor antagonist in a number of in vitro NK₁ preparations, i.e., it antagonizes the pharmacological action of the selective NK₁ receptor

-18-

agonist substance-P methylester on these tissues with a pK_B of about 8. Therefore, it could be of use in therapeutic disorders where attenuation of the NK_1 receptor response is an appropriate form of intervention.

These compounds are active in vivo as NK_1 receptor antagonists (see Table II). They antagonize the ability of a NK_1 receptor selective agonist (SPOMe) to induce plasma protein extravasation in the guinea pig bladder. The protocol is similar to that described by Eglezos, et al., Eur J Pharmacol 1991;209:277-279.

TABLE II

Guinea Pig Plasma Extravasation		
Example	ID ₅₀ (mg/kg IV)	
22	0.64	
45	0.61	
47	0.13	
53	0.071	
54	0.051	

The compounds of the invention were also evaluated in three tachykinin binding assays. For the NK_1 receptor measurement of the binding of [^{125} I]-BH]. Substance-P, 0.1 nM to guinea pig cerebral cortex membranes was measured as in Lee CM, et al, Eur J Pharmacol 1986;130:209 and in Br J Pharmacol 1990;99:767.

For the NK_2 receptor measurement of the binding of [^{125} I]-iodohistidyl neurokinin A (0.1 nM) to hamster urinary bladder membrane was measured as described in Buck, Shatzer Life Sci 1988;42:2701.

For the NK_3 receptor measurement of the binding of [^{3} H]-Senktide (2 nM) to a guinea pig cerebral cortex membrane was taken as described in Lee CM, above.

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See Table III below for the binding data for representative compounds of the invention. This table shows in vitro NK₁ receptor binding data for certain compounds of the invention.

5

TABLE III

<u>In Vitro NK₁ Receptor Binding Data</u>		
	<u>Example</u>	<u>Binding IC₅₀ (nM)</u>
10	1	341
	3	218
	4	198
	6	75
	7	306
15	15	36
	16	702
	20	64
	21	27
	22	17
20	23	168
	24	185
	27	306
	29	487
	35	233
25	36	70
	37	290
	38	100
	39	10,000
	40	210
30	41	>10,000
	42	140
	43	100
	44	110
	45	14
35	46	110
	47	10
	48	230
	49	120
	50	120
40	51	230
	52	49
	53	39
	54	19
	55	>1000

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TABLE III (cont.)

Example	Binding IC ₅₀ (nM)
56	3200
57	3400
58	1700
60	>1000

Table II shows the concentration of the compounds of the instant invention which is needed to displace 50% of a specific radioligand ($[^{125}\text{I}]$ Bolton Hunter labeled Substance-P) from tachykinin NK₁ receptor sites in guinea pig cerebral cortex membranes. It is a measure of the affinity these compounds have for this receptor.

As can be seen from the binding data above, several of these compounds have high affinity for the NK₁ receptor.

Compounds of the invention are expected to be useful in treating disorders mediated by tachykinins such as respiratory disorders, especially asthma.

They are also expected to be useful in treating inflammation such as arthritis, gastrointestinal disorders such as colitis, Crohn's disease, and irritable bowel syndrome.

They are further expected to be useful in treating and/or preventing eye diseases such as dry eye and conjunctivitis.

They are further expected to be useful in treating allergies such as rhinitis (common cold), and eczema.

The compounds are expected to treat vascular disorders such as angina and migraine.

They are further expected to be useful in preventing and/or treating diseases of the central nervous system such as schizophrenia.

Scheme I below illustrates the synthesis of Examples 1-8 and 35, CBZ-Trp-OPFP (carbobenzoxy-Trp-

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pentafluorophenyl) was treated with N-methyl benzylamine in EtOAc to give Examples 1-3 when using the appropriate tryptophan stereochemistry (i.e., Example 2 uses R-Trp etc). Examples 4-8 were prepared using the same pentafluorophenyl ester of tryptophan as above but this time it was reacted with RS,R or S α -methylbenzylamine using EtOAc as the solvent. The compound of Example 35 was prepared by reacting the above PFP ester with 3,5 di- CF_3 benzyl alcohol.

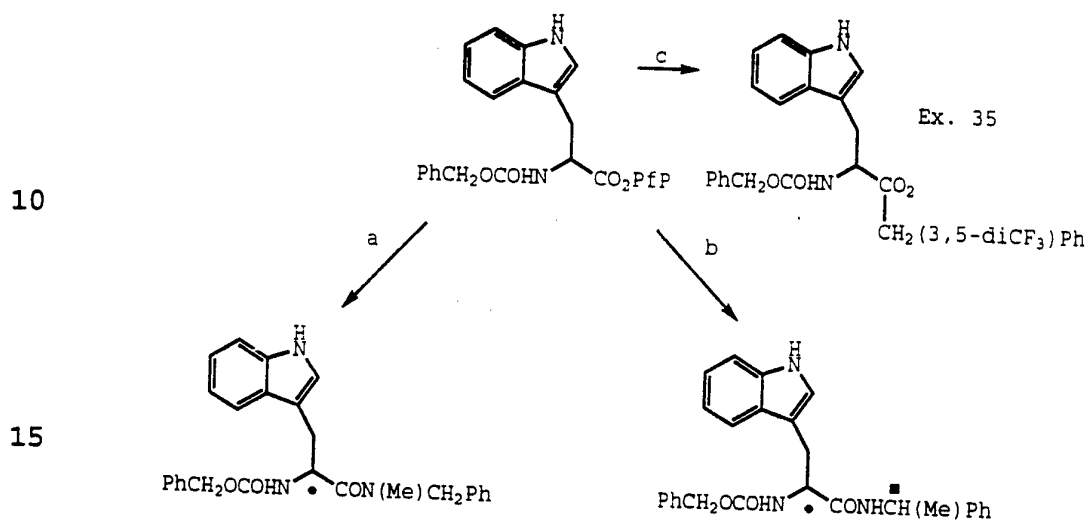
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SCHEME I

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Example Number	•	Example Number	•	■
1	RS	4	RS	RS
2	R	5	R	R
3	S	6	R	S
		7	S	S
		8	S	R

25 Reagents: a) PhCH₂N(Me)H; b) PhCH(Me)NH₂; c) (3,5-diCF₃)PhCH₂OH

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In Scheme II (see below) the versatile intermediate, CBZ-tryptophanyl pentafluorophenyl ester was treated with a variety of arylmethanamines. Example 9 was prepared using 4-chlorobenzylamine in ethyl acetate. Similarly, Example 10 was prepared using 1,2,3,4-tetrahydronaphthyl-1-amine under similar conditions to that for Example 9. Another versatile intermediate shown in Scheme II is the N-terminal unprotected tryptophanyl benzylamide, treatment of this in dry dichloromethane with 1-phenylethanol in the presence of 4-nitrophenylchloroformate yielded Example 11.

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SCHEME II

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Example 9 • = S, Ar = C₆H₄-4Cl

Example 10 • = S, ■ = RS

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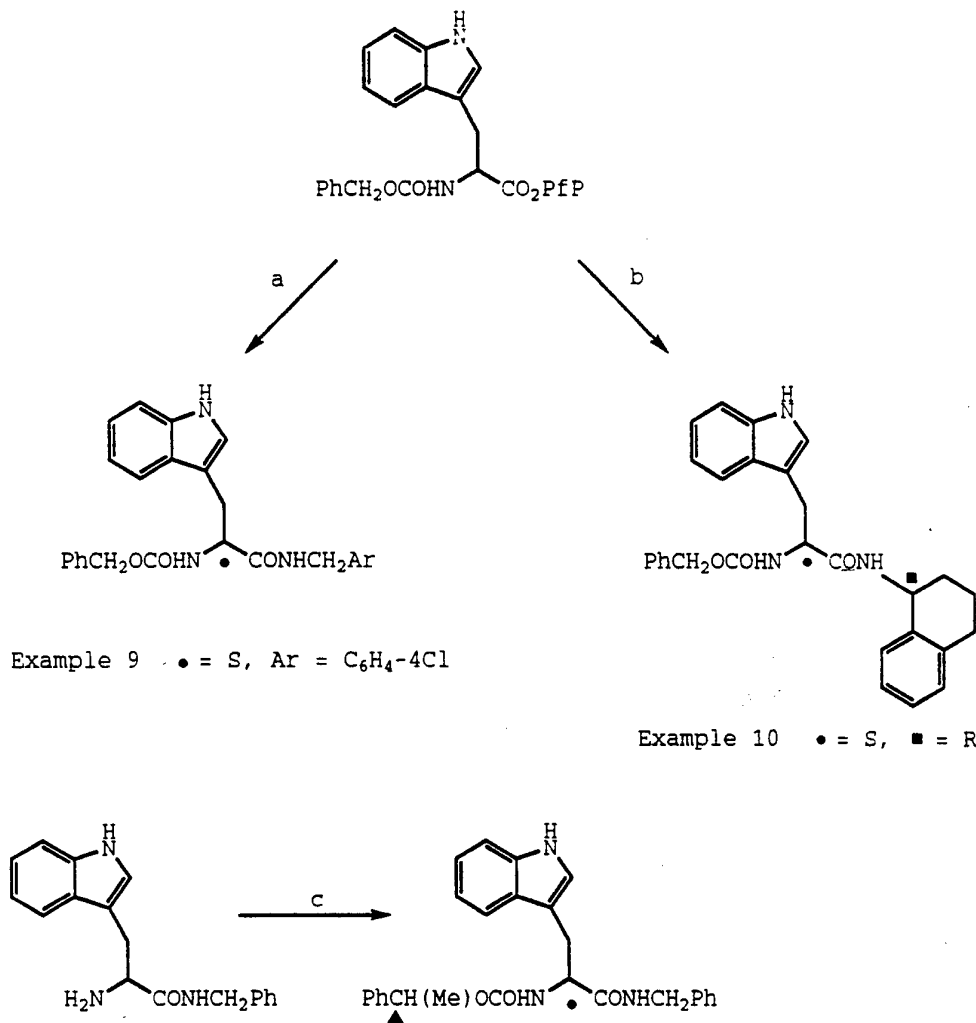
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Example 11 • = RS, ▲ = RS

Reagents: a) ArCH₂NH₂; b) 1,2,3,4-tetrahydronaphthyl-1-amine;
c) 1-phenylethanol and nitrophenylchloroformate

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-25-

Scheme III below outlines the synthesis of Examples 12-18, α -Methyl tryptophan methylester was initially treated with benzylchloroformate in aqueous 1,4-dioxane and in the presence of base to give the

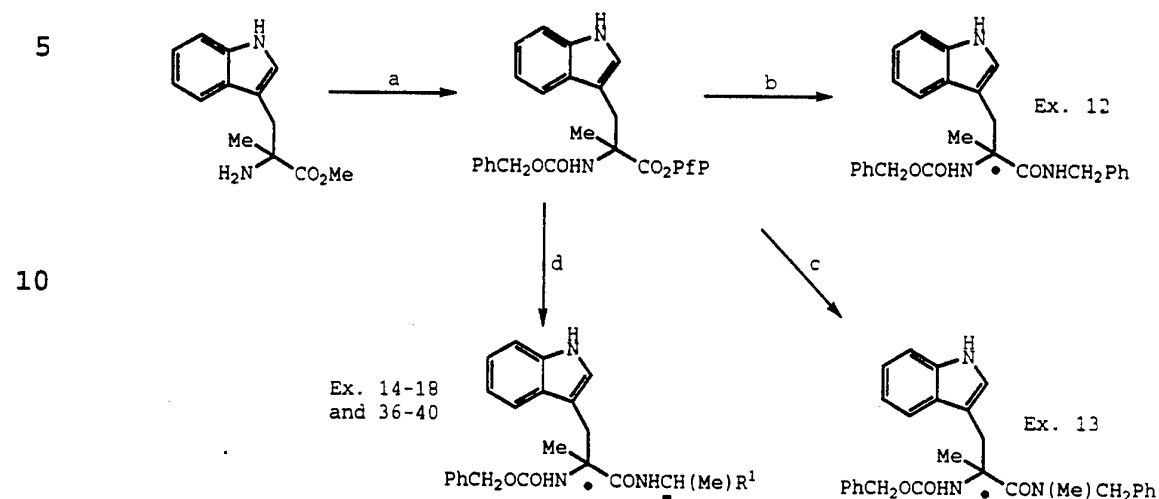
5 CBZ-protected ester. This ester was then saponified with lithium hydroxide to the corresponding acid which was then treated with dicyclohexylcarbodiimide (DCC) in the presence of pentafluorophenol (PFP-OH) to give

10 CBZ- α -methyl tryptophan pentafluorophenyl ester. This active ester was treated with benzylamine to give Example 12. The same ester was also treated with N-methylbenzylamine to yield Example 13.

Examples 14-18, 36, 37, 38, 39, and 40 were prepared again from this PFP-ester using the appropriate amine.

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SCHEME III



Example Number	•	■	R ¹
12	RS	-	-
13	R	-	-
14	R	RS	4ClPh
15	R	S	Ph
16	S	S	Ph
17	S	R	Ph
18	R	R	Ph
36	R	R or S	4-CH ₃ Ph
37	R	R or S	4-CH ₃ Ph
38	R	S	c-Hexyl
39	R	R,S	(3,5-diCF ₃)Ph
40	R	R,S	4-OCH ₃ Ph

Reagents: a) i. PhCH₂OCOCl; ii. LiOH; iii. DCC, Pfp;
 b) PhCH₂NH₂; c) PhCH₂N(Me)H; d) R¹CH(Me)NH₂

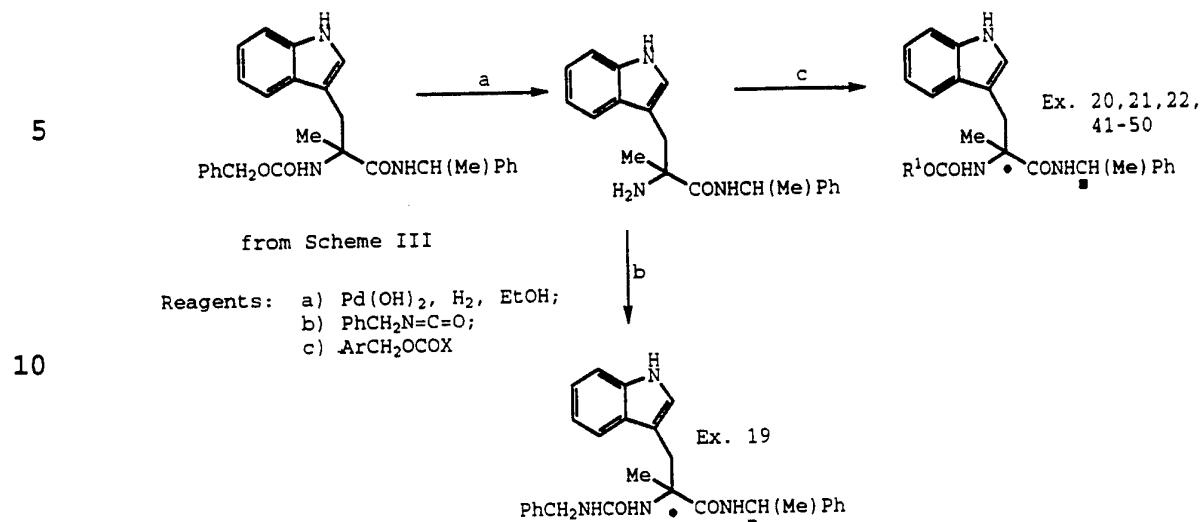
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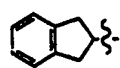
-27-

5 The synthetic routes described in Scheme IV below involve the very useful intermediate α -methyltryptophanyl-1-phenethylamide which can be synthesized from Example 15 by hydrogenation of the CBZ-N-terminal protecting group using Pearlmans catalyst in ethanol. This free amine may then be reacted with the appropriate chloroformate or active carbonate to give Examples 20-22 and 41-54. Example 19 was prepared by the action of the amine on benzyl isocyanate.

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SCHEME IV



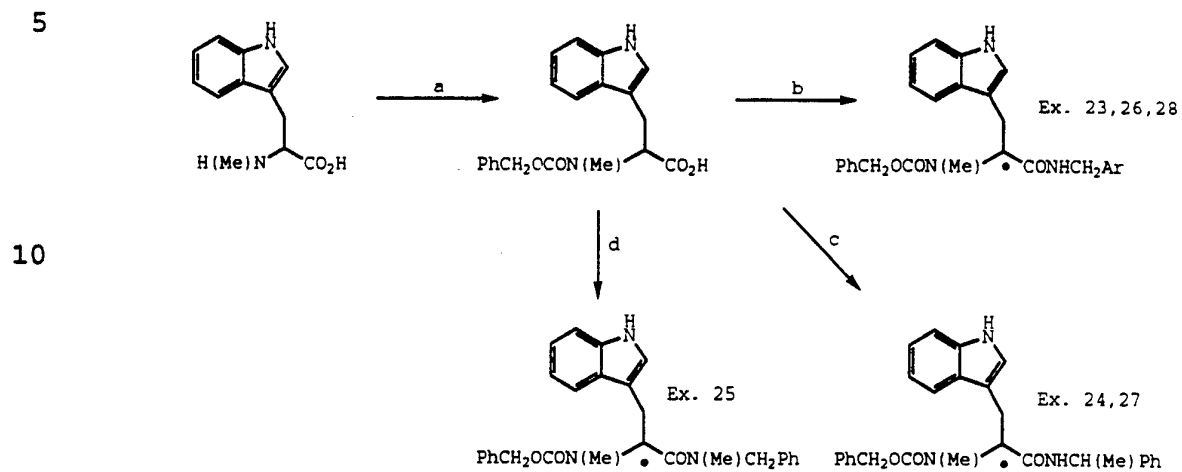
Example Number	•	■	R^1
19	R	S	
20	R	S	4MeO-PhCH ₂
21	R	S	4Cl-PhCH ₂
22	R	S	4CH ₃ -PhCH ₂
41	S	S	4-pyridylCH ₂
42	S	S	3-thienylCH ₂
43	R	S	2-thienylCH ₂
44	R	S	 (R, S)
45	R	S	2-Naphthalene CH ₂
46	R	S	
47	R	S	2-FPhCH ₂
48	R	S	3-FuranylCH ₂
49	R	S	2-FuranylCH ₂
50	R	S	3-FPhCH ₂
51	R	S	4-FPhCH ₂
52	R	S	2,3 diF-PhCH ₂
53	R	S	2,4 diF-PhCH ₂
54	R	S	2,5 diF-PhCH ₂

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As illustrated in Scheme V below, abrine (N-methyl tryptophan) gave benzyloxycarbonyl-abrine when exposed to benzylchloroformate in aqueous 1,4-dioxane in the presence of base. This N-protected abrine was then used to prepare many derivatives having various C-terminal groups. Example 25 was synthesized by preparing an active ester of the abrine derivative with pentafluorophenol and dicyclohexylcarbodiimide then reacting this with N-methylbenzylamine. Similarly, Examples 23, 26, and 28 were prepared by the reaction of this active ester with various aryl amines such as 4-trifluoromethylbenzylamine (Example 26) and 4-chlorobenzylamine (Example 28). Examples 24 and 27 were made by reaction of the same active ester with α -methylbenzylamine (1-phenethylamine).

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SCHEME V



Reagents: a) $\text{PhCH}_2\text{OCOCl}$;
 b) i. DCC, PfP; ii. ArCH_2NH_2 ;
 c) i. DCC, PfP; ii. $\text{PhCH}_2(\text{Me})\text{NH}_2$;
 d) i. DCC, PfP; ii. $\text{PhCH}_2\text{N}(\text{Me})\text{H}$

Example Number	•	■	Ar
23	S	-	Ph
24	S	S	-
25	S	-	-
26	S	-	$\text{C}_6\text{H}_4\text{-4CF}_3$
27	S	R	-
28	S	-	$\text{C}_6\text{H}_4\text{-4Cl}$

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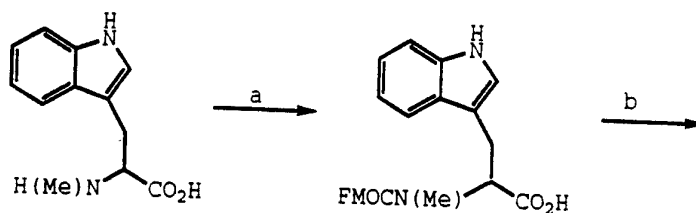
-31-

Methods for derivatizing the N-terminus of the
abrine-containing compounds were carried out via the
methods shown in Scheme VI below. Abrine was treated
with 9-fluorenylmethylchloroformate in aqueous
5 1,4-dioxane with sodium carbonate to give the FMOC-
protected abrine. The active ester of this
(PFP-OH,DCC) was then treated with benzylamine in ethyl
acetate to give the amide which was deprotected under
the standard conditions of 20% piperidine in DMF. This
10 free amine was then treated with 4-chlorobenzyl
chloroformate, 4-trifluoromethylbenzylchloroformate,
and 2,3 dimethoxybenzyl-4'-nitrophenyl carbonate to
give Examples 29, 30, and 31, respectively.

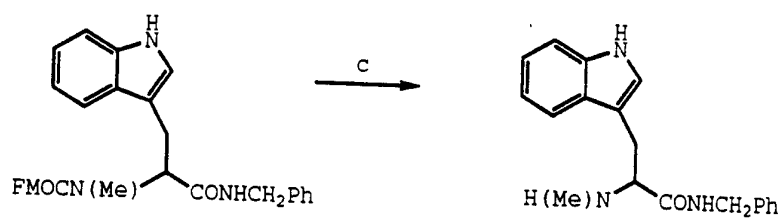
- 32 -

SCHEME VI

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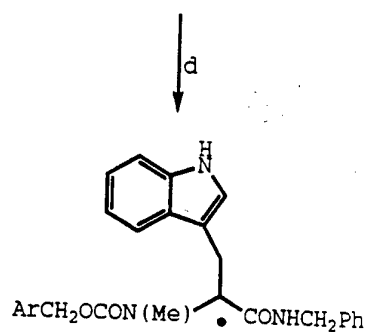
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Example Number	•	Ar
29	S	C ₆ H ₄ -4Cl
30	S	C ₆ H ₄ -4CF ₃
31	S	C ₆ H ₃ -2,3,diMeO

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Reagents: a) Fmoc-Cl;
 b) i. DCC, Pfp; ii. PhCH₂NH₂;
 c) piperidine, DMF;
 d) ArCH₂OCOX

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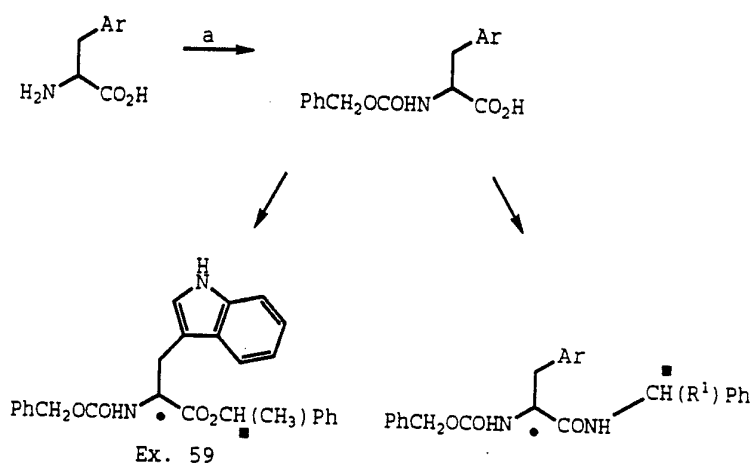
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-33-

5 Examples 32, 33, 34, and 55-59 were prepared according to Scheme VII below. The appropriate amino acids were reacted to give their CBZ-protected derivatives. These compounds were then treated via their active esters with the appropriate amine or alcohol to produce the desired product.

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SCHEME VII



Example Number	•	■	Ar	R ¹
32	R,S	-	(4-Cl)Ph	H
33	R,S	-	(4-Br)Ph	H
34	R,S	-	(3,4-diOH)Ph	H
55	R,S	S	3-Indazole	CH ₃
56	R,S	S	3-((5-F)Indole)	CH ₃
57	R,S	R,S	3(N-Me Indole)	CH ₃
58	R	S	2-Naphthalene	CH ₃
59	R,S	S		

Reagents: a) PhCH₂OCOX; X is a leaving group
 b) i. activation of carboxylic acid; ii. PhCH(R¹)NH₂
 c) DCC, PhCH(CH₃)OH

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Example 60 was prepared by the method shown in Scheme VIII below. The methyl ester of 3-benzothio-phenylalanine was reacted with dibenzylidicarbonate to give the CBZ-protected derivative. This was then
5 treated with base to give the carboxylic acid, which subsequently was activated and reacted with the appropriate amine.

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SCHEME VIII

EXAMPLE 60

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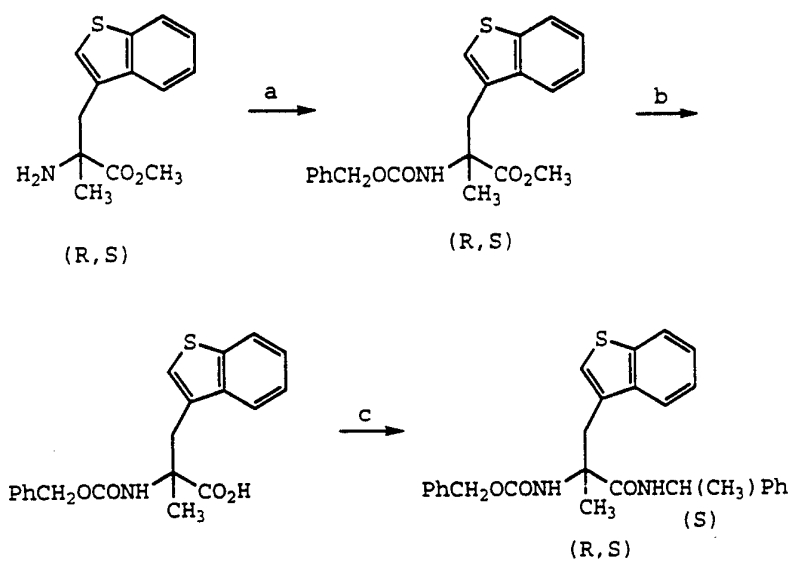
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Reagents: a) $(\text{PhCH}_2\text{OCO})_2$; b) LiOH;
c) i. HOBt, DCC, ii. (S)- $\text{PhCH}(\text{CH}_3)\text{NH}_2$

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5 Example 61 was prepared by the method shown in Scheme IX below. CBZ α -Me tryptophan was activated to give the pentafluorophenyl ester (described in Scheme III) and reacted with the appropriate amino alcohol. This was then cyclized with Lawesson's reagent to give product.

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SCHEME IX

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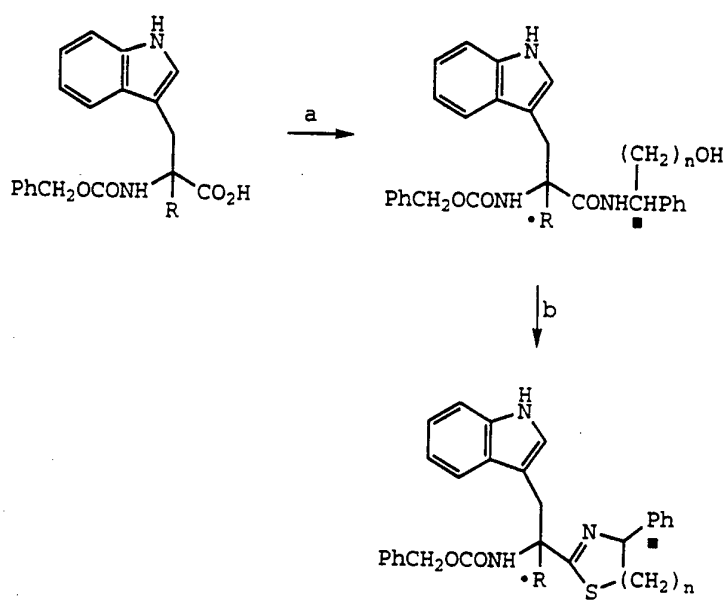
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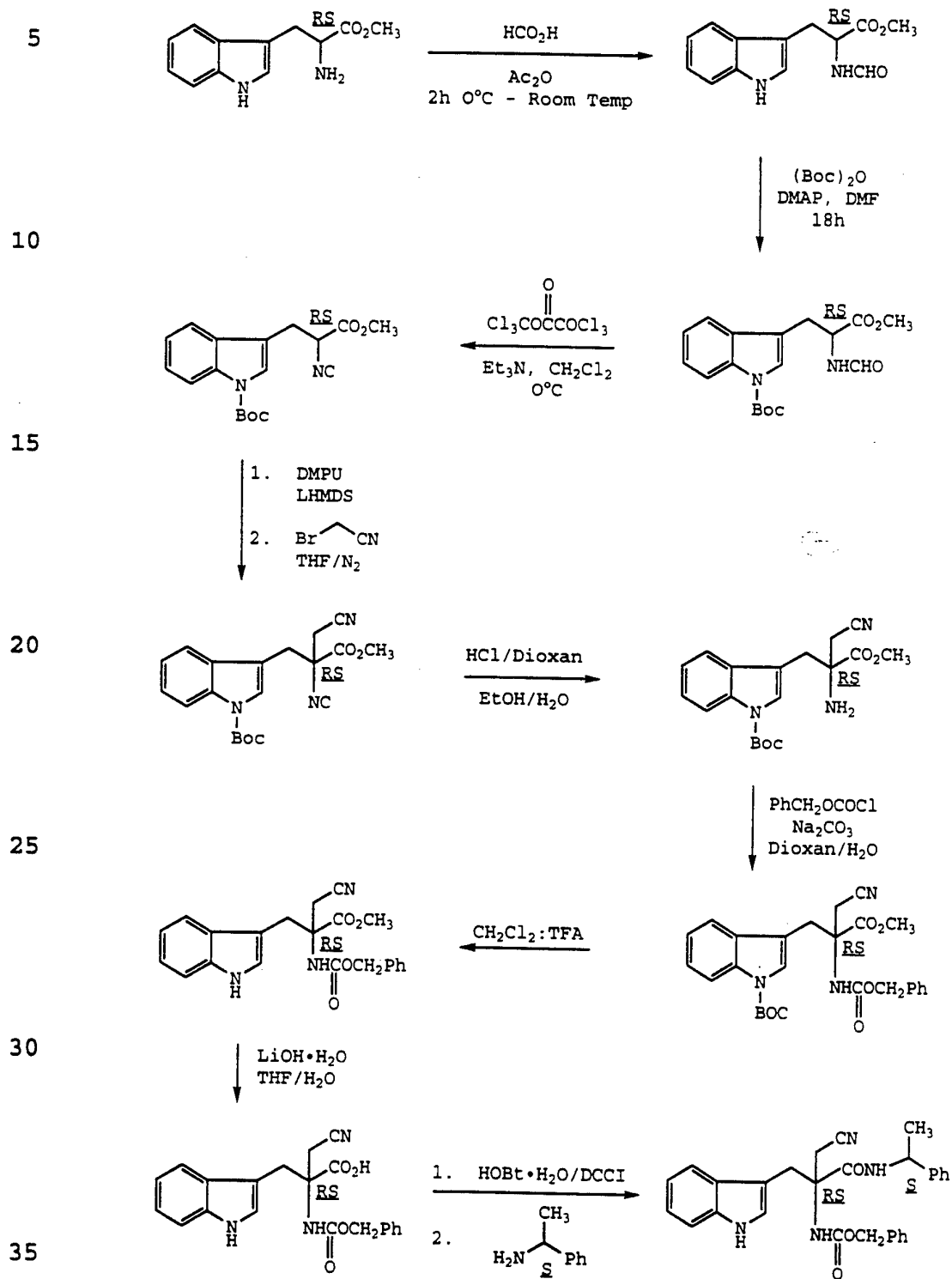
Example Number	R	n	•	■
61	CH_3	1	R	R

Reagents: a) i. activation of acid; ii. amino alcohol
b) Lawesson's reagent

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Example 62 was prepared by the method shown in Scheme X below. The methyl ester of tryptophan was converted to the N-formyl derivative which was subsequently treated with (BOC)₂O to protect the indole nitrogen. The isonitrile was then formed and alkylated with bromoacetonitrile. The resulting product was treated with hydrochloric acid followed by benzylchloroformate to give the urethane. Next, the BOC-group was removed and the ester hydrolysed with lithium hydroxide. The acid was then activated and subsequently condensed with α -methylbenzylamine.

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SCHEME X
(Example 62)

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For preparing pharmaceutical compositions from the compounds of this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets, and suppositories.

A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, or tablet disintegrating agents; it can also be an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

For preparing suppository preparations, a low-melting wax such as a mixture of fatty acid glycerides and cocoa butter is first melted and the active ingredient is dispersed therein by, for example, stirring. The molten homogeneous mixture is then poured into convenient sized molds and allowed to cool and solidify.

The powders and tablets preferably contain 5% to about 70% of the active component. Suitable carriers are magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low-melting wax, cocoa butter, and the like.

The compounds of the invention include solvates, hydrates, pharmaceutically acceptable salts, and polymorphs (different crystalline lattice descriptors) of the compounds of Formula I.

The compounds of the present invention can have multiple chiral centers in the above Formula I

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depending on their structures. In particular the compounds of the present invention may exist as diastereomers, mixtures of diastereomers, or as the mixed or the individual optical enantiomers. The present invention contemplates all such forms of the compounds. The mixtures of diastereomers are typically obtained as a result of the reactions described more fully below. Individual diastereomers may be separated from mixtures of the diastereomers by conventional techniques such as column chromatography or repetitive recrystallizations. Individual enantiomers may be separated by conventional methods well known in the art such as conversion to a salt with an optically active compound, followed by separation by chromatography or recrystallization and reconversion to the nonsalt form.

Where it is appropriate to form a salt, the pharmaceutically acceptable salts are acetate, benzenesulfonate, benzoate, bicarbonate, bitartrate, bromide, calcium acetate, camsylate, carbonate, chloride, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate, mandelate mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, pamoate (embonate), pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, sulfate, tannate, tartrate, theoclate, triethiodide, benzathine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine, procaine, aluminum, calcium, lithium, magnesium, potassium, sodium, and zinc.

Cyclodextrin is one suitable inclusion in a pharmaceutical preparation.

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5 The term "preparation" is intended to include the formulation of the active component with encapsulating material as a carrier providing a capsule in which the active component (with or without other carriers) is surrounded by a carrier which is thus in association with it. Similarly, cachets are included.

Tablets, powders, cachets, and capsules can be used as solid dosage forms suitable for oral administration.

10 Liquid form preparations include solutions, suspensions, and emulsions. Sterile water or water-propylene glycol solutions of the active compounds may be mentioned as an example of liquid preparations suitable for parenteral administration. Liquid
15 preparations can also be formulated in solution in aqueous polyethylene glycol solution.

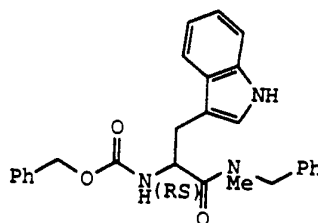
Aqueous solutions for oral administration can be prepared by dissolving the active component in water and adding suitable colorants, flavoring agents,
20 stabilizers, and thickening agents as desired. Aqueous suspensions for oral use can be made by dispersing the finely divided active component in water together with a viscous material such as natural synthetic gums, resins, methyl cellulose, sodium carboxymethyl
25 cellulose, and other suspending agents known to the pharmaceutical formulation art.

Preferably the pharmaceutical preparation is in unit dosage form. In such form, the preparation is divided into unit doses containing appropriate
30 quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of the preparation, for example, packeted tablets, capsules, and powders in vials or ampoules. The unit dosage form can also be a
35 capsule, cachet, or tablet itself, or it can be the appropriate number of any of these packaged forms.

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EXAMPLE 1

(Scheme I)

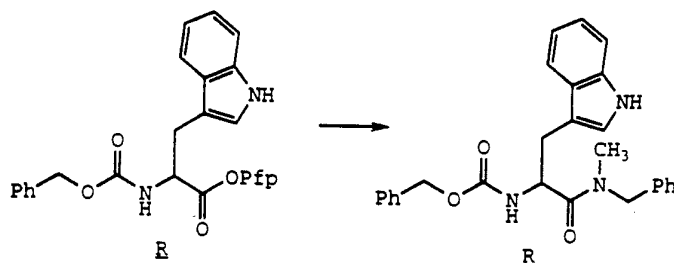


10 N-Methylbenzylamine (0.17 mL, 0.00126 mol) was added to a solution of CBZ-RS-Tryptophan pentafluorophenyl ester (0.64 g, 0.00126 mol) in EtOAc (5 mL) and the residue stirred at room temperature for 2 hours. The solvent was removed in vacuo and the residue dissolved in EtOAc (50 mL) and washed with 2 M
15 hydrochloric acid (2 x 20 mL), water (2 x 10 mL), brine (20 mL), dried (MgSO₄) and the solvent evaporated in vacuo. The residue was purified via column chromatography eluting with dichloromethane:methanol (9:1) to give the product as a white solid (0.31 g, 55%) mp 51-55°C;
20 IR (film): 3301 (NH, urethane), 1708 (C = O, urethane), 1636 (C = O, amide), 1496, 1342, and 1232 cm⁻¹;
25 NMR (CDCl₃): 2.51 and 2.74 (3H, s, CH₃N); 3.20 (2H, d, $\underline{J}$ = 7 Hz, Trp-CH₂); 4.0-4.4 (2H, 2 x m, ArCH₂N amide ROT); 4.9-5.1 (3H, m, ArCH₂O, α CH); 5.83 and 5.89 (1H, d, $\underline{J}$ = 8 Hz, NH carbamate amide ROT); 6.7-7.7 (15H, m, aromatics); 8.2 and 8.3 (1H, s, NH, indole);
30 MS m/e (CI) 442 (M⁺+1).

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EXAMPLE 2

(Scheme I)



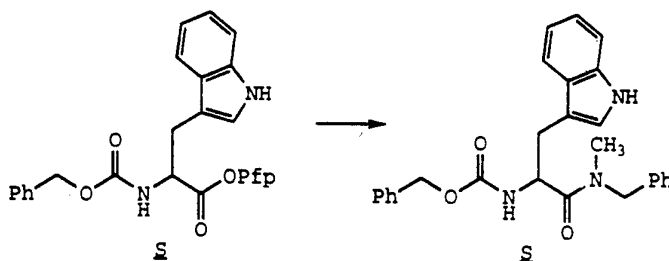
Method as described for Example 3, Scheme I, but using CBZ-R-Tryptophan pentafluorophenyl ester. Yield (0.08 g, 35%); mp 50-53°C; $[\alpha]_D^{23}$ -27.2 (C = 0.25, MeOH);

IR (film): 3296-2928, 1712 (urethane co), 1636 (amide I) and 1525 cm^{-1} (amide II);

NMR (DMSO- d_6): δ 2.75 (3H, s, CH_3); 3.01 (1H, d, d, J = 7.5 and 13.9 Hz, one of Trp βCH_2); 4.44 (2H, s, CH_2Ph); 4.54 (1H, m, αCH), 5.01 (2H, s, PhCH_2O); 6.97-7.37 (15H, m, aromatics); 7.57 (1H, d, J = 7.7 Hz, urethane NH); 10.7 (1H, s, indole NH); MS m/e (CI) 442 $[\text{M}^+]$.

EXAMPLE 3

(Scheme I)



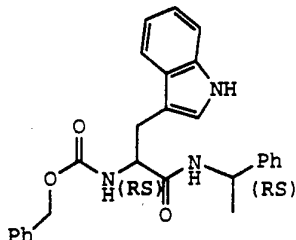
CBZ-L-tryptophan pentafluorophenyl ester (0.50 g, 1 mmol) was prepared in situ and reacted with benzylmethylaniline (0.13 mL, 1 mmol) in ethylacetate

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(5 mL). The reaction mixture was stirred overnight at room temperature then washed with diluent HCl (1 x 10 mL), water (4 x 10 mL), and dried over MgSO_4 . Removal of the solvent in vacuo resulted in a clear oil which was chromatographed to give the product (0.175 g, 40%); mp 48-50°C; $[\alpha]_D^{23} = +30.4$ ($c = 0.25$, MeOH); IR (film): 3305-2927, 1710 (urethane CO), 1635 (amide I) and 1530 cm^{-1} (amide II); NMR (DMSO-d_6 , 1340K): δ 2.50 (3H, s, CH_3); 3.01 (1H, d.d, $J = 7.3$ and 13.8 Hz, one of βCH_2); 4.43 (2H, s, NCH_2Ph); 4.72 (1H, m, $\text{Trp}\alpha\text{CH}$); 5.00 (2H, s, OCH_2Ph); 7.02-7.35 (15H, m, aromatics); 7.57 (1H, b, urethane NH); 10.65 (1H, s, indole NH); MS m/e (CI) 442 $[\text{M}^+]$.

EXAMPLE 4

(Scheme I)



(RS) α -Methylbenzylamine (0.128 mL, 0.001 mol) was added to a solution of (CBZ-RS-tryptophan pentafluorophenyl ester (0.533 g, 0.001 mol) in EtOAc (15 mL) and the mixture stirred at room temperature for 15 min. The solvent was removed in vacuo and the residue dissolved in EtOAc (50 mL) and washed with 2 M hydrochloric acid (2 x 20 mL), water (2 x 10 mL), brine (20 mL), dried (MgSO_4) and the solvent evaporated in vacuo. The residue was purified via column chromatography eluting with hexane:ethyl acetate (8:2)

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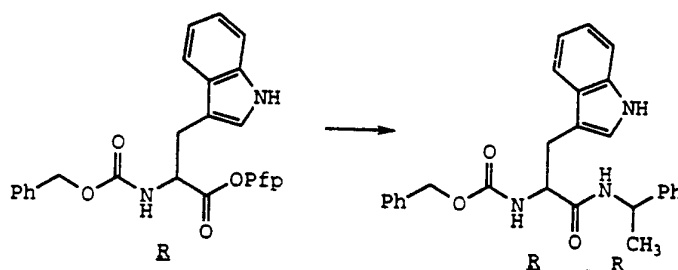
to give Example 4 Scheme I as a white solid (0.33 g, 76%) mp 59-62°C;

NMR: (CD₃SOCD₃): δ 1.23 and 1.34 (3H, d, J = 7 Hz, CHCH₃); 2.8-3.2 (2H, m, IndCH₂); 4.3 (1H, m, CH); 4.9 (3H, m, ArCH₂O and NHCH); 6.9-7.4 (15H, aromatics and NH carbamate); 7.63 (1H, d, J = 8 Hz, 4H-indole); 8.33 and 8.41 (1H, d, J = 8 Hz NH amide); 10.8 (1H, s, indole NH);

MS m/e (CI) 442 (M⁺+H).

EXAMPLE 5

(Scheme I)



CBZ-DL Tryptophan pentafluorophenyl ester (0.25 g, 0.5 mmol) was prepared in situ, dissolved in ethylacetate (2.5 mL) and (R)-(+)- α -methylbenzylamine (0.06 mL, 0.5 mmol) was added. The reaction mixture was stirred at room temperature until no starting material remained. The white precipitate was collected by filtration and recrystallized from ethylacetate to give Example 5 Scheme I (0.10 g, 44%); mp 169-170°C; $[\alpha]_D^{23}$ = +12.8° (c = 0.5, MeOH);

IR (film): 3306, 1705 (urethane co), 1657 (amide I), and 1531 cm⁻¹ (amide II);

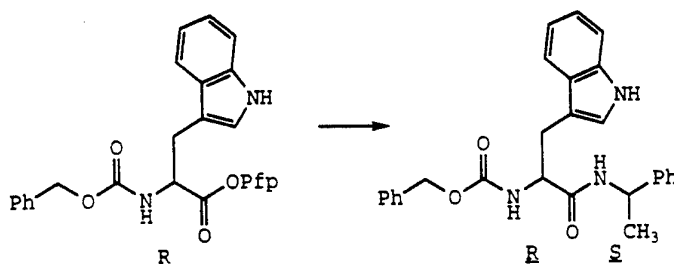
NMR (DMSO-d₆): δ 1.35 (3H, d, J = 6.7 Hz, CH₃); 2.87 (1H, d.d, J = 9.2 and 14.3 Hz, one of Trp β CH₂); 3.06 (1H, d.d, J = 4.8 and 14.3 Hz, one of Trp β CH₂); 4.36 (1H, m, CH(CH₂Ph), 4.90-4.96 (3H, m, CH₂ Ph, α CH); 6.94-7.35 (15H, m, aromatics); 7.63 (1H, d, J = 7.8 Hz,

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urethane NH); 8.41 (1H, d, $J = 7.8$ Hz, amide NH); 10.8 (1H, s, indole NH);
MS m/e (CI) 442 [M^+].

EXAMPLE 6

(Scheme I)

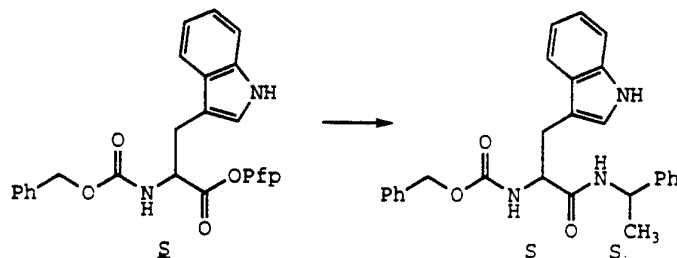


Method as described for Example 5, Scheme 1, but using (S)-(-)- α -methylbenzylamine. Yield (0.09 g, 21%); mp 160-161°C;
 $[\alpha]_D^{23} = -26.0$ ($c = 0.5$, MeOH);
 IR (film): 3330, 1709 (urethane co), 1658 (amide I) and 1514 cm^{-1} (amide II);
 NMR (DMSO- d_6): δ 1.23 (3H, d, $J = 6.8$ Hz, CH_3); 2.95 (1H, d.d, $J = 9.4$ and 14.3 Hz, one of Trp βCH_2); 3.08 (1H, d.d, $J = 5.4$ and 14.3 Hz, one of Trp βCH_2); 4.32 (1H, m, $\text{CH}(\text{CH}_3)\text{Ph}$), 4.86-4.94 (3H, m, PhCH_2 , αCH); 6.95-7.34 (15H, m, aromatics); 7.63 (1H, α , $J = 7.7$ Hz, urethane NH); 8.33 (1H, d, $J = 7.5$ Hz, amide NH); 10.8 (1H, s, indole NH);
 MS m/e (CI) 442 [M^+].

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EXAMPLE 7

(Scheme I)



Example 5, Scheme I, but using (S)-(-)- α -methylbenzylamine method as described for Example 5, Scheme I. Recrystallization from ethyl acetate gave (0.057 g, 13%); mp 168-170°C;

15 $[\alpha]_D^{23} = -11.6$ (c = 0.5, MeOH);

IR (film): 3294, 1704 (urethane CO), 1656 (amide I) and 1536 cm^{-1} (amide II);

20 NMR (DMSO- d_6): δ 1.35 (3H, d, $J = 6.9$ Hz, CH_3); 2.86 (1H, d.d, $J = 9.2$ and 14.3 Hz, one of βCH_2); 3.06 (1H, d.d, $J = 4.8$ and 14.3 Hz, one of βCH_2); 4.36 (1H, m, $\text{CH}(\text{CH}_3)\text{Ph}$); 4.90-4.96 (3H, m, PhCH_2 , Trp αCH);

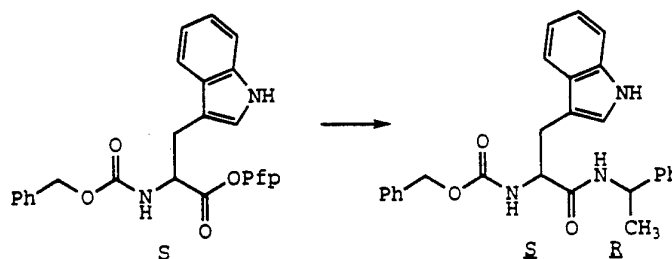
6.94-7.35 (15H, m, aromatics); 7.63 (1H, d, $J = 7.9$ Hz, urethane NH); 8.41 (1H, d, $J = 7.7$ Hz, amide NH); 10.8 (1H, s, indole NH);

25 MS m/e (CI) 442 $[\text{M}^+]$.

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EXAMPLE 8

(Scheme I)

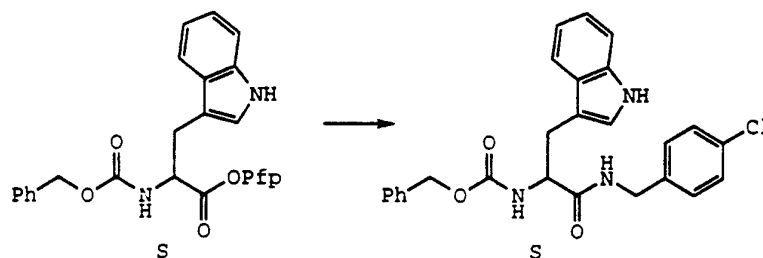


CBZ-S-Trp pentafluorophenyl ester (0.50 g, 1 mmol)
 was prepared in situ, then dissolved in ethyl acetate
 and (R)-(+)- α -methylbenzylamine (0.13 mL, 1 mmol) was
 added. The reaction mixture was stirred at room
 temperature until no starting material remained. The
 white precipitate was collected by filtration and
 purified by chromatography to give the product
 (0.077 g, 17%); mp 160-163°C;
 $[\alpha]_D^{23} = +24.4$ (c = 0.5, MeOH);
 IR (film): 3307, 1704 (urethane CO), 1657 (amide I)
 and 1517 cm^{-1} (amide II);
 NMR (DMSO- d_6): δ 1.24 (3H, d, $J = 7.0$ Hz, CH_3); 2.95
 (1H, d.d, $J = 9.4$ and 14.3 Hz, one of βCH_2); 3.08 (1H,
 d.d, $J = 5.4$ and 14.3 Hz, one of βCH_2); 4.32 (1H, m,
 $\text{CH}(\text{CH}_3)\text{Ph}$); 4.86-4.94 (3H, m, PhCH_2 , Trp αCH);
 6.95-7.34 (15H, m, aromatics); 7.63 (1H, d, $J = 7.7$ Hz,
 urethane NH); 8.32 (1H, d, $J = 7.8$ Hz, amide NH); 10.8
 (1H, s, indole NH);
 MS m/e (CI) 442 M^+ .

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EXAMPLE 9

(Scheme II)



Method as described for Example 3, Scheme I, but using 4-chlorobenzylamine. Yield (0.05 g, 11%); mp 177-179°C;

$[\alpha]_D^{23} = +10.8$ ($c = 0.5$, MeOH);

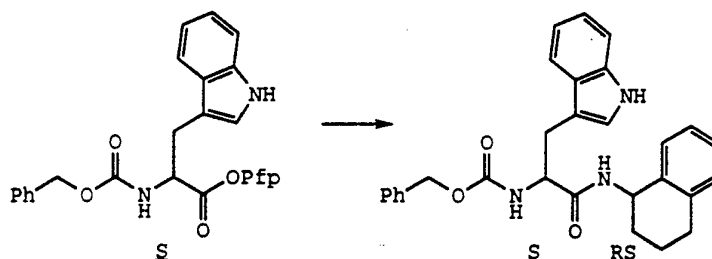
IR (film): 3291, 1704 (urethane CO), 1658 (amide II), and 1535 cm^{-1} (amide I);

NMR (DMSO- d_6): δ 2.95 (1H, d.d, $J = 9.1$ and 14.5 Hz, one of Trp βCH_2); 3.13 (1H, d.d, $J = 5.3$ and 14.5 Hz, one of Trp βCH_2); 4.20-4.36 (3H, m, αCH , NHCH_2); 4.97 (2H, s, PhCH_2O); 6.94-7.46 (14H, m, aromatics); 7.62 (1H, d, $J = 7.8$ Hz, urethane NH); 8.52 (1H, bt, amide NH); 10.8 (1H, s, indole NH);

MS m/e (CI) 462 M^+ .

EXAMPLE 10

(Scheme II)

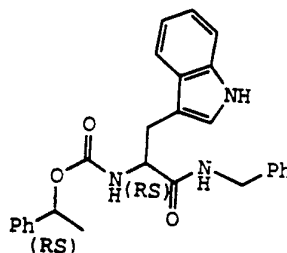


Method as described for Example 3, Scheme I; but using 1,2,3,4-tetrahydro-1-naphthylamine. Yield (0.298 g, 64%); mp 73-76°C;

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IR (film): 3298-2863, 1707 (urethane CO), 1651
(amide I) and 1538 cm^{-1} (amide II);
NMR (DMSO-d_6): δ 1.52-1.87 (4H, m, CH_2CH_2); 2.70 (2H,
m, $\text{CH}_2\text{CH}_2\text{Ph}$); 2.91-3.16 (2H, m, Trp βCH_2); 4.32 (1H, m,
5 αCH); 4.96 (3H, m, PhCH_2 , NHCHPh); 6.74-7.37 (14H, m,
aromatics); 7.63 (1H, m, urethane NH); 8.21 (1/2H, d,
 $J = 9.4$ Hz, amide NH); 8.32 (1/2H, d, $J = 8.8$ Hz, amide
NH); 10.81, 10.79 (1H, 2 x s, indole NH);
MS m/e (CI) 468 [M^+].

EXAMPLE 11
(Scheme II)



A solution of (RS) sec-phenethyl alcohol (2 g,
0.0163 mol) and dry pyridine (1.3 mL, 0.0163 mol) in
dry dichloromethane (10 mL) was cooled to 0°C. A
solution of 4-nitrophenyl chloroformate (3.28 g,
25 0.0163 mol) in dry dichloromethane (25 mL) was added
dropwise over 15 minutes and the resulting solution
stirred at room temperature for 15 hours. The solvent
was removed in vacuo (the temperature being kept below
30°C) and ether (50 mL) was added and the precipitate
30 was removed by filtration. The solvent was removed
in vacuo below 30°C to give the crude mixed carbonate,
 ν_{max} 1765 cm^{-1} ($c = 0$), which was used without further
purification.

R,S-Tryptophan benzylamide (0.5 g, 0.0018 mol) and
35 triethylamine (0.18 mL, 0.0018 mol) were dissolved in
dry DMF (5 mL). A solution of the mixed carbonate

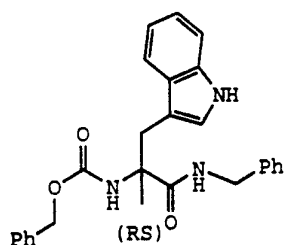
-53-

(0.52 g, 0.0025 mol) in DMF (5 mL) was added dropwise over 5 minutes, there was an immediate yellow coloration upon addition of the mixed carbonate, and the yellow solution was stirred at room temperature for 5 hours. The reaction mixture was poured into water (50 mL) and extracted with EtOAc (3 x 10 mL). The organic phase was washed with dilute aqueous NaOH (approx. 1 M) until the disappearance of the yellow color (approx. 5 x 20 mL) and then with saturated aqueous citric acid (5 x 20 mL), water (10 mL), brine (20 mL), dried (MgSO_4), and the solvent removed in vacuo. The crude product was purified by column chromatography, eluting with dichloromethane:ethanol (9:1) to give the urethane, Example 11, Scheme II, as a white solid (0.61 g, 77%); mp 128-132°C; IR (film): 3317 (NH), 1706 (C = O, carbamate), 1659 (C = O, amide), 1497, 1456, 1378, and 1355 cm^{-1} ; NMR (DMSO-d_6): 1.35 and 1.4 (3H, d, $J = 7$ Hz, CHCH_3); 2.8-3.2 (2H, m, IndCH_2), 4.3 (3H, m, CONHCH_2Ph , CH); 5.1 (1H, m, PhCHO); 6.9-7.3 (15H, aromatics and carbamate NH); 7.6 (1H, m, 4H-indole); 8.45 (1H, m, amide NH); 10.7 (1H, m, indole NH); MS m/e (CI): 442 ($\text{M}^+ + \text{H}$).

25

EXAMPLE 12
(Scheme III)

30



35

Benzyl chloroformate (0.85 mL, 0.005 mol) was added in one portion to a vigorously stirred suspension of R,S- α -Me-Trp methyl ester (1 g, 0.0043 mol) and

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potassium carbonate (2 g, 0.015 mol) in dioxane (15 mL) and water (1 mL). The mixture was stirred at room temperature for 2 hours, after which time t.l.c. analysis indicated the consumption of starting material. The solvent was removed in vacuo. The residue was treated with 2 M hydrochloric acid (10 mL), water (40 mL), and extracted with EtOAc (3 x 20 mL). The organic phase was washed with water (2 x 20 mL), brine (10 mL), dried (MgSO_4), and the solvent removed in vacuo to give the N-protected amino ester as an off-white solid (1.39 g, 87%) which was used in the next reaction without further purification.

ν_{max} (film): 3345 br (NH), 1718 br (C = O, ester and carbamate) cm^{-1} . δ (CDCl_3): 1.63 (3H, s, $\alpha\text{-CH}_3$); 3.60 (5H, br.m, OCH_3 and $\text{CH}_2\text{-Ind}$); 5.08 (2H, m, ArCH_2O); 5.5 (1H, br.s, NH urethane); 6.8-7.5 (11H, aromatics); 8.3 (1H, br.s, NH indole).

A-mixture of this ester (1.49 g, 0.004 mol) and lithium hydroxide monohydrate (0.84 g, 0.02 mol) in THF (15 mL) and water (5 mL) was stirred vigorously at room temperature for 15 hours. The solution was extracted with EtOAc (3 x 10 mL) and the organic phase discarded. The aqueous phase was acidified with 2 M hydrochloric acid (approx. 20 mL) and extracted with EtOAc (3 x 20 mL). The organic phase was washed with water (20 mL), brine (20 mL), dried (MgSO_4), and the solvent removed in vacuo to give the acid (Scheme III) as a light brown oil (1.31 g, 88%) which was used in the next step without further purification.

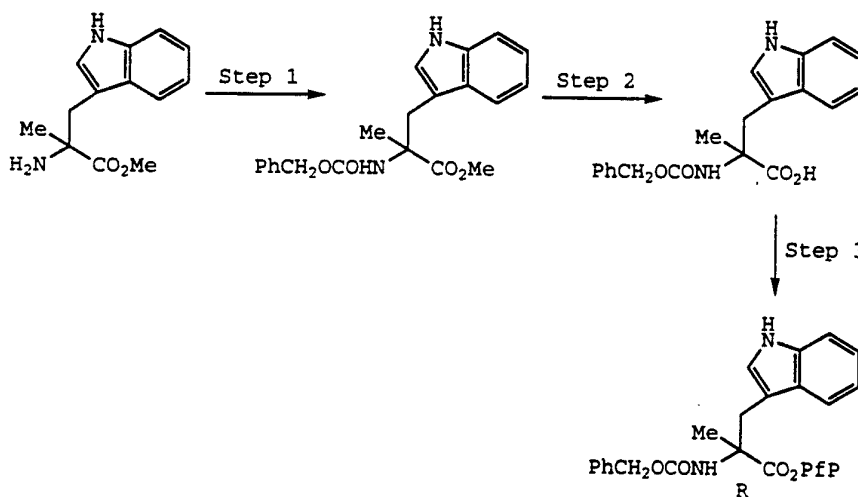
ν_{max} (film): 3389 (OH), 1770 (C = O, acid), and 1708 (C = O, carbamate) cm^{-1} .

This crude carboxylic acid (1.1 g, 0.003 mol), *N,N'*-dicyclohexylcarbodiimide (DCC) (0.618 g, 0.003 mol) and pentafluorophenol (PFP) (0.6 g, 0.0033 mol) were dissolved in EtOAc (20 mL) and the reaction mixture stirred at room temperature for

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1 hour. The mixture was filtered to remove the white solid and benzylamine (0.35 mL, 0.0033 mol) was added and the mixture stirred for 10 hours at room temperature. The solvent was removed in vacuo and the crude product was purified by column chromatography, eluting with dichloromethane:methanol (8:2), giving the benzamide, Example 12, Scheme III, as a white solid (0.97 g, 73%); mp 117-119°C; IR (film): 3337 (NH), 1709 (C = O, carbamate), 1657 (C = O, amide), 1517, 1456, and 1352 cm⁻¹; NMR (DMSO-d₆): 1.37 (3H, s, α-Me); 3.33 (2H, m, Ind-CH₂); 4.28 (2H, d, J = 5 Hz, NCH₂Ph); 5.04 (2H, m, Ph-CH₂O); 6.9-7.5 (16H, aromatics and carbamate); 8.2 (1H, br.s, amide NH); 10.83 (1H, s, indole NH); MS m/e (CI); 442 (M⁺+H).

EXAMPLE 13
(Scheme III)



Step 1

A solution of *R*-α-methyl tryptophan methylester (37.16 g, 160.0 mmol) in dry THF (800 mL) and triethylamine (19.43 g, 192 mmol) was cooled to 0°C and treated with benzylchloroformate (30.03, 176 mmol) in dry THF (200 mL) dropwise. This was allowed to warm to

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room temperature slowly, then the solvent removed in vacuo. The residue was redissolved in EtOAc (500 mL), washed with H₂O (500 mL), 2N HCl (500 mL), saturated NaHCO₃ solution (500 mL), then H₂O (500 mL).
5 The organic phase was dried over MgSO₄, filtered, and evaporated to dryness in vacuo. The residue was purified by silica gel chromatography using 60% Et₂O in n-hexane as eluant to give the product.
[α]_D²⁰ = +31.7° (c = 1, MeOH).

10

Step 2

The CBZ- α Me-R-tryptophan methyl ester (69.15 g, 150 mmol) was dissolved in THF (800 mL), cooled to 0°C, and treated with LiOH (30 g in 250 mL H₂O). MeOH was
15 added (150 mL) and the mixture stirred for 3 hours. The solvent was removed in vacuo. The residue was diluted with H₂O (500 mL) and extracted with CH₂Cl₂ (2 x 300 mL). The aqueous phase was acidified using 2 M citric acid and extracted with CH₂Cl₂ (2 x 500 mL).
20 The organic phase was washed with water, dried (MgSO₄), and filtered and evaporated to dryness to give the crude acid, 57.5 g (2:1 mix acid:ester). This crude material was used in Step 3.

25 Step 3

The crude carboxylic acid from Step 2 above was redissolved in EtOAc (320 mL) and treated with pentafluorophenol (21 g, 114 mmol), followed by the dropwise addition of a solution of N,N'-dicyclo-
30 hexylcarbodiimide (23.5 g, 114 mmol) in EtOAc (150 mL). This was stirred 18 hours at room temperature. The reaction mixture was then filtered, and the filtrate evaporated to dryness. The solid residue was redissolved in CH₂Cl₂ (200 mL) and absorbed onto
35 silica, and purified by chromatography using 50% EtOAc

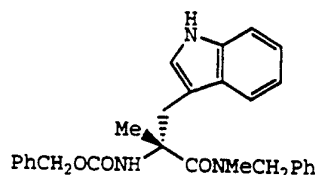
-57-

in *n*-hexane to give the product 49.77 g (64%) from α -methyl-*R*-tryptophan methylester;

IR (film): 1785, 1709, and 1520 cm^{-1} ;

5 NMR (CDCl_3): δ 1.72 (3H, s); 3.44 (1H, d, $J = 14.7$ Hz); 3.66 (1H, d, $J = 14.7$ Hz); 5.15 (2H, m,); 5.22 (1H, br.s); 6.97 (1H, d, $J = 2$ Hz); 7.09 (1H, t, $J = 7.5$ Hz); 7.22 (1H, t, $J = 8.0$ Hz, 7.34 (6H, m); 7.58 (1H, d, $J = 7.9$ Hz); 8.11 (1H, br.s).

10



15

A solution of CBZ- α -methyl-*R*-tryptophan pentafluorophenyl ester (250 mg, 0.50 mmol) in EtOAc (50 mL) was treated with *N*-benzylmethylamine (900 mg, 7.40 mmol) and stirred at room temperature for 18 hours. This mixture was washed with 2N HCl (50 mL), then H_2O (50 mL). The organic phase was dried (MgSO_4),

20

filtered, and evaporated to give a crude residue which was purified by reverse-phase chromatography using 50% MeOH in H_2O as eluant to give the product as a white foam (40 mg, 18%); mp 64-68°C (MeOH/ H_2O);

25

IR (nujol mull): 1703 and 1620 cm^{-1} ;

NMR ($\text{DMSO}-d_6$): δ 1.30 (3H, s); 2.90 (3H, brs); 3.20 (1H, d, $J = 14$ Hz); 3.50 (1H, d, $J = 14$ Hz); 4.60 (2H, br); 5.00 (2H, br); 6.8-7.6 (16H, m); 10.9 (1H, br.s); MS (CI) m/e 456 (11, $\text{M}^+ + \text{H}$), 335 (30), 304 (48) 263 (4.5), 91 (100);

30

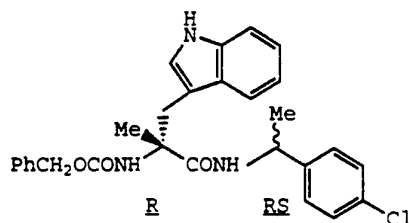
Analysis calculated for C, H, N; $\text{C}_{23}\text{H}_{29}\text{N}_3\text{O}_3 \cdot 0.25\text{CCl}_4$:

C, 68.68; H, 5.92; N, 8.51.

Found: C, 68.68; H, 5.90; N, 8.38.

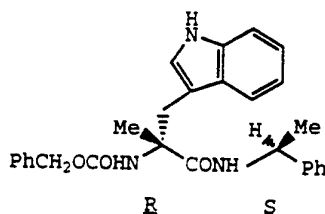
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EXAMPLE 14
(Scheme III)



10 A solution of CBZ- α -methyl-R-tryptophan
 pentafluorophenyl ester (1000 mg, 1.929 mmol) in EtOAc
 (50 mL) was treated at room temperature with 4 chloro-
 15 α -methylbenzylamine (1100 mg, 7.069 mmol) for 1 hour
 with stirring. The reaction mixture was then washed
 with 2N HCl (80 mL), then H₂O (100 mL). The organic
 phase was dried over MgSO₄, filtered, and evaporated to
 dryness in vacuo. The residue was purified by
 20 chromatography using 20% Et₂O in CH₂Cl₂ as eluant to
 give the product as a white foam and a 1:1 mixture of
 diastereoisomers (820 mg, 87%); mp 56-58°C
 (Et₂O/CH₂Cl₂);
 IR (nujol mull): 710 and 1651 cm⁻¹;
 NMR (DMSO-d₆): δ 1.20-1.40 (6H, m); 3.10-3.50 (2H, m);
 4.80 (1H, m); 5.00 (2H, s); 6.80-7.50 (14H, m);
 25 7.90 1H, d, J = 8 Hz); 8.1 (1H, d, J = 8 Hz); 10.80
 (1H, s).

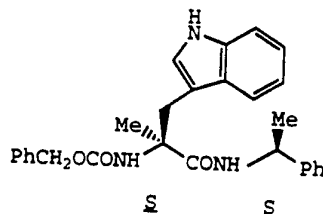
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EXAMPLE 15
(Scheme III)

10 A solution of CBZ- α -methyl-R-tryptophan
 pentafluorophenyl ester (730 mg, 1.40 mmol) in EtOAc
 (15 mL) was treated with S(-)- α -methylbenzylamine
 (940 mg, 7.76 mmol) and left stirring at room
 temperature for 1 hour. The mixture was washed with
 15 2 M HCl (20 mL) then H₂O (20 mL). The organic phase
 was dried over MgSO₄, filtered, and evaporated to
 dryness in vacuo. The residue was then subject to
 reverse phase chromatography using 80% MeOH; 20% H₂O as
 eluant to give the product as a white foam (150 mg,
 20 24%); mp 107-109°C (H₂O/MeOH);
 $[\alpha]_D^{20} = +13^\circ$ (c = 0.5, MeOH);
 IR (film): 3460-3400, 1711, 1658, 1495, and 1251 cm⁻¹;
 NMR (DMSO-d₆): δ 1.32 (3H, d, $J = 7$ Hz); 1.38 (3H, s);
 3.20-3.40 (2H, m); 4.90 (1H, m); 5.00 (2H, s); 6.80
 25 (1H, s); 6.90 (1H, t, $J = 7$ Hz); 7.00 (1H, t,
 $J = 7$ Hz); 7.01-7.40 (12H, m); 7.50 (1H, d, $J = 8$ Hz);
 8.00 (1H, d, $J = 8$ Hz); 10.80 (1H, s);
 MS (CI) 456 (30, M⁺+H), 130 (100), 91 (57), 105 (33).
 Analysis calculated for C, H, N, C₂₈H₂₉N₃O₃·0.5H₂O:
 30 C, 72.39; H, 6.51; N, 9.04%.
 Found: C, 72.53; H, 6.48; N, 8.98%.

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EXAMPLE 16



Method as for Example 15, Scheme III except using
 CBZ- α -methyl-S-tryptophan pentafluorophenyl ester

(142 mg, 23%); mp 107-110°C (MeOH:H₂O);

IR (film): 3327, 1716, and 1653 cm⁻¹;

NMR (DMSO-d₆): δ 1.20-1.40 (6H, m); 3.10-3.40 (2H, m);
 4.90 (1H, m); 5.00 (2H, s); 6.80-7.50 (16H, m); 7.90
 (1H, d, J = 8 Hz); 10.80 (1H, br.s).

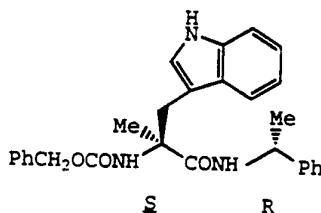
Analysis calculated for C, H, N, C₂₈H₂₉N₃O₃·0.25H₂O:

C, 73.10; H, 6.46; N, 9.13%.

Found: C, 73.40; H, 6.41; N, 9.18%.

EXAMPLE 17

(Scheme III)



Method as for Example 15, Scheme III except using
 CBZ- α -methyl-S-tryptophan pentafluorophenyl ester and
 R(+)- α -methylbenzylamine (190 mg, 30%); mp 109-111°C
 (MeOH/H₂O);

$[\alpha]_D^{24}$ = -13.2° (c = 0.5, MeOH);

IR (film): 1719 and 1654 cm⁻¹;

NMR (DMSO-d₆): 1.34 (3H, d, J = 7.9 Hz); 1.39 (3H, s);
 3.28-3.36 (2H, m); 4.92 (1H, m); 5.04 (2H, s); 6.82
 (1H, s); 6.87 (1H, br); 6.93 (1H, t, J = 7.6 Hz); 7.02

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(1H, t, J = 7.0 Hz); 7.22-7.47 (11H, m); 7.50 (1H, d, J = 7.8 Hz); 8.02 (1H, d, J = 8.2 Hz); 10.8 (1H, s);
MS (CI) m/e 456 (25, $M^+ + H$), 130 (100), 91 (73), 105 (35), 304 (29);

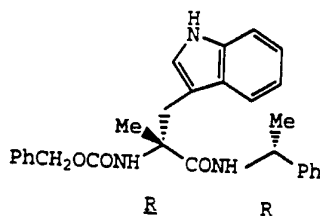
5 Analysis calculated for C, H, N, $C_{28}H_{29}N_3O_3 \cdot 0.25H_2O$:

C, 73.10; H, 6.46; N, 9.13%.

Found: C, 73.27; H, 6.45; N, 9.22%.

EXAMPLE 18

10 (Scheme III)



Method as for Example 15, Scheme III, except using
(R) (+)- α -methylbenzylamine (150 mg, 24%); mp 63-68°C
(MeOH/H₂O);

20 $[\alpha]_D^{28} = +9.4^\circ$ (c = 0.5, MeOH);

IR (film): 17H, 1658 cm⁻¹;

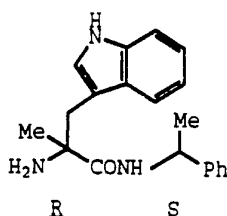
NMR (DMSO-d₆): δ 1.28 (3H, d, J = 6.8 Hz); 1.34 (3H, s); 3.16-3.30 (2H, m); 4.89 (1H, m); 5.04 (2H, s); 6.89 (1H, s); 7.00 (1H, t, J = 7.9 Hz); 7.20-7.45 (13H, m);
25 7.48 (1H, d, J = 7.8 Hz); 7.88 (1H, d, J = 7.5 Hz);
16.80 (1H, s);

MS (CI) m/e 456 (20, $M^+ + H$), 130 (100, 191, 150).

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EXAMPLE 19

(Scheme IV)



5
10 A solution of Example 15, Scheme III (17 g, 37 mmol) in EtOH (200 mL) was treated with 20% Pd(OH)₂ (1 g, 6% w/w) and put under an atmosphere of hydrogen at 30°C at a pressure of 45 psi for 3 hours. The reaction mixture was then filtered and evaporated to dryness in vacuo, the residue was purified by SiO₂ chromatography using 0.5% NH₄OH, 5% MeOH, 94.5% CH₂Cl₂ as eluant to give the product (8.1 g, 62%);

mp 124.5-125°C;

$[\alpha]_D^{20} = +7.0^\circ$ (c = 1, MeOH);

IR (film): 1643, 1512, and 1454 cm⁻¹;

20 NMR (CDCl₃): δ 1.42 (3H, d, J = 6.9 Hz); 1.46 (3H, s); 1.53 (2H, br.s); 2.81 (1H, d, J = 14.2 Hz); 3.46 (1H, d, J = 14.2 Hz); 5.02 (1H, dq, J = 7 Hz); 6.71 (1H, d, J = 2.2 Hz); 7.17 (7H, m); 7.33 (1H, d, J = 8.0 Hz); 7.59 (1H, d, J = 7.8 Hz); 7.82 (1H, d, J = 8 Hz); 8.02 (1H, s);

25 MS (CI) m/e 322 (100, M⁺+H);

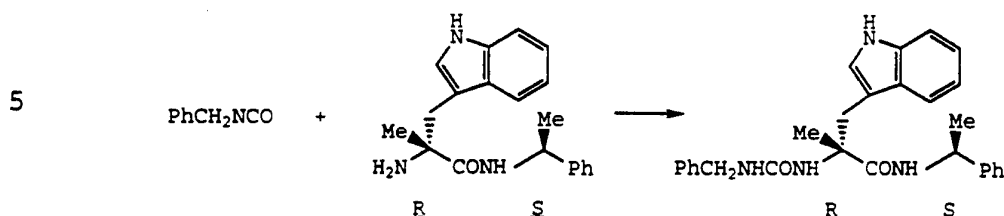
Analysis calculated for C, H, N, C₂₀H₂₃N₃O:

C, 74.74; H, 7.21; N, 13.07%.

Found: C, 74.7; H, 7.25; N, 13.04%.

30

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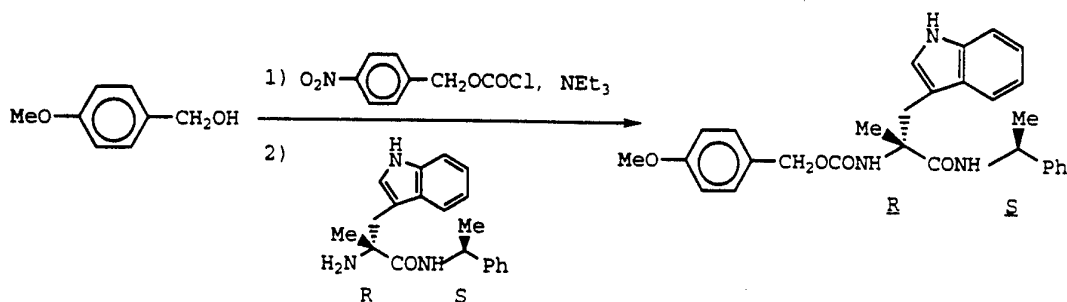
Step 7

To a stirred solution of the amine (Scheme IV)
 10 (321 mg, 1.0 mmol) in THF (10 mL) was added a solution
 of benzyl isocyanate (146 mg, 1.1 mmol) in THF (5 mL)
 dropwise. After 1 hour the solvent was removed
 in vacuo and the residue chromatographed using 4%
 MeOH/CH₂Cl₂. Crystallization from ether gave product
 15 (404 mg, 89%); mp 184-187°C;
 $[\alpha]_D^{20} = 27^\circ$ (c = 1, MeOH);
 IR (film): 3500-3200 (NH), 1646 (broad, CO, urea and
 amide), 1557, 1455, 1265, 741, and 700 cm⁻¹;
 NMR (CDCl₃): δ 1.28 (3H, d, $J = 6.9$ Hz, CHC₃); 1.48
 20 (3H, s, CCH₃); 3.11 (1H, d, $J = 14.6$ Hz, one of
 CH₂indole); 3.41 (1H, d, $J = 14.6$ Hz, one of
 CH₂indole); 4.14 (1H, d, $J = 15.1$ and 5.8 Hz, one of
 CH₂Ph); 4.24 (1H, dd, $J = 15.1$ and 5.9 Hz, one of
 CH₂Ph); 4.82-4.92 (1H, m, CHCH₃); 5.12 (1H, s,
 25 CH₂NHCONH); 5.20-5.30 (1H, m, CH₂NHCONH); 6.74 (1H, d,
 $J = 2.2$ Hz, indole, C₂H); 7.00-7.30 (14H, m, aromatics
 and CONHCH); 7.51 (1H, d, $J = 7.7$ Hz, indole C₄-H);
 8.22 (1H, s, indole NH);
 MS m/e (CI⁺): 455 (52) (M⁺+H), 348 (11), 334 (27), 322
 30 (100), 304 (49), 173 (47), 131 (25), 130 (61), 105
 (40), 91 (85);
 Analysis calculated for C, H, N.

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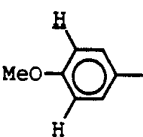
EXAMPLE 20

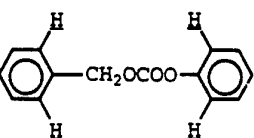
(Scheme V)

Step 8

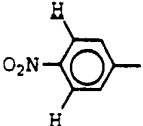
1) To a stirred solution of 4 nitrophenylchloroformate (2.01 g, 10 mmol) in acetone (30 mL), cooled in an ice bath, was added 4-methoxybenzylalcohol (1.38 g, 10 mmol) followed by the dropwise addition of a solution of triethylamine (1.01 g, 10 mmol) in acetone (10 mL). Left to stir overnight, filtered off triethylaminehydrochloride, solvent removed under vacuum. Residue taken up in ethyl acetate (50 mL), washed with citric acid solution (2 x 30 mL), sodium carbonate solution (5 x 30 mL), brine (2 x 30 mL), dried over MgSO_4 , and solvent removed in vacuo. Crystallization from ether gave carbonate (2.7 g, 89%); mp 99-100°C;

IR (film): 1747 (CO, carbonate), 1617, 1519, 1353, 1279, 1255, 1034, 866 cm^{-1} ;
NMR (CDCl_3): δ 3.83 (3H, s, CH_3O); 5.24 (2H, s, CH_2O);

6.90-6.95 (2H, m, );

7.35-7.40 (4H, m, );

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8.23-8.30 (2H, m, );

MS m/e (CI⁺): 303 (10) (M⁺+H), 277 (2), 260 (5), 241 (3), 149 (9), 140 (61), 122 (44), 121 (100);

Analysis calculated for C, H, N.

2) A solution of carbonate (364 mg, 1.2 mmol), the amine (321 mg, 1.0 mmol), and 4-dimethylamino-pyridine (122 mg, 1.0 mmol) in DMF (20 mL) was stirred overnight before solvent was removed under vacuum. Residue taken up in ethyl acetate (50 mL) and washed with citric acid solution (2 x 50 mL), brine (30 mL), 2N NaOH solution (5 x 50 mL), brine (30 mL), dried over MgSO₄, filtered, and solvent removed under vacuum. Residue chromatographed using 2% MeOH/CHCl₃ and crystallization from ether gave product (360 mg, 80%); mp 86-94°C; [α]_D¹⁷ = +16.7° (c = 1, MeOH);

IR (film): 3500-3200 (NH), 1713 (CO, urethane), 1652 (CO, amide), 1614, 1515, 1457, 1246, 1176, 1070, 822, 742, and 701 cm⁻¹;

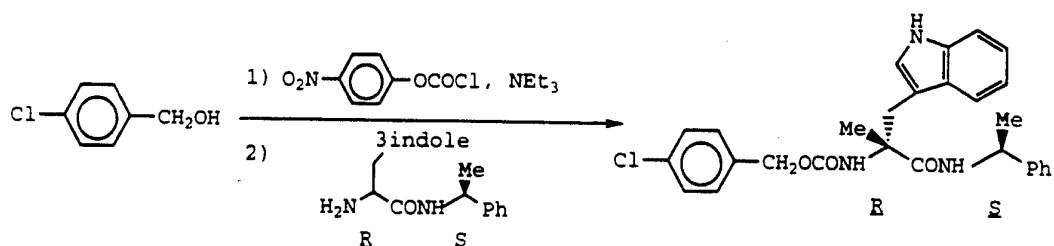
NMR (CDCl₃): δ 1.31 (3H, d, J = 6.9 Hz, CHCH₃); 1.60 (3H, s, CCH₃); 3.24 and 3.46 (each 1H each d, J = 14.7 Hz, each one of CH₂indole); 3.79 (3H, s, OMe); 4.95-5.05 (3H, m, CH₂OCONH and CONHCH); 5.27 (1H, s, OCONH); 6.35-6.45 (1H, br.d, CONHCH); 6.75 (1H, s, indole C₂-H); 6.85 (2H, d, J = 8.6 Hz, ortho protons to OMe group); 7.09 (1H, t, J = 7.4 Hz, indole C₅ or C₆-H); 7.15-7.30 (8H, m, CH₂Ph, indole C₅ or C₆H, meta protons to OMe group); 7.33 (1H, d, J = 8.0 Hz, indole C₇-H); 7.57 (1H, d, J = 7.8 Hz, indole C₄-H); 7.95 (1H, s, indole NH);

Analysis calculated for C, H, N.

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EXAMPLE 21

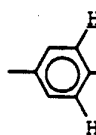
(Scheme IV)

Step 9

1) Method as for Example 20, Scheme IV, except used 4-chlorobenzyl alcohol (1.42 g, 10 mmol) to give a crystalline carbonate (2.9 g, 94%) from ether; mp 135-138°C;

15 IR (film): 1761 (CO, carbonate), 1524, 1492, 1350, 1261, 1215 cm⁻¹;

NMR (CDCl₃): δ 5.26 (2H, s, CH₂O); 7.35-7.40 (6H, m,

20 aromatics); 8.25-8.30 (2H, m, );

MS m/e (CI⁺): 308 (6) (M⁺+H), 292 (4), 278 (7), 266 (15), 264 (41), 140 (43), 127 (82), 125 (100);

Analysis calculated for C, H, N, Cl.

25 2) Method as for Example 20, Scheme IV, except used 4-chlorobenzyl carbonate (368 mg, 1.2 mmol).

Chromatography using 3% MeOH/CH₂Cl₂ followed by crystallization from ether gave a crystalline product (434 mg, 89%); mp 98-100°C;

30 [α]_D²⁰ = +12.5° (c = 1, MeOH);

IR (film): 3450-3200 (NH), 1712 (CO, urethane), 1651 (CO, amide), 1494, 1457, 1251, 1073, 742, and 700 cm⁻¹;

NMR (CDCl₃): δ 1.29 (3H, d, J = 6.9 Hz, CHCH₃); 1.63 (3H, s, CCH₃); 3.26 (1H, d, J = 14.8 Hz, one of

35 CH₂indole); 3.45 (1H, d, J = 14.8 Hz, one of

CH₂indole); 4.95-5.05 (3H, m, CH₂O and CHCH₃); 5.43

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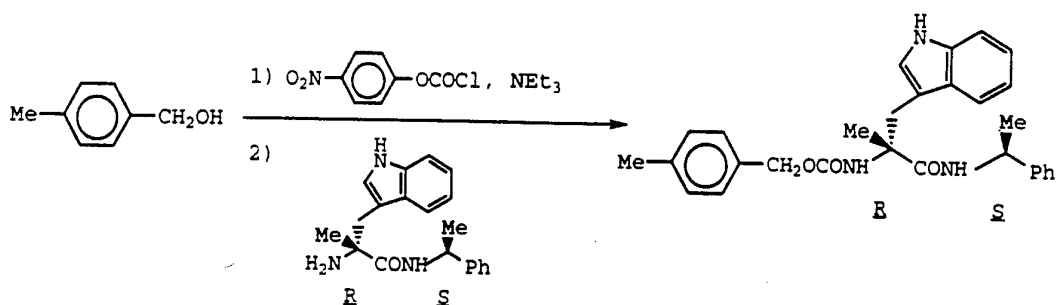
(1H, s, OCONH); 6.27 (1H, d, J = 7.5 Hz); 6.80 (1H, s, indole, C₂-H); 7.05-7.30 (11H, m, CHPh, Cl-Ar, indole C₅ and C₆-H); 7.34 (1H, d, J = 8.0 Hz, indole C₇-H); 7.58 (1H, d, J = 7.9 Hz, indole C₄-H); 8.01 (1H, s, indole NH);

Analysis calculated for C, H, N.

EXAMPLE 22

(Scheme IV)

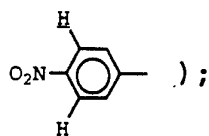
Step 10



1) Method as for Example 20, Scheme IV except used α -methylbenzylalcohol (1.22 g, 10 mmol) to give a crystalline carbonate (2.3 g, 80%) for ethyl acetate; mp 93-95°C;

IR (film): 1750 (CO, carbonate), 1536, 1349, 1268, 1218, 865 cm^{-1} ;

NMR (CDCl_3): δ 2.37 (3H, s, CH_3); 5.26 (2H, s, CH_2O); 7.15-7.40 (6H, m, aromatics); 8.24-8.30 (2H, m,



MS m/e (CI^+): 288 (6) (M^+H); 244 (41), 239 (12), 198 (49), 140 (36), 122 (25), 106 (51), 105 (100);

Analysis calculated for C, H, N.

2) Method as for Example 20, Scheme IV, except used 4-methylbenzylcarbonate (345 mg, 1.2 mmol). Residue chromatographed using 2% MeOH/ CH_2Cl_2 and

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crystallization from ether gave product (350 mg, 75%);

mp 85-95°C (Needles);

$[\alpha]_D^{24} = +15.5^\circ$ (c = 1, MeOH);

IR (film): 3500-3200 (NH, 3059, 3028, 2977, 2930, 1709

5 (CO, urethane), 1652 (CO, amide), 1494, 1457, 1251, 1071, 742, and 700 cm^{-1} ;

NMR (CDCl_3): δ 1.30 (3H, d, $J = 6.9$ Hz, CHCH_3); 1.61

(3H, s, CCH_3); 2.34 (3H, s, Me-aryl); 3.24 (1H, d,

$J = 14.7$ Hz, one of CH_2 indole); 3.46 (1H, d,

10 $J = 14.8$ Hz, one of CH_2 indole); 4.95-5.07 (3H, m, CH_2O and CHCH_3); 5.31 (1H, s, OCONH); 6.38 (1H, d,

$J = 7.7$ Hz, CONHCH); 6.77 (1H, d, $J = 2.2$ Hz, indole

$\text{C}_2\text{-H}$); 7.05-7.30 (11H, m, CHPh , pMe-Ph , indole C_5 and

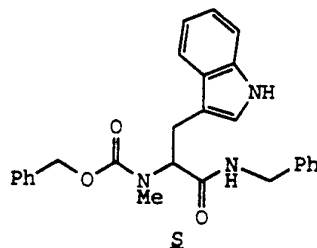
$\text{C}_6\text{-H}$); 7.33 (1H, d, $J = 8.1$ Hz, indole $\text{C}_7\text{-H}$); 7.58 (1H,

15 d, $J = 7.7$ Hz, indole $\text{C}_4\text{-H}$); 7.98 (1H, s, indole NH);

Analysis calculated for C, H, N.

EXAMPLE 23

(Scheme V)



Benzylchloroformate (0.85 mL, 0.005 mol) was added in one portion to a vigorously stirred suspension of S-abrine (1 g, 0.0040 mol), potassium carbonate (1.2 g, 0.009 mol) in dioxane (15 mL) and water (1 mL). The mixture was stirred at room temperature for 1 hour, after which time t.l.c. analysis indicated the consumption of starting material. The solvent was removed in vacuo. The residue was treated with 2 M

30

35 hydrochloric acid (20 mL), water (40 mL), and extracted with EtOAc (3 x 30 mL). The organic phase was washed

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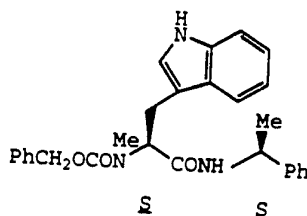
with water (10 mL), brine (2 x 10 mL), dried (MgSO_4), and the solvent removed in vacuo to give the N-protected amino acid (Scheme V) as a dark straw-colored oil (1.25 g, 77%) which was used in the next reaction without further purification;
5 ν_{max} (film): 3345 br (OH), 1740 shoulder (C = O acid) and 1684 cm^{-1} v. broad (C = O, carbamate).

The carboxylic acid (0.85 g, 0.0024 mol), N,N'-dicyclohexylcarbodiimide (DCC) (0.56 g, 0.0024 mol) and pentafluorophenol (PFP) (0.44 g, 0.0027 mol) were dissolved in EtOAc (20 mL) and the reaction mixture stirred at room temperature for 1 hour. The mixture was filtered to remove the white solid. Benzylamine (0.3 mL, 0.0026 mol) was added and the mixture stirred for 10 hours at room temperature.
10 The solvent was removed in vacuo and the crude product was purified by column chromatography, eluting with dichloromethane:methanol (9:1) giving Example 23 as a white solid (0.66 g, 63%); mp 48-54°C;
15 IR (film): 3326 (NH), 1695 (shoulder, C = O, carbamate), 1662 (C = O, amide), 1547, 1497, and 1402 cm^{-1} ;
20 NMR ($\text{DMSO}-d_6$): 2.88 (3H, br.s, NHCH_3); 3.10 (1H, br, m, $\text{CH}_2\text{H}_b\text{Ind}$); 3.33 (1H, m, $\text{CH}_2\text{H}_p\text{Ind}$); 4.32 (2H, d, $J = 6$ Hz, NHCH_2Ph); 4.8-5.2 (3H, m, ArCH_2O and CH);
25 6.8-7.7 (15H, m, aromatics and carbamate NH); 8.65 (1H, s, br, amide NH); 10.85 (1H, s, indole NH);
MS m/e (CI) 442 ($\text{M}^+ + \text{H}$).

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EXAMPLE 24

(Scheme V)

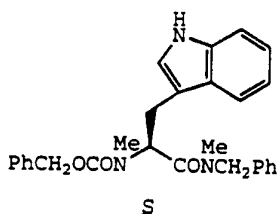


10 A solution of CBZ-S-abrine pentafluorophenyl ester
(100 mg, 0.20 mmol) in EtOAc (10 mL) was treated with
S-(-)- α -methylbenzylamine (470 mg, 4.00 mmol) at room
temperature for 10 minutes with stirring. The mixture
15 was then washed with diluent HCl (20 mL) then H₂O
(20 mL). The organic phase was dried over MgSO₄,
filtered, and evaporated to dryness in vacuo. The
residue was purified by chromatography using 10%
Et₂O:90% CH₂Cl₂ as eluant to give the product as a
white foam (68 mg, 77%); mp 58-60°C (Et₂O/CH₂Cl₂);
20 IR (nujol mull): 1681 and 1656 cm⁻¹;
NMR (DMSO-d₆): δ 1.40 (3H, d, J = 7 Hz), 2.80 (3H, s);
3.00 (1H, m); 3.20 (1H, m); 4.80-5.10 (4H, m);
6.80-7.70 (15H, m); 8.50 (1H, d, J = 9 Hz); 10.80 (1H,
br);
25 MS (CI) m/e, 456 (55, M⁺+H), 290 (100), 91 (55).
Analysis calculated for C, H, N, C₂₈H₂₉N₃O₃·0.25H₂O:
C, 73.10; H, 6.46; N, 9.13%.
Found: C, 73.34; H, 6.41; N, 9.19%.

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EXAMPLE 25

(Scheme V)



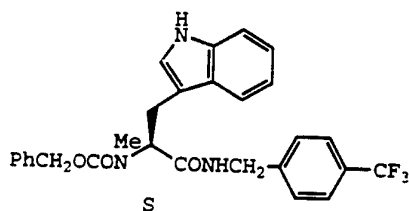
10 A solution of CBZ-S-abrine pentafluorophenyl ester (100 mg, 0.20 mmol) in EtOAc (20 mL) was treated with N-methyl benzylamine (470 mg, 3.90 mmol) for 10 minutes at room temperature. The mixture was washed with 2N HCl (20 mL, then H₂O (20 mL). The organic phase was dried (MgSO₄), filtered, evaporated, and the residue

15 subject to reverse phase chromatography using 60%-70% MeOH in H₂O to give the product as a white foam (66 mg, 75%); mp 44-45°C (MeOH/H₂O); [α]_D²⁰ = -49° (c = 0.1, MeOH); IR (nujol mull): 1683 and 1633 cm⁻¹;

20 NMR (DMSO-d₆, 360°K): δ 2.80 (3H, s); 2.90 (3H, s); 3.0-3.4 (2H, m); 4.50 (2H, m); 5.00-5.60 (3H, br, m); 6.90-7.60 (15H, m); 10.60 (1H, br); MS (CI) m/e 456 (42, M⁺+H), 335, 2.90 (100), 91 (62).

EXAMPLE 26

(Scheme V)



35 A solution of CBZ-S-abrine pentafluorophenyl ester (100 mg, 0.20 mmol) in EtOAc (20 mL) was treated with 4-trifluoromethylbenzylamine (1.23 g, 7.03 mmol) for

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10 minutes at room temperature. The organic phase was washed with diluent HCl (25 mL) then H₂O (25 mL), dried (MgSO₄), filtered, and evaporated to dryness in vacuo. The residue was purified by silica gel chromatography using CH₂Cl₂ then 20% Et₂O in CH₂Cl₂ as eluant to yield the product as a white foam (84 mg, 85%); mp 55-57°C (Et₂O/CH₂Cl₂);

[α]_D²⁰ = -58° (c = 0.1, MeOH);

IR (nujol mull): 1689 and 1660 cm⁻¹;

NMR (DMSO-d₆): δ 2.80 (3H, s); 3.10 (1H, m); 3.30 (1H, m); 4.40 (2H, d, J = 6 Hz); 4.80-5.10 (3H, br.m); 6.90-7.70 (14H, m); 8.70 (1H, br); 10.90 (1H, br);

MS (CI) m/e 510 (50, M⁺+H), 344 (72), 130 (62), 91 (100).

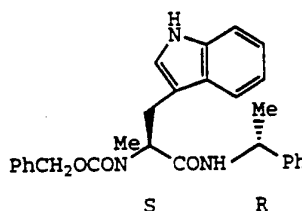
Analysis calculated for C, H, N, C₂₈H₂₆N₃O₃F₃:

C, 66.00; H, 5.14; N, 8.25%.

Found: C, 66.17; H, 5.15; N, 8.24%.

EXAMPLE 27

(Scheme V)



A solution of CBZ-S-abrine pentafluorophenyl ester (100 mg, 0.20 mmol) in EtOAc (10 mL) was treated with R-(+)- α -methylbenzylamine (470 mg, 4.00 mmol) at room temperature for 10 minutes with stirring. The mixture was then washed with 2N HCl (20 mL) then H₂O (20 mL). The organic phase was dried over MgSO₄, filtered, and evaporated in vacuo to give a residue that was purified by chromatography using 10% Et₂O in CH₂Cl₂ as eluant to give the product as a white foam (62 mg, 71%); mp 51-56°C (Et₂O/CH₂Cl₂);

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$[\alpha]_D^{20} = -40^\circ$ ($c = 0.1$, MeOH);

IR (nujol mull): 1690 and 1653 cm^{-1} ;

NMR (DMSO- d_6): δ 1.30 (3H, d, $J = 7$ Hz); 2.80 (3H, br.s); 3.00-3.30 (2H, m); 4.81-5.10 (4H, br.m);

5 6.90-7.70 (15H, m); 8.40 (1H, br.d, $J = 9$ Hz); 10.80 (1H, br.s);

MS (CI) m/e 456 (33, $M^+ + H$); 412 (30), 335 (55), 290 (100), 91 (58).

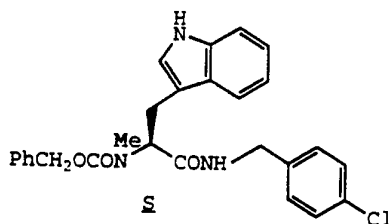
10 Analysis calculated for C, H, N, $\text{C}_{28}\text{H}_{29}\text{N}_3\text{O}_3 \cdot 0.25\text{H}_2\text{O}$:
C, 73.10; H, 6.46; N, 9.13%.

Found: C, 73.26; H, 6.32; N, 9.11%.

EXAMPLE 28

(Scheme V)

15



20

A solution of CBZ-S-abrine pentafluorophenyl ester (100 mg, 0.20 mmol) in EtOAc (30 mL) was treated at room temperature with 4-chlorobenzylamine (600 mg, 4.20 mmol) at room temperature for 10 minutes. The reaction mixture was then washed with 2N HCl (50 mL) then H₂O (50 mL). The organic phase was dried over MgSO₄, filtered, and evaporated to dryness in vacuo. The residue was purified by chromatography using 10% Et₂O:CH₂Cl₂ as eluant to give the product as a white foam (62 mg, 60%); mp 56-58°C (Et₂O/CH₂Cl₂);

30 $[\alpha]_D^{20} = -65^\circ$ ($c = 0.25$, MeOH);

IR (nujol mull): 1683 and 1659 cm^{-1} ;

35 NMR (DMSO- d_6 , 340°C): δ 2.80 (3H, s); 3.00-3.40 (2H, m); 4.30 (2H, d, $J = 6$ Hz); 5.00 (3H, br); 6.90-7.60 (14H, m); 8.40 (1H, br); 10.60 (1H, br);

-74-

MS (CI) m/e 476 (55, $M^+ + H$), 432 (45), 335 (51), 310 (75), 130 (65), 91 (100).

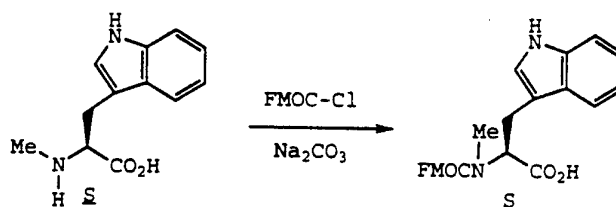
Analysis calculated for C, H, N, $C_{27}H_{26}N_3O_3Cl$:

C, 68.13; H, 5.51; N, 8.83%.

5 Found: C, 68.02; H, 5.40; N, 8.76%.

EXAMPLE 29

(Beginning of Scheme VI)



Step 1

To a stirred solution of S-abrine (4.00 g, 18.3 mmol) and sodium carbonate (4.27 g, 40.3 mmol) in aqueous dioxan (1:2, 60 mL), cooled in an ice bath, was added 9-fluorenylmethyl chloroformate (5.69 g, 22 mmol) dropwise in dioxan (40 mL). Mixture was stirred for 4 hours with cooling, then overnight at room temperature. Dioxin was removed in vacuo before diluting with water (100 mL) to obtain a clear solution. Extracted with ether (3 x 100 mL), ether discarded, aqueous layer acidified using 2N HCl and extracted with ethyl acetate (3 x 200 mL). Organic layers combined, washed with brine (2 x 100 mL), dried over $MgSO_4$, filtered, and solvent removed in vacuo to obtain product (8 g, 99%) as a white noncrystalline solid; mp 80-85°C; $[\alpha]_D^{20} = -67.7^\circ$ (c = 1, MeOH); IR (film): 3500-2400, 1715 (CO, carboxylic acid), 1685 (CO, urethane), 1479, 1452, 1404, 1323, 1266, 1198, 1153, 759, and 740 cm^{-1} ;

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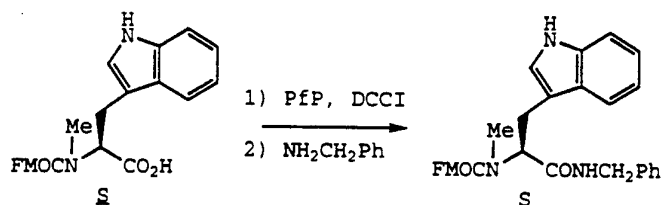
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-75-

NMR (DMSO- d_6) (340K): δ 2.77 (3H, s, NCH_3); 3.05-3.20 (1H, m, one of CH_2 indole); 3.30 (1H, d.d, $J = 15.2$ and 5.0 Hz, one of CH_2 indole); 4.00-4.30 (3H, br.m, $CHCH_2OCONH$); 4.89 (1H, d.d, $J = 10.2$ and 5.0 Hz, CH_2CHCO_2H); 6.90-7.10 (3H, m, aromatics); 7.20-7.55 (8H, m, aromatics); 7.83 (2H, d, $J = 7.5$ Hz, fluorenyl, CH_3); 10.65 (1H, s, indole NH);
 MS m/e (CI^+): 441 (2) ($M^+ + H$), 245 (2), 219 (14), 207 (9), 188 (5), 179 (100), 130 (17).

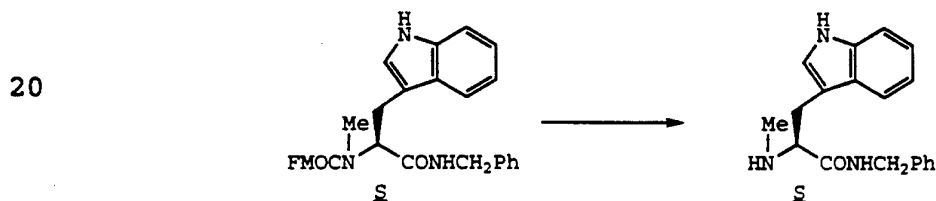
Step 2

To a stirred solution of Fmoc-S-abrine (4.40 g, 10 mmol) in ethyl acetate (100 mL), cooled in an ice bath, was added pentafluorophenol (1.84 g, 10 mmol) followed by solid N,N' -dicyclohexylcarbodiimide (2.06 g, 10 mmol). After 4 hours at $0^\circ C$, dicyclohexylurea was filtered off and the residue washed with cold ethyl acetate (10 mL). A solution of benzylamine (1.07 g, 10 mmol) was added to the filtrate dropwise over 10 minutes (reaction complete after 15 minutes by IR). Reaction mixture was washed with citric acid solution (2 x 20 mL), sodium hydrogen carbonate solution (2 x 20 mL), brine (1 x 20 mL), dried over $MgSO_4$, and solvent removed under vacuum. Residue was chromatographed using 30 then 40% ethyl acetate in hexane to give (4.98 g, 94%) as white noncrystalline solid; mp $74-79^\circ C$; $[\alpha]_D^{20} = -47^\circ$ ($c = 1$, MeOH);

-76-

IR (film): 3317 (NH), 3061, 2950, 1669 (br., CO, amide and urethane), 1526, 1453, 1402, 1318, 1248, 1152, 1102, 741, and 700 cm^{-1} ;

NMR (DMSO-d_6) (340K): δ 2.83 (3H, s, NCH_3); 3.06 (1H, d.d, $J = 15.0$ and 9.7 Hz, one of CH_2 indole); 3.33 (1H, d.d, $J = 15.0$ and 5.8 Hz, one of CH_2 indole); 4.00-4.40 (3H, brm, CHCH_2OCO); 4.30 (2H, d, $J = 5.9$ Hz, NHCH_2Ph); 4.97 (1H, d.d, $J = 9.6$ and 5.9 Hz, CHCH_2 indole); 6.95 (1H, t, $J = 7.3$ Hz, indole CH); 7.00-7.08 (2H, m, indole CH_2); 7.15-7.40 (10H, m, aromatics); 7.44 (1H, d, $J = 7.3$ Hz); 7.51 (1H, d, $J = 7.4$ Hz); 7.61 (1H, d, $J = 7.8$ Hz); 7.82 (2H, d, $J = 7.6$ Hz, fluorenyl CH_2); 8.20-8.30 (1H, br.m, CONH); 10.65 (1H, s, indole NH); MS m/e (CI^+): 530 (1) ($\text{M}^+ + \text{H}$), 309 (8), 308 (35), 276 (6), 207 (24), 180 (36), 179 (100), 178 (90).

Step 3

A solution of Fmoc-S-abrine benzylamide (4.0 g, 7.55 mmol) in 20% piperidine in DMF (20 mL) was stirred at room temperature for 5 minutes before removing the solvent under vacuum. Solid residue was stirred vigorously in pet. ether (100 mL), decanted liquid off, and repeated 5 times before leaving to stir overnight in pet. ether (200 mL). Filtered off crystalline product (2.2 g, 95%); mp 140-142°C; $[\alpha]_D^{20} = +29.1^\circ$ ($c = 1$, MeOH); IR (film): 3306 (NH), 1651 (CO, amide), 1523, 1455, 1340, 1103, 742, and 698 cm^{-1} ;

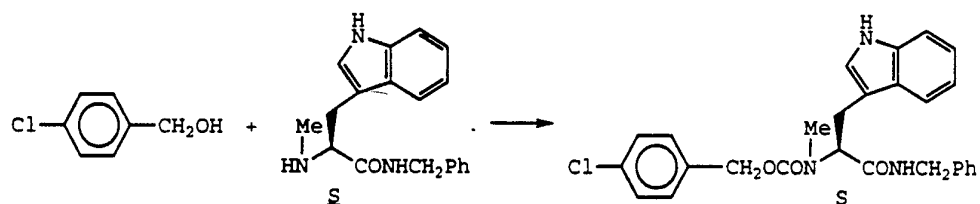
NMR (DMSO-d_6) (340K): δ 1.75 (1H, s, NH); 2.20 (3H, s, NCH_3); 2.85 (1H, d, $J = 14.2$ and 7.2 Hz, one of

- 77 -

CH₂indole); 3.02 (1H, d.d, J = 14.2 and 6.3 Hz, one of CH₂indole); 3.24 (1H, t, J = 6.8 Hz, CHCH₂indole); 4.19 (1H, d.d, J = 15.1 and 5.6 Hz, one of CH₂Ph); 4.30 (1H, d.d, J = 15.0 and 5.9 Hz, one of CH₂Ph); 6.96 (1H, t, J = 7.2 Hz, indole C₅ or C₆H); 7.00-7.30 (7H, m, CH₂Ph and 2 indole CH₃); 7.34 (1H, d, J = 8.0 Hz, indole C₇-H); 7.54 (1H, d, J = 7.8 Hz, indole C₄-H); 8.25 (1H, t, J = 6.0 Hz, CONH); 10.80 (1H, s, indole NH); MS m/e (CI⁺): 308 (100 (M⁺+H), 277 (21), 276 (12), 178 (34), 177 (64), 173 (80), 132 (22), 131 (46), 130 (30), 91 (25).

(Scheme VI)

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**Step 4**

To a stirred solution of 4-chlorobenzylalcohol (214 mg, 1.5 mmol) in ethyl acetate (10 mL) at 0°C was added solid triphosgene (148 mg, 0.5 mmol) followed by the dropwise addition of pyridine (119 mg, 1.5 mmol) in ethyl acetate (5 mL) over 5 minutes. (After 30 minutes IR peak at 1776 cm⁻¹.) Filtered off pyridine hydrochloride, removed solvent under vacuum, residue taken up in THF (5 mL) and added dropwise to a solution of S-abrine benzylamide (307 mg, 1 mmol) and pyridine (119 mg, 1.5 mmol) in THF (20 mL). Intense yellow color as chloroformate added, followed by the precipitation of pyridine hydrochloride. After 30 minutes removed solvent under vacuum and residue chromatographed using 4% MeOH/CH₂Cl₂ to give product (270 mg, 56%) as noncrystalline solid; mp 52-55°C; $[\alpha]_D^{20}$ = -64.1 (c = 1, MeOH);

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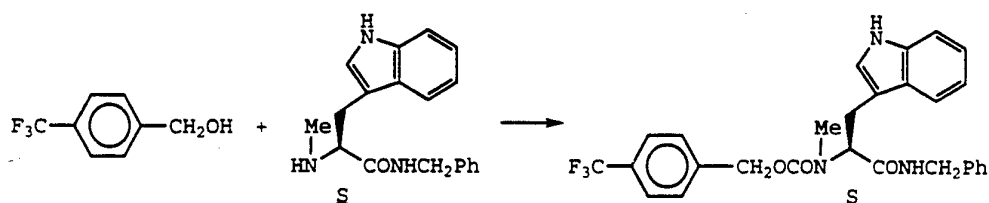
IR (film): 3316 (NH), 1685 (CO, urethane), 1662 (amide), 1530, 1493, 1455, 1399, 1318, 1142, 1092, 1014, and 742 cm^{-1} ;

NMR (DMSO-d_6) (340K): δ 2.85 (3H, s, NCH_3); 3.07 (1H, d.d, $J = 15.0$ and 9.9 Hz, one of CH_2 indole); 3.32 (1H, d.d, $J = 15.0$ and 5.8 Hz, one of CH_2 indole); 4.29 (2H, d, $J = 5.9$ Hz, NHCH_2Ph); 4.80-5.05 (3H, br.m, $\text{CH}_2\text{OCONHCH}$); 6.94 (1H, t, $J = 7.4$ Hz, indole CH); 7.00-7.30 (11H, m, aromatics); 7.34 (1H, d, $J = 8.5$ Hz, indole C₇-H); 7.57 (1H, d, $J = 7.5$ Hz, indole C₄-H); 8.30-8.40 (1H, br.s, CONHCH_2); 10.65 (1H, s, indole NH);

MS m/e (CI^+): 476 (32) ($\text{M}^+ + \text{H}$), 434 (17), 432 (44), 369 (23), 297 (17), 276 (100), 177 (24), 171 (24), 130 (57), 125 (51), 91 (24).

EXAMPLE 30

(Scheme VI)

25 Step 5

Method as for Step 4, Example 29 using 4-trifluoromethylbenzyl alcohol (264 mg, 1.5 mmol) to give product (388 mg, 76%) as noncrystalline solid; mp 53-57°C;

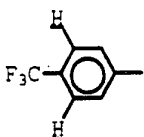
30 $[\alpha]_{\text{D}}^{20} = -63.1^\circ$ ($c = 1$, MeOH);

IR (film): 3307 (NH), 1663 (br, CO, amide and urethane), 1531, 1326, 1124, 1067, 1018, 824, and 742 cm^{-1} ;

35 NMR (DMSO-d_6) (340K): δ 2.88 (3H, s, NCH_3); 3.10 (1H, d.d, $J = 14.9$ and 10.0 Hz, one of CH_2 indole); 3.33 (1H, d.d, $J = 14.9$ and 5.7 Hz, one of CH_2 indole); 4.30 (2H,

-79-

d, $J = 5.8$ Hz, NHCH_2Ph); 4.90-5.10 (3H, m, CH_2OCO and $\text{CHCH}_2\text{indole}$); 6.93 (1H, t, $J = 7.3$ Hz, indole CH); 7.00-7.35 (10H, m, aromatics); 7.50-7.65 (3H, m,

5 indole C₇-H and ); 8.30-8.40 (1H, br.s,

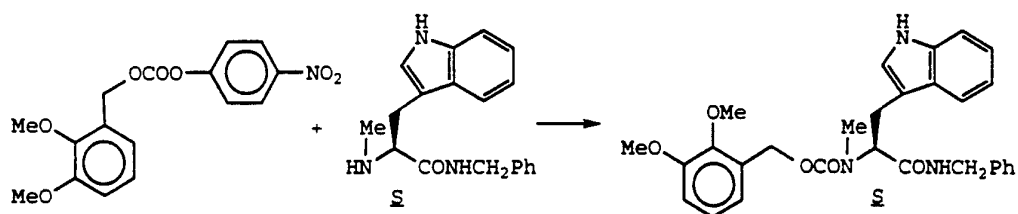
CONH); 10.70 (1H, s, indole NH);

MS m/e (CI^+): 510 (89) ($\text{M}^+\text{+H}$), 490 (12), 446 (15), 403
 10 (41), 277 (34), 276 (100), 171 (26), 159 (30), 130
 (63), 91 (24).

EXAMPLE 31

(Scheme VI)

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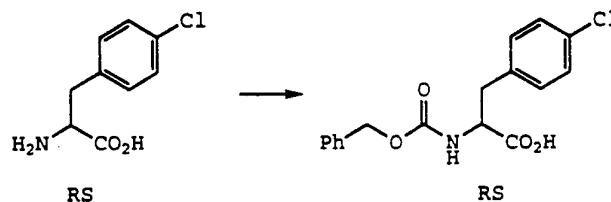
Step 6

A mixture of 2,3-dimethoxybenzyl-4' nitrophenyl carbonate (400 mg, 1.2 mmol) 4-dimethylaminopyridine (122 mg, 1.0 mmol), and S-abrine benzylamide (307 mg, 1.0 mmol) was stirred in DMF (5 mL) for 3 hours before solvent removed under vacuum. Residue taken up in ethyl acetate (50 mL) and washed with citric acid solution (2 x 50 mL), brine (30 mL), 2N NaOH solution (5 x 50 mL), brine (30 mL), dried over MgSO_4 , filtered,
 30 and solvent removed under vacuum. Residue chromatographed using 4% $\text{MeOH}/\text{CH}_2\text{Cl}$ to give product (500 mg, 100%) as white noncrystalline solid;
 mp 49-54°C;
 $[\alpha]_D^{20} = -45.3^\circ$ ($c = 1$, MeOH);

-80-

IR (film): 3631, 3521, 3411, 3321, 2936, 2836, 1665
(br, CO, urethane and amide), 1589, 1527, 1484, 1456,
1400, 1186, 1151, 1085, 1009, 743, and 701 cm^{-1} ;
NMR (DMSO-d_6) (340K): δ 2.84 (3H, s, NCH_3); 3.07 (1H,
5 d.d, $J = 14.9$ and 9.7 Hz, one of CH_2 indole); 3.32 (1H,
d.d, $J = 14.9$ and 5.9 Hz, one of CH_2 indole); 3.65 (3H,
s, OCH_3); 3.79 (3H, s, OMe); 4.29 (2H, d, $J = 5.9$ Hz,
 NHCH_2Ph); 4.90-5.05 (3H, m, CH_2OCONCH); 6.65-6.75 (1H,
br.s, one of CH_3 on OMe ring); 6.90-7.10 (5H, m,
10 aromatics); 7.15-7.30 (5H, m, aromatics); 7.33 (1H, d,
 $J = 8.1$ Hz, indole $\text{C}_7\text{-H}$); 7.57 (1H, d, $J = 7.8$ Hz,
indole $\text{C}_9\text{-H}$); 8.25-8.35 (1H, m, CONHCH_2); 10.65 (1H, s,
indole NH);
MS m/e (CI^+): 502 (13) ($\text{M}^+\text{+H}$), 459 (31), 458 (100),
15 277 (21), 276 (92), 151 (87), 130 (35).

EXAMPLE 32
(Scheme VII)



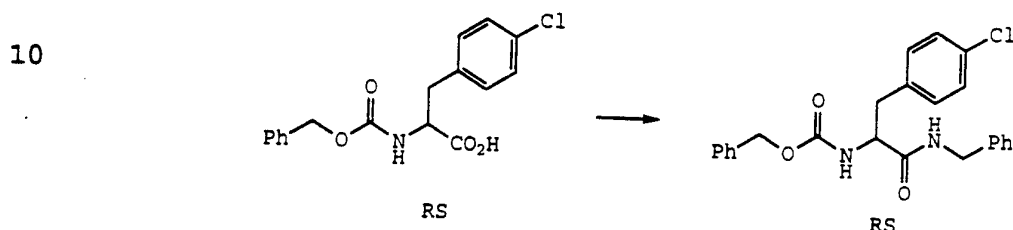
Benzylchloroformate (0.94 g, 5.5 mmol) was added
dropwise to a suspension of RS-4-chlorophenylalanine
(1.0 g, 5.0 mmol) in 1 M Na_2CO_3 (20 mL), cooled to 0°C .
The reaction mixture was stirred for 5 hours at room
30 temperature, then acidified to pH 1 with concentrated
HCl. The white precipitate formed was collected by
filtration and recrystallized from ethyl acetate/hexane
to give CBZ-RS-4-chlorophenylalanine (0.95 g, 57%);
mp $152\text{-}155^\circ\text{C}$;
35 IR (film): 3309, 1692 (urethane CO) and 1592 cm^{-1}
(amide II);

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NMR (DMSO- d_6): δ 2.83 (1H, d.d, J = 10.9 and 13.7 Hz, one of βCH_2); 3.07 (1H, d.d, J = 4.3 and 13.7 Hz, one of βCH_2); 4.19 (1H, m, αCH); 4.97 (2H, s, CH_2Ph); 7.31 (9H, m, aromatics); 7.65 (1H, d, J = 8.5 Hz, NH);

5 MS m/e (FAB) 334 $[\text{MH}]^+$.

(Scheme VII)



CBZ-RS-4-chlorophenylalanine (0.5 g, 1.5 mmol) was dissolved in ethyl acetate (5 mL) and dicyclohexylcarbodiimide (0.31 g, 1.5 mmol) was added. Pentafluorophenol (0.28 g, 1.5 mmol) was added and the reaction was stirred overnight at room temperature.

20 The white precipitate formed was removed by filtration and the filtrate concentrated in vacuo to give the activated amino acid as a white solid which was redissolved in ethyl acetate (10 mL). Benzylamine (0.16 mL, 1.5 mmol) was added and the reaction was

25 stirred at room temperature for 1 hour. The white precipitate was collected by filtration and purified by chromatography, followed by recrystallization from ethyl acetate to give the product (0.38 g, 60%); mp 157-158°C;

30 IR (film): 3232, 1698 (urethane CO), 1657 (amide I), and 1553 cm^{-1} (amide II);

NMR (DMSO- d_6): δ 2.82 (1H, d.d., J = 10.3 and 13.4 Hz, one of βCH_2); 3.01 (1H, d.d., J = 4.5 and 13.4 Hz, one of βCH_2); 4.29 (3H, m, αCH , NHCH_2Ph); 4.97 (2H, s,

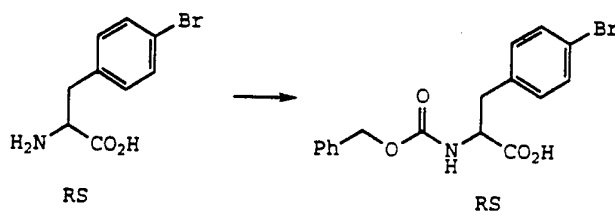
- 82 -

PhCH₂O); 7.17-7.36 (14H, m, aromatics); 7.58 (1H, d, $J = 8.6$ Hz, NH); 8.53 (1H, t, $J = 5.8$ Hz, NHCH₂Ph); MS m/e (CI) 423 M⁺.

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EXAMPLE 33
(Scheme VII)

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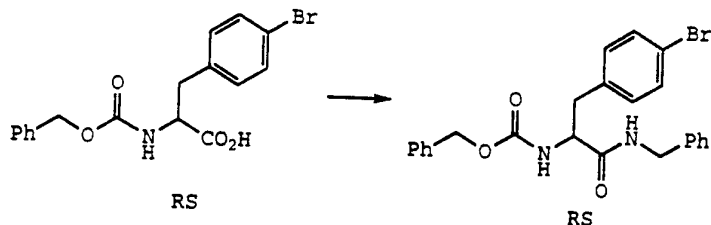
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RS-4-Bromophenylalanine (0.98 g, 4 mmol) was suspended in a 1:1 mixture of dioxan/water (20 mL). NaHCO₃ (0.67 g, 8 mmol) was added followed by a solution of dibenzylidicarbonate (1.37 g, 4.8 mmol) in dioxan (5 mL). The reaction was stirred at room temperature overnight, then diluted with water (20 mL). After washing with ether (2 x 20 mL), the aqueous layer was acidified to pH 1 with concentrated HCl and then was extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were washed with water (3 x 30 mL), dried over MgSO₄, and the solvent was removed in vacuo. The white solid obtained was crystallized from ethyl acetate/hexane to give the product (1.16 g, 77%); mp 161-165°C; IR (film): 3310, 1694 (urethane CO), and 1532 cm⁻¹ (amide II); NMR (DMSO-d₆): 2.81 (1H, d.d, $J = 10.7$ and 13.7 Hz, one of β CH₂); 3.06 (1H, d.d, $J = 4.3$ and 13.7 Hz, one of β CH₂); 4.19 (1H, m, α CH); 4.97 (2H, s, CH₂Ph); 7.31 (9H, m, aromatics); 7.76 (1H, d, $J = 8.5$ Hz, NH); MS m/e (FAB) 378, 380 M⁺.

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- 83 -

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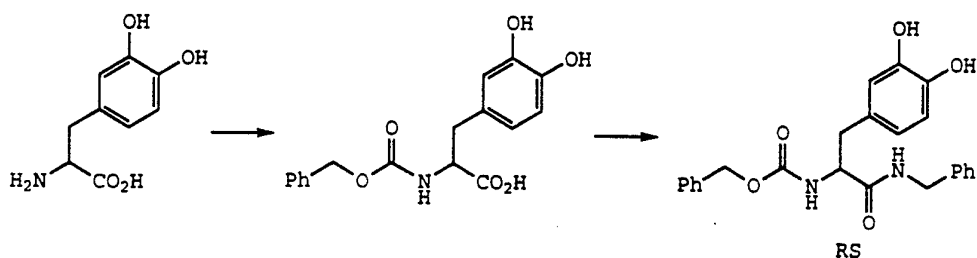


Method as for Example 32, Scheme VII. Yield
 (0.43 g, 61%); mp 163-164°C;
 IR (film): 3296, 1698 (urethane CO), 1656 (amide I),
 and 1548 cm⁻¹ (amide II);
 NMR (DMSO-d₆): δ 2.78 (1H, d.d, J = 10.1 and 13.5 Hz,
 one of βCH₂); 2.98 (1H, d.d, J = 4.4 and 13.5 Hz, one
 of βCH₂); 4.27 (3H, m, αCH, NHCH₂Ph); 4.95 (2H, s,
 PhCH₂O); 7.16-7.45 (14H, m, aromatics); 7.55 (1H, d,
 J = 8.6 Hz, NH); 8.51 (1H, t, J = 5.6 Hz, NHCH₂Ph);
 MS m/e (CI) 467, 469 M⁺.

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EXAMPLE 34 (Scheme VII)

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RS-3,4-Dihydroxyphenylalanine (0.99 g, 5 mmol) was
 suspended in a 1:1 mixture of dioxan water. NaHCO₃
 (0.84 g, 10 mmol) was added followed by a solution of
 dibenzylidencarbonate (1.72 g, 6 mmol) in dioxan (5 mL).
 The reaction was stirred overnight at room temperature
 under an atmosphere of nitrogen. The solution was
 diluted with water (20 mL) and was washed with ether

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- 84 -

(2 x 20 mL). The aqueous layer was then acidified to pH 1 with concentrated HCl and was extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were washed with water (3 x 30 mL) and then were dried over MgSO₄. The solvent was removed in vacuo and the brown oil obtained was partially purified by chromatography to give a brown oil (1.49 g, 90%). The oil (1.49 g, 4.5 mmol) was dissolved in ethyl acetate (15 mL), dicyclohexylcarbodiimide (0.93 g, 4.5 mmol), and pentafluorophenol (0.83 g, 4.5 mmol) were added and the reaction was stirred overnight at room temperature. The precipitate formed was removed by filtration. Concentration of the filtrate in vacuo resulted in an orange oil (2.24 g) which was redissolved in ethyl acetate (10 mL). Benzylamine (0.49 mL, 4.5 mmol) was added and the reaction was stirred at room temperature under an atmosphere of nitrogen for 2 hours. Removal of the solvents in vacuo gave a brownish solid which was purified by chromatography to give the product (0.29 g, 16%); mp 207-208°C; IR 3500-3000: 1703 (urethane CO), 1662 (amide I), 1609 (aromatic) and 1547 cm⁻¹ (amide I); NMR (DMSO-d₆): δ 2.62 (1H, d.d, J = 9.0 and 13.5 Hz, one of βCH₂); 2.81 (1H, d.d, J = 4.6 and 13.5 Hz, one of βCH₂); 4.18-4.33 (3H, m, αCH, NHCH₂Ph); 4.97 (2H, s, PhCH₂O); 6.50 (1H, d, J = 7.7 Hz, dihydroxy Phe H₅); 6.60 (1H, d, J = 7.7 Hz, dihydroxyPhe H₆); 6.67 (1H, s, dihydroxyPhe H₂); 7.14-7.34 (10H, m, aromatics); 7.40 (1H, d, J = 8.2 Hz, NH); 8.42 (1H, b.t, NHCH₂Ph); 8.66 (2H, s, OH x 2); MS m/e (CI) 421 [M⁺].

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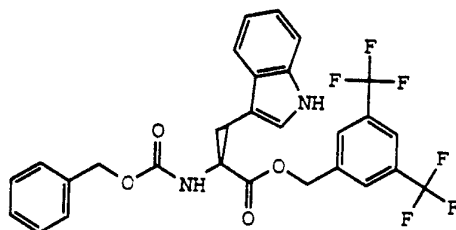
EXAMPLE 35

(Scheme I)

Methyl N-[(phenylmethoxy)carbonyl]-
[3,5-bis(trifluoromethyl)phenyl]-L-tryptophan

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Z-Trp-OPFP (0.2 g, 0.4 mmol) in EtOAc (30 mL) was treated with 3,5-bis(trifluoromethyl)benzyl alcohol (0.12 g, 0.5 mmol) and DMAP (0.03 g). This mixture was warmed to reflux for 20 minutes. The reaction mixture was washed with 2 M HCl (2 x 50 mL), then H₂O (2 x 50 mL), dried over MgSO₄, and evaporated to dryness in vacuo. The residue was purified by silica gel chromatography using 30% EtOAc in CH₂Cl₂ as eluant, then by reverse phase silica chromatography using 90% MeOH in H₂O as eluant to give the product as a white solid (0.192 g, 85%); mp = 134-136°C (MeOH/H₂O); $[\alpha]_D^{20} = -8^\circ$ ($c = 0.25$, MeOH); IR (film): 3409, 1745, 1715, 1506 cm⁻¹; NMR (DMSO-d₆): δ 3.15 (2H, m); 4.38 (1H, m); 4.98 (2H, s); 5.20 (1H, d, $J = 13.3$ Hz); 5.32 (1H, d, $J = 13.4$ Hz); 6.96 (1H, t, $J = 7.4$ Hz); 7.05 (1H, t, $J = 8.1$ Hz); 7.16 (1H, s); 7.30 (6H, m); 7.48 (1H, d, $J = 8.0$ Hz); 7.90 (1H, d, $J = 7.4$ Hz); 7.99 (2H, s), 8.05 (1H, s); 10.82 (1H, br s); MS m/e (CI): 565 (22%), 564 (21%), 521 (31%), 504 (36%), 131 (53%), 130 (100%), 91 (83%); Analysis calculated for C₂₈H₂₂N₂O₄F₆: C, 59.58; H, 3.93; N, 4.96%. Found: C, 59.87; H, 4.03; N, 4.98%.

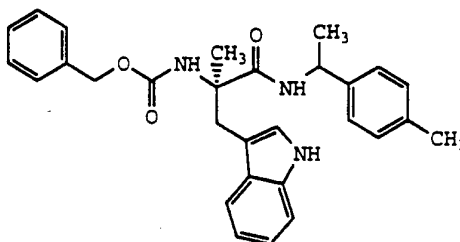
-86-

EXAMPLES 36 and 37

Phenylmethyl [1-(1H-indol-3-ylmethyl)-1-methyl-
2-[[1-(4-methylphenyl)ethyl]amino]-2-oxoethyl]carbamate
Stereoisomer I

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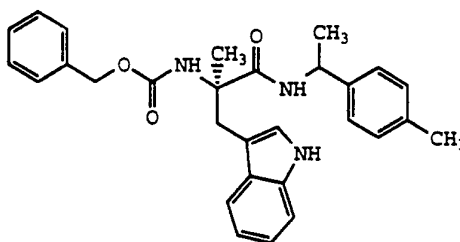
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Phenylmethyl [1-(1H-indol-3-ylmethyl)-1-methyl-
2-[[1-(4-methylphenyl)ethyl]amino]-2-oxoethyl]carbamate
Stereoisomer II

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Step 1

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4'-Methylacetophenone (93.9 g, 0.70 mol) was treated with EtOH (330 mL), H₂O (400 mL), hydroxylamine hydrochloride (51.1 g, 0.735 mol), potassium hydroxide (94.7 g (85%), 1.44 mmol) and stirred for 12 hours. Solution poured into 1 L of water and treated with excess solid carbondioxide. Filtration and recrystallization from ether/hexane gave pure product (92 g, 88%); mp 82-84°C; IR (film): 3327 (broad), 2925, 1607, 1515, 1456, 1369, 1313, 1304, 1180, 1127, 1012, 927, 821, 749 cm⁻¹; NMR (CDCl₃): δ, 2.29 and 2.37 [each 3H, each s, CH₃ and Ar-CH₃]; 7.19 (2H, d, J = 8.0 Hz, meta to Me);

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7.52 (2H, d, J = 8.1 Hz, ortho to Me); 9.27 (1H, s, OH);

Analysis calculated for $C_9H_{11}NO$:

C, 72.46; H, 7.43; N, 9.39%.

5 Found: C, 72.35; H, 7.46; N, 9.38%.

Step 2

Oxime (29.83 g, 0.2 mol) dissolved in absolute EtOH (200 mL) and 10% palladium on carbon (2 g) added. Shaken for 3 hours under an atmosphere of hydrogen at 50 psi before filtering off catalyst using celite. Solvent removed under reduced pressure and residue taken up in 250 mL of ether and amine extracted into 15% hydrochloric acid (50 mL), aqueous phase basified using 50% NaOH solution and product extracted with ether (2 x 250 mL). Organic phase dried over K_2CO_3 , ether removed under reduced pressure, and residue distilled to give pure product (24.6 g, 91%); bp 120°C 10 mm Hg;

20 NMR ($CDCl_3$): δ 1.37 (3H, d, J = 6.6 Hz, $CHCH_3$); 1.47 (2H, s, NH_2); 2.33 (3H, s, MeAr); 4.08 (1H, q, J = 6.6 Hz, $CHCH_3$); 7.13 (2H, d, J = 7.13 Hz); 7.23 (2H, d, J = 7.23 Hz);

Analysis calculated for $C_9H_{13}N \cdot 0.05H_2O$:

25 C, 79.42; H, 9.70; N, 10.29%.

Found: C, 79.36; H, 9.76; N, 10.26%.

Step 3

To a stirred solution CBZ-(R)- α -methyltryptophan-pentafluorobenzyl ester (0.259 g, 0.5 mmol) in EtOAc (30 mL) was added amine (0.081 g, 0.6 mmol) and left to stir overnight at room temperature. Reaction mixture washed with 10% citric acid solution (3 x 30 mL), H_2O (30 mL), saturated $NaHCO_3$ solution (2 x 30 mL), brine (2 x 30 mL), dried over $MgSO_4$, and solvent removed under reduced pressure. Residue chromatographed

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using ether as eluant or normal phase silica.
Crystallization from ether (2 mL) over 2 days in
freezer gave pure Isomer I (CAM 2676) (0.09 g, 38%).
The filtrate was taken, solvent removed under reduced
5 pressure, and a foam obtained from dichloromethane to
give CAM 2677 (Mainly Isomer II, de >70% by NMR, 80 mg,
34%).

Isomer I

10 mp 155-158°C;
[α]_D²² = 8.1° (c = 0.5, MeOH);
IR (film): 3328 (br, NH), 2926, 1713 (CO, urethane),
1651 (CO, amide), 1505, 1456, 1249, 1070, 81 cm⁻¹;
NMR (CDCl₃): δ 1.28 (3H, t, CHCH₃, J = 6.9 Hz); 1.61
15 (3H, s, CCH₃); 2.32 (3H, s, CH₃Ar); 3.26 (1H, d,
J = 14.8 Hz, one of CH₂ indole); 3.46 (1H, d,
J = 14.7 Hz, one of CH₂ indole); 4.97 (1H, p,
J = 7.2 Hz, NHCHCH₃); 5.07 (2H, s, CH₂Ph); 5.37 (1H, s,
OCONH); 6.25-6.35 (1H, br.d, NHCH); 6.80 (1H, s, indole
20 C₂H); 7.03-7.35 (12H, m, aromatics); 7.58 (1H, d,
J = 7.7 Hz, indole C₄-H); 7.95 (1H, s, indole NH);
MS m/e (CI⁺): 469 (M⁺, 0.2%), 362 (1%), 340 (1%), 318
(3%), 244 (3%), 130 (16%), 119 (13%), 108 (20%), 91
(100%);
25 Analysis calculated for C₂₉H₃₁N₃O₃·0.2H₂O:
C, 73.61; H, 6.69; N, 8.88%.
Found: C, 72.68; H, 6.63; N, 8.82%.

Isomer II

30 mp 62-65°C;
[α]_D²⁰ = +45° (c = 0.5, MeOH);
IR (film): 3325 (br, NH₃), 3057, 2976, 2925 (CH str),
1715 (CO, urethane), 1652 (CO, amide), 1506, 1456,
1341, 1250, 1070, 817, 74 cm⁻¹;
35 NMR (CDCl₃): δ 1.30 (3H, d, J = 6.8 Hz, CH₃CH); 1.56
(2.55H, s, CH₃C for major diastereoisomer); 1.60

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(0.45H, s, CH_3C for minor diastereoisomer); 2.31 (3H, s, Ar Me); 3.28 and 3.47 (each 1H, each d, $J = 14.7$ Hz, each one of CH_2 indole); 4.92-5.06 (2H, m, CHCH_3 , one of CH_2O), 5.11 (1H, d, $J = 12.1$ Hz, one of CH_2O); 5.27 (0.85H, s, OCONH); 5.40 (0.15H, s, OCONH); 6.30-6.40 (1H, br.d, CHNH); 6.79 (1H, s, indole C_2H); 7.05-7.35 (12H, m, aromatics); 7.57 (1H, d, $J = 7.9$ Hz, indole C_4H); 8.06 (1H, s, indole NH);
 MS m/e (CI^+): 470 ($\text{M}^+\text{+H}$, 9%), 426 (2%), 352 (2%), 340 (11%), 318 (20%), 244 (12%), 130 (94%), 119 (100%), 91 (88%);

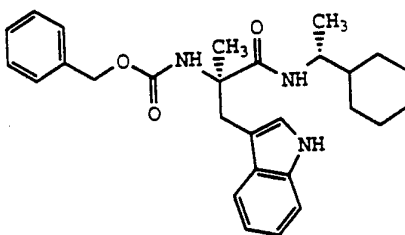
Analysis calculated for $\text{C}_{29}\text{H}_{31}\text{N}_3\text{O}_3 \cdot 0.2\text{H}_2\text{O}$:

C, 73.61; H, 6.69; N, 8.88%.

Found: C, 70.56; H, 6.69; N, 8.88%.

EXAMPLE 38

Phenylmethyl [R-(R*, R*)]-(2-[(1-cyclohexylethyl)-amino]-1-(1H-indol-3-ylmethyl)-1-methyl-2-oxoethyl]carbamate



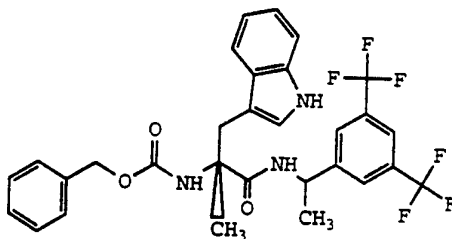
A solution of Z- α -Me-R-Trp-OPFP ester (0.5 g, 0.1 mmol) in EtOAc (30 mL) was treated with cyclohexyl-1-ethyl amine (R isomer) (0.15 g, 1.2 mmol) and stirred for 2 hours at room temperature. The solvent was evaporated and the residue purified by silica gel chromatography using 0-1% MeOH in CH_2Cl_2 as eluant then by reverse phase silica gel chromatography using 30%

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MeOH in H₂O as eluant to give the product as an amorphous white solid (0.277 g, 62%); mp 51-73°C; IR (film): 3318, 1709, 1650, 1516, 1655 cm⁻¹; NMR (CDCl₃): δ 0.73-0.98 (2H, m); 0.89 (3H, d, J = 6.7 Hz); 1.00-1.30 (4H, m); 1.47-1.87 (5H, m); 1.56 (3H, s); 3.28 (1H, d, J = 14.7 Hz); 3.48 (1H, d, J = 14.5 Hz); 3.64-3.82 (1H, m); 5.08 (2H, br.s); 5.46 (1H, s); 6.13 (1H, d, J = 8.8 Hz); 6.87 (1H, d, J = 2.2 Hz); 7.06 (1H, dt, J = 1.0 and 7.0 Hz); 7.14 (1H, dt, J = 1.0 and 7.0 Hz); 7.30 (5H, m); 7.55 (1H, d, J = 7.8 Hz); 8.61 (1H, s); Analysis calculated for C₂₈H₃₄N₃O₃·0.25H₂O: C, 72.31; H, 7.48; N, 9.08%. Found: C, 72.24; H, 7.58; N, 8.81%.

EXAMPLE 39

Phenylmethyl (R,RS)-[2-[[1-[3,5-bis(trifluoromethyl)-phenyl]ethyl]aminol-1-(1H-indol-3-ylmethyl)-1-methyl-2-oxoethyl]carbamate



A solution of Z- α Me-R-Trp-OPFP ester (0.25 g, 0.50 mmol) in EtOAc (50 mL) was treated with 3,5-bis-(trifluoromethyl)- α -methyl-benzylamine (RS mixture) (0.245 g, 0.950 mmol). The reacting mixture was stirred at room temperature for 1 hour, washed 2 M HCl (2 x 50 mL) and H₂O (2 x 50 mL). The organic phase was dried (MgSO₄), filtered, and evaporated to dryness in vacuo. The residue was purified by silica gel chromatography using a 10-80% gradient of EtOAc in

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hexane as eluant, then by reverse phase silica gel chromatography using 80% MeOH in H₂O as eluant to give the product as a white foam (0.232 g, 81%); mp 69-73°C (CH₂Cl₂);

5 $[\alpha]_D^{20} = +29$ ($c = 0.25$, MeOH);

IR (film): 3327, 1716, 1661, 1506, 1279 cm⁻¹;

NMR (DMSO-d₆) (340 K): δ 1.25-1.45 (6H, m); 3.20 (1H) and 3.36 (1H) both obscured by H₂O; 5.04 (3H, m); 6.79 (1H, br.s); 6.87-7.10 (3H, m); 7.33 (6H, m); 7.46 (1H, d, $J = 7.8$ Hz); 7.87-8.15 (4H, m); 10.70 (1H, br.s);

Analysis calculated for C₃₀H₂₇N₃O₃F₆:

C, 60.91; H, 4.60; N, 7.10%.

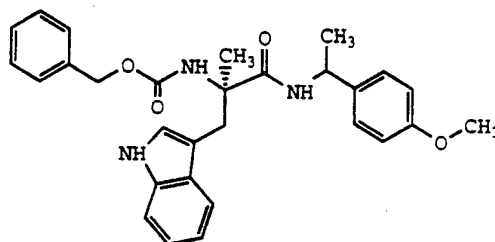
Found: C, 60.93; H, 4.68; N, 6.96%.

15

EXAMPLE 40

Phenylmethyl (R,RS)-[1-(1H-indol-3-ylmethyl)-2-[[1-(4-methoxyphenyl)ethyl]amino]-1-methyl-2-oxoethyl]-carbamate

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Z-R- α -Me-Trp-OPFP ester (0.2 g, 0.4 mmol) in EtOAc (30 mL) was treated with racemic 4-methoxy- α -methylbenzylamine (0.15 g, 1.00 mmol) as the mixture stirred at room temperature for 20 minutes. Triethylamine (1 g, 9 mmol) was then added and the solution stirred a further 30 minutes. The reaction mixture was washed with 1 M HCl (2 x 50 mL) then H₂O (2 x 50 mL), dried (MgSO₄), filtered, and evaporated to dryness in vacuo.

35 The residue was separated by chromatography over silica gel using CH₂Cl₂ then 20% Et₂O in CH₂Cl₂ as eluant to

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give the product as a white foam (0.176 g, 94%);

mp 62-65°C (MeOH);

$[\alpha]_D^{20} = +19^\circ$ ($c = 0.5$, MeOH);

IR (film): 3338, 2933, 1716, 1652, 1513, 1456,

5 1247 cm^{-1} ;

NMR (DMSO- d_6): δ 1.26 (1.5H, d, $J = 7.1$ Hz); 1.30

(1.5H, d, $J = 7.1$ Hz); 1.33 (1.5H, s); 1.38 (1.5H, s);

3.30 (2H, obscured by H_2O); 3.72 (1.5H, s); 3.73 (1.5H,

s); 4.85 (1H, m); 5.04 (2H, s); 6.79-6.95 (5H, m); 7.02

10 (1H, t, $J = 7.1$ Hz); 7.20 (2H, dd, $J = 8.7$ and

12.6 Hz); 7.34 (6H, m); 7.47 (1H, t, $J = 7.2$ Hz); 7.81

(0.5H, d, $J = 8.0$ Hz); 7.93 (0.5H, d, $J = 8.0$ Hz);

10.80 (1H, br.s);

MS m/e (FAB): 486 (75%), 356 (100%), 264 (98%);

15 Analysis calculated for $\text{C}_{29}\text{H}_{31}\text{N}_3\text{O}_4 \cdot 0.25\text{H}_2\text{O}$:

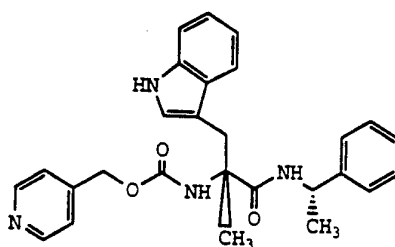
C, 71.07; H, 6.48; N, 8.57%.

Found: C, 71.08; H, 6.58; N, 8.40%.

EXAMPLE 41

20 4-Pyridinylmethyl [1-(1H-indol-3-ylmethyl)-1-methyl-
2-oxo-2-[(1-phenylethyl)amino]carbamate

25



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To a stirred solution of

(Veber, et al., J Org Chem 1977;42:3256) (302 mg,

1.1 mmol) and α -methyltryptophanyl-1-phenethylamide

(321 mg, 1 mmol) in DMF (10 mL, anhydrous) was added

35 solid DMAP (122 mg, 1 mmol). After stirring overnight
at room temperature, the DMF was removed at 60°C under

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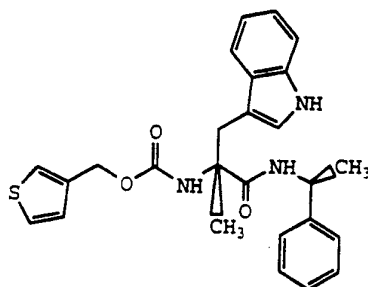
reduced pressure and the residue suspended between EtOAc (50 mL) and 1N NaOH solution (50 mL). The organic phase was washed with 5 x 30 mL portions of 1N NaOH solution, brine (30 mL), dried over MgSO_4 ,
5 filtered, and solvent removed under reduced pressure. Residue chromatographed using normal phase silica with EtOAc/MeOH/ NH_3 (90:10:1) to obtain desired product which crystallized from ether giving white needles (180 g, 39%); mp 146-148°C;
10 $[\alpha]_D^{20} = +4$ (c = 0.5, MeOH);
IR (film): 3309 (br, NH), 1721 (CDCl urethane), 1650 (CO, amide), 1609, 1494, 1455, 1417, 1342, 1252, 1077, 910, 735, 700, 666 cm^{-1} ;
NMR (CDCl_3): δ 1.27 (3H, d, $J = 6.9$ Hz, CH, CH_3); 1.67
15 (3H, s, CCH_3); 3.32 (1H, d, $J = 14.7$ Hz, one of CH_2 indole); 3.47 (1H, d, $J = 14.7$ Hz, one of CH_2 indole); 5.00 (1H, p, $J = 7.0$ Hz, CH_3CHNH); 5.07 (2H, s, CH_2O); 6.20 (1H, d, $J = 7.3$ Hz CONHCH); 5.67 (1H, s, OCONH); 6.87 (1H, d, $J = 2.3$ Hz, indole C_2H); 7.05-7.30 (9H, m, CHPh , 2 indole CH's and 2 pyridyl CH's); 7.36 (1H, d, $J = 3.0$ Hz, indole C_7H); 7.59 (1H, d, $J = 7.9$ Hz indole C_4H); 8.09 (1H, s, indole NH); 8.54 (2H, d.d, $J = 4.4$ and 1.6 Hz, pyridyl CH's);
20 MS m/e (CI^+): 457 ($\text{M}^+ + \text{H}$, 2%), 348 (5%), 244 (4%), 219 (1%), 201 (3%), 138 (10%), 130 (24%), 110 (100%), 92 (52%);
25 Analysis calculated for $\text{C}_{27}\text{H}_{28}\text{N}_4\text{O}_3 \cdot 0.25\text{H}_2\text{O}$:
C, 70.34; H, 6.23; N, 12.15%.
Found: C, 70.31; H, 6.08; N, 11.99%.

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EXAMPLE 42

3-Thienylmethyl [R-(R*,S*)]-[1-(1H-indol-3-ylmethyl)-1-methyl-2-oxo-2-[(1-phenylethyl)amino]ethyl]carbamate

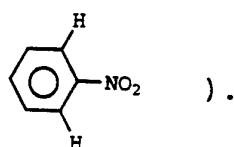
Step 1

To a stirred solution of 3-thiophenmethanol (1.14 g, 10 mmol) and 4-nitrophenylchloroformate (2.01 g, 10 mmol) in dichloromethane (50 mL) at 0°C was added dropwise a solution of pyridine (0.79 g, 10 mmol) in dichloromethane (10 mL). Reaction mixture allowed to warm to room temperature overnight. Solvent removed under reduced pressure and residue taken up between EtOAc (50 mL) and 10% citric acid solution (50 mL). Organic phase washed successively with 10% citric acid solution (2 x 30 mL), H₂O (30 mL), saturated NaHCO₃ solution (2 x 50 mL), and brine (50 mL). Organic phase dried over MgSO₄, filtered, and solvent removed under reduced pressure. Two crystallizations from EtOAc gave pure product (1.11 g, 40%); mp 75.0-78.4°C;

IR (film): 1763 (C = O), 1593 (aromatic C-H), 1522 (NO₂), 1491, 1347 (NO₂), 1211, 1164, 862 cm⁻¹;

NMR (CDCl₃): δ 5.30 (2H, s, CH₂); 7.16-7.18 (1H, m, aromatic C-H); 7.35-7.45 (2H, m, aromatic); 7.37 (2H,

d, J = 9.1 Hz,); 8.27 (2H, d, J = 9.2 Hz



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Analysis calculated for $C_{12}H_9NO_5S$:

C, 51.61; H, 3.25; N, 5.02; S, 11.48%.

Found: C, 51.57; H, 3.21; N, 5.03; S, 11.34%.

5 Step 2

10 To a stirred solution of the carbonate (154 mg, 0.55 mmol) and α -methyltryptophanyl-1-phenethylamide (160 mg, 0.5 mmol) in DMF (5 mL, anhydrous) was added solid DMAP (61 mg, 0.5 mmol) and left to stir overnight at room temperature. Solvent removed at 60°C under reduced pressure and the residue taken up in EtOAc (30 mL) and washed successively with 10% citric acid solution (2 x 30 mL), H_2O (30 mL), 1N NaOH (5 x 30 mL, until aqueous phase no longer intense yellow in color), and brine (2 x 30 mL). Organic phase dried over $MgSO_4$, filtered, solvent removed under reduced pressure, and residue crystallized from ether to give pure product (197 mg, 85%); mp 117-121°C;

20 IR (film): 3327 (br, NH), 1711 (CO, urethane), 1651 (CO, amide), 1494, 1454, 1247, 1071, 909, 741 cm^{-1} ;
NMR ($CDCl_3$): δ 1.32 (3H, d, J = 6.9 Hz, CH_3CH); 1.61 (3H, s, CH_3C), 3.25 (1H, d, J = 14.8 Hz, one of CH_2 indole); 3.46 (1H, d, J = 15 Hz, one of CH_2 indole); 4.95-5.15 (3H, m, CH_2O and $CHPh$); 5.33 (1H, s, $CONH$);
25 6.35-6.45 (1H, br.d, $CONHCH$); 6.76 (1H, s, indole C_2H); 7.05-7.35 (11H, m, aromatics); 7.57 (1H, d, J = 7.7 Hz, indole C_4-H); 8.01 (1H, s, indole NH);
30 MS m/e (Cl^-): 462 (M^+H , 0.2%), 348 (4%), 304 (2%), 244 (5%), 219 (1%), 158 (1%), 130 (37%), 114 (94%), 97 (100%), 85 (71%);

Analysis calculated for $C_{26}H_{27}N_3O_3S$:

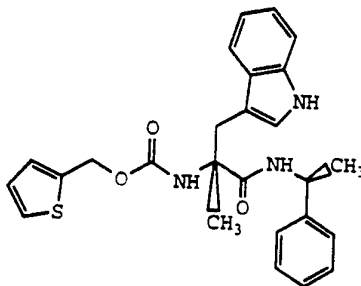
C, 67.66; H, 5.90; N, 9.10; O, 6.95%.

Found: C, 67.51; H, 5.88; N, 9.03; O, 6.94%.

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EXAMPLE 43

2-Thienylmethyl [R-(R*,S*)]-[1-(1H-indol-3-ylmethyl)-
1-methyl-2-oxo-2-[(1-phenylethyl)amino]ethyl]carbamate

Step 1

See Method as for Example 42. Yield = 2.09 g, 75%;
 mp 67.5-68.5°C;

IR (film): 1766 (CO, carbonate), 1616 and 1594
 (aromatic CH); 1523 (NO₂); 1493; 1347 (NO₂); 1248,
 1213, 863 cm⁻¹;

NMR (CDCl₃): δ 5.45 (2H, s, CH₂O; 6.98-7.07 (1H, m,
 aromatic CH); 7.18-7.25 (1H, m, aromatic CH); 7.30-7.43
 (1H, m, aromatic CH); 7.38 (2H, d, J = 9.2 Hz, CH meta
 to NO₂); 8.28 (2H, d, J = 9.2 Hz, CH ortho to NO₂);

Analysis calculated for C₁₂H₉NO₅S:

C, 51.61; H, 3.25; N, 5.02%.

Found: C, 51.56; H, 3.20; N, 4.94%.

Step 2

See Method as for Example 42. Product
 chromatographed on normal phase silica using 2% MeOH in
 CH₂Cl₂ followed by crystallization from ether gave pure
 product (220 mg, 95%); mp 125-127°C;

[α]_D²⁰ = +5.7° (c = 0.5 MeOH);

IR (film): 3327 (br, NH), 1713, 1651, 1494, 1456,
 1247, 1068, 740, 699 cm⁻¹;

NMR (CDCl₃): δ 1.32 (3H, d, J = 6.9 Hz, CH₃CH); 1.62
 (3H, s, CCH₃); 3.24 (1H, d, J = 14.7 Hz, one of CH₂
 indole); 3.51 (1H, d, J = 14.8 Hz, one of CH₂ indole);

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5.01 (1H, p, $J = 7.1$ Hz, NHCHCH_3); 5.19 (1H, d, $J = 12.8$ Hz, one of CH_2O); 5.25 (1H, d, $J = 12.8$ Hz, one of CH_2O); 5.33 (1H, s, OCONH); 6.30-6.40 (1H, br.d, CONHCH); 6.77 (1H, s, indole C_2H); 6.93-7.30 (10H, m, aromatics); 7.33 (1H, d, $J = 8.0$ Hz, indole $\text{C}_7\text{-H}$); 7.57 (1H, d, $J = 7.8$ Hz, indole $\text{C}_4\text{-H}$); 7.95 (1H, s, indole NH);

MS m/e (CI^+): 462 ($\text{M}^+\text{+H}$, 0.2%), 461 (M^+ , 0.2%), 418 (2%), 348 (3%), 304 (3%), 244 (4%), 191 (2%), 130 (30%), 114 (34%), 97 (100%), 85 (47%);

Analysis calculated for $\text{C}_{26}\text{H}_{27}\text{N}_3\text{O}_3\text{S}$:

C, 67.66; H, 5.90; N, 9.10; S, 6.95%.

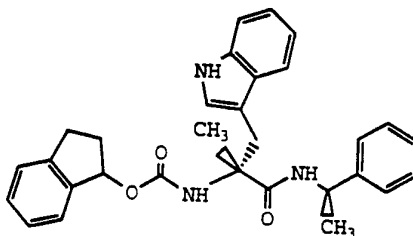
Found: C, 67.38; H, 5.82; N, 9.02; S, 7.08%.

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EXAMPLE 44

2,3-Dihydro-1H-inden-3-yl [R-(R*,S*)]-[1(1H-indol-3-ylmethyl)-1-methyl-2-oxo-2-[(phenylethyl)amino]-ethyl]carbamate

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25

Step 1

See Method for Example 42. Product unstable on standing and unable to obtain a pure crystalline sample. A sample about 90% by NMR was used as soon as possible for Step 2.

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Step 2

See Method for Example 42. Crude product chromatographed using normal phase silica using 1.5% MeOH in CH_2Cl_2 then rechromatographed using

35

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35% EtOAc in hexane to give pure product (1:1 mix of diastereoisomers, 30 mg, 12%); mp 75-80°C;

$[\alpha]_D^{20} = +13.8^\circ$ (c = 0.5 MeOH);

5 IR (film): 3331 (br, NH), 3057, 2976, 2935, 1705 (CO, urethane), 1653 (CO, amide), 1494, 1458, 1376, 1341, 1248, 1070, 742, 700 cm^{-1} ;

NMR (CDCl_3) mix of 2 diastereoisomers: δ 1.31 (1.5H, CH_3CH of one diastereoisomer, d, $J = 6.9$ Hz); 1.39 (1.5H, d, $J = 6.9$ Hz, CH_3CH of one diastereoisomer);
10 1.61 and 1.62 (each 1.5H, each s, CH_3C for both diastereoisomers); 2.00-2.10 (1H, m, CH of indane); 2.40-2.55 (1H, m, CH of indane); 2.80-2.90 (1H, m, CH of indole); 3.00-3.15 (1H, m, CH of indole); 3.22 (0.5H, d, $J = 14.7$ Hz, one of CH_2 indole for one
15 diastereoisomer); 3.27 (0.5H, d, $J = 14.6$ Hz, one of CH_2 indole for one diastereoisomer); 3.47 (0.5H, d, $J = 14.1$ Hz, one of CH_2 indole for one diastereoisomer); 3.49 (0.5H, d, $J = 14.0$ Hz, one of CH_2 indole for one diastereoisomer); 4.98-5.12 (1H, m, CHCH_3);
20 5.20 (1H, s, OCONH); 6.10-6.15 (1H, m, CHOCO); 6.40-6.50 (1H, m, CONHCH); 6.80 and 6.84 (each 0.5H, each s, each half of $\text{C}_2\text{-H}$, indole); 7.05-7.43 (12H, m, aromatics); 7.59 (1H, d, $J = 8.0$ Hz, indole $\text{C}_7\text{-H}$); 7.96 and 8.00 (each 0.5H, each s, each half of indole NH);
25 MS m/e (FAB): 5043 ($\text{M}^+ + \text{Na}$, 20%), 482.3 ($\text{M}^+ + \text{H}$, 12%), 4383 (4%), 366.2 (55%), 322.2 (100%), 304.2 (36%);

Analysis calculated for $\text{C}_{30}\text{H}_{31}\text{N}_3\text{O}_3$:

C, 74.82; H, 6.49; N, 8.73%.

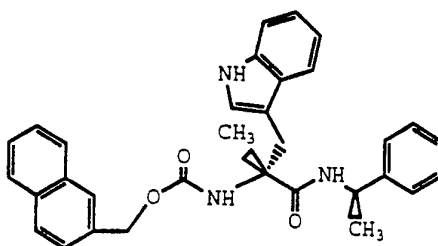
Found: C, 74.62; H, 6.46; N, 8.66%.

30

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EXAMPLE 45

1-Naphthalenylmethyl [R-(R*,S*)]-[1-(1H-indol-3-ylmethyl)-1-methyl-2-oxo-2-[(1-phenylethyl)amino]-ethyl]carbamate

Step 1

See Method for Example 42. Crystallization of product from crude residue using EtOAc followed by washing with 10% citric acid solution (2 x 30 mL) and multiple water washes gave pure product (2.37 g, 73%); mp 150.5-152.5°C;

IR (film): 1752 (C = O), 1615, 1595 (aromatic C-H); 1536 (NO₂); 1360 (NO₂); 1281 cm⁻¹;

NMR (DMSO-d₆): δ 5.48 (2H, s, Ar CH₂O; 7.50-7.65 (3H, m, aromatics CH); 7.59 (2H, d, J = 9.2 Hz, meta to NO₂ group); 7.90-8.05 (4H, m, aromatic CH); 8.32 (2H, d, J = 9.1 Hz, ortho to NO₂ group);

Analysis calculated for C₁₈H₁₃NO₅:

C, 66.87; H, 4.05; N, 4.33%.

Found: C, 66.74; H, 4.06; N, 4.27%.

Step 2

See Method for Example 45. Crude product chromatographed on normal phase silica using 3% MeOH/CH₂Cl₂ then crystallized from ether to give pure product (220 mg, 87%); mp 121-122°C; [α]_D²⁰ = +21.2° (c = 0.5, MeOH);

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IR (film): 3342 (br), 3052, 2924 and 2926 (CH, str);
1717 (CO, urethane); 1653 (CO, amide); 1495, 1457,
1250, 1073, 819, 742 cm^{-1} ;

NMR (CDCl_3): δ 1.28 (3H, d, J = 6.9 Hz, CH_3CH); 1.63
5 (3H, s, CH_3C); 3.26 (1H, d, J = 14.7 Hz, one of CH_2
indole); 3.48 (1H, d, J = 14.7 Hz, one of CH_2 indole);
5.00 (1H, p, J = 7.0 Hz, NHCHCH_3); 5.24 (1H, d,
 J = 12.5 Hz, one of CH_2O); 5.26 (1H, d, J = 12.1 Hz,
one of CH_2O); 5.40 (1H, s, OCONH); 6.30-6.40 (1H, br.d,
10 CONHCH); 6.74 (1H, s, indole C2-H); 7.05-7.30 (7H, m,
aromatics); 7.31 (1H, d, J = 8.0 Hz, indole C7-H);
7.40-7.52 (3H, m, aromatics); 7.58 (1H, d, J = 8.4 Hz,
indole C4-H); 7.75-7.85 (5H, m, aromatics and indole
NH);

15 MS m/e (FAB): 506.3 (M^+H , 100%), 462.3 (5%), 429.1
(15%), 401.0 (14%), 376.2 (18%), 341.4 (50%), 304.2
(54%), 281.1 (34%), 257.3 (34%);

Analysis calculated for $\text{C}_{32}\text{H}_{31}\text{N}_3\text{O}_3$:

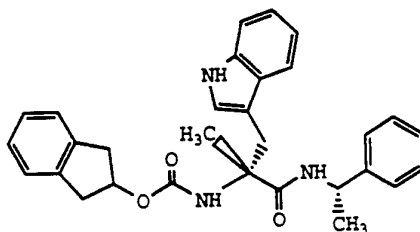
C, 76.02; H, 6.18; N, 8.31%.

20 Found: C, 75.88; H, 6.19; N, 8.28%.

EXAMPLE 46

2,3-Dihydro-1H-inden-2-yl [1-(1H-indol-3-ylmethyl)-
1-methyl-2-oxo-2-[(1-phenylethyl)amino]ethyl]carbamate

25



30

Step 1

See Method for Example 42. Product crystallized
35 from EtOAc and washed with ether to give product
(1.8 g, 60%); mp 110.5-113.5°C;

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IR (film): 1765 (CO), 1616, 1594 (aromatic C-H); 1525, 1349 (NO₂); 1261; 1226; 1187; 858 cm⁻¹;

NMR (DMSO-d₆): δ 3.21 (2H, d.d, J = 17 and 2.8 Hz

CH_AH_BCHCH_AH_B; 3.41 (2H, d.d, J = 17 and 6.1 Hz,

5 CH_AH_BCHCH_AH_B); 5.51-5.62 (1H, m, CHOCOO); 7.18-7.32 (4H, m, aromatic H); 7.37 (2H, d, J = 9.2 Hz, H's meta to NO₂ group); 8.27 (2H, d, J = 9.2 Hz, H's ortho to NO₂ group);

Analysis calculated for C₁₆H₁₃NO₅:

10 C, 64.21; H, 4.38; N, 4.68%.

Found: C, 64.36; H, 4.38; N, 4.68%.

Step 2

15 See Method for Example 42. Used 180 mg (0.6 mmol) of carbonate. Crude product chromatographed using normal phase silica using 2% MeOH/CH₂Cl₂ then crystallized from ether to give product (170 mg, 71%); mp 152-157°C;

$[\alpha]_D^{22}$ = +15.3° (c = 1, MeOH);

20 IR (film): 3326 (br, NH str), 2924 and 2852 (CH, str), 1705 (CO urethane), 1652 (CO, amide), 1494, 1457, 1252, 1073, 819, 741 cm⁻¹;

NMR (CDCl₃): δ 1.35 (3H, d, J = 6.9 Hz, CH₃CH); 1.58

(3H, s, CCH₃); 2.90-2.98 (2H, m, indane CH); 3.20-3.32

25 (3H, m, 2 indane CH and one of CH₂ indole); 3.46 (1H, d, J = 14.5 Hz, one of CH₂ indole); 5.02 (1H, p,

J = 6.9 Hz, NHCHCH₃); 5.20 (1H, s, OCONH); 5.38-5.48

(1H, m, CHOCONH); 6.30-6.40 (1H, br.d, CONHCH); 6.87

(1H, s, indole, C₂H); 7.10-7.35 (12H, m, aromatic CH₃);

30 7.59 (1H, d, J = 8.1 Hz, indole C₄-H); 8.00 (1H, s, indole NH);

m/e (CI⁺): 482 (M⁺+H, 6%), 348 (14%), 304 (11%), 244

(12%), 145 (14%) 134 (78%), 130 (72%), 117 (100%), 105 (88%), 91 (24%);

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Analysis calculated for $C_{30}H_{31}N_3O_3$:

C, 74.82; H, 6.49; N, 8.73%.

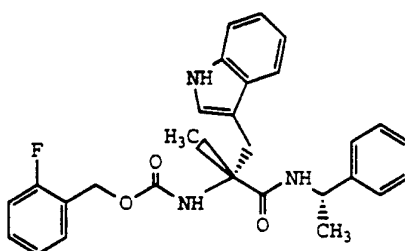
Found: C, 74.72; H, 6.50; N, 8.76%.

5

EXAMPLE 47

(2-Fluorophenyl)methyl [R-(R*,S*)]-[1-(1H-indol-3-ylmethyl)-1-methyl-2-oxo-[1-phenylethyl]aminoethyl]-carbamate

10



15

Step 1

See Method for Example 42. Crude residue chromatographed using 10% EtOAc in hexane on normal phase silica then crystallized from ethyl acetate to give pure product (0.990 g, 34%); mp 84-84.5°C; IR (film): 1752 (CO, carbonate), 1526 (NO₂), 758 cm⁻¹; NMR (CDCl₃): δ 5.38 (2H, s, PhCH₂); 7.08-7.23 (2H, m, aromatic CH); 7.32-7.54 (2H, m, aromatic CH); 7.39 (2H, d, J = 9.2 Hz, CH meta to NO₂); 8.27 (2H, d, J = 9.2 Hz, CH's ortho to NO₂);

25

Analysis calculated for $C_{14}H_{10}NO_5F$:

C, 57.73; H, 3.46; N, 4.81%.

Found: C, 57.77; H, 3.52; N, 4.81%.

30

Step 2

See Method for Example 42 except used 174 mg (0.6 mmol) of carbonate. Crude product chromatographed on normal phase silica using 2% MeOH/CH₂Cl₂ then crystallized from ether to give pure product (96 mg, 41%); mp 107-111°C;

35

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$[\alpha]_D^{22} = +8^\circ$ ($c = 0.25$, MeOH);

IR (film): 3338 (br, NH), 1713 (CO, urethane); 1652 (CO, amide), 1494, 1456, 1341, 1233, 1111, 1071, 909, 743 cm^{-1} ;

5 NMR (CDCl_3): δ 1.30 (3H, d, $J = 6.9$ Hz, CH_3CH); 1.62 (2H, s, CH_3C); 3.26 (1H, d, $J = 14.7$ Hz, one of CH_2 indole); 3.47 (1H, d, $J = 14.9$ Hz, one of CH_2 indole); 5.01 (1H, p, $J = 7.1$ Hz, NHCHCH_3); 5.13 (1H, d, $J = 12.5$ Hz, one of CH_2O); 5.19 (1H, d, $J = 12.8$ Hz, one of CH_2O); 5.38 (1H, s, OCONH); 6.35 (1H, d, $J = 7.6$ Hz, NHCH); 6.81 (1H, d, $J = 2.2$ Hz, indole C_2H); 7.00-7.38 (12H, m, aromatics); 7.58 (1H, d, $J = 7.8$ Hz, indole $\text{C}_4\text{-H}$); 8.00 (1H, s, indole NH);
 10 MS m/e (CI^+): 474 ($\text{M}^+\text{+H}$, 5%), 348 (20%), 347 (10%), 304 (9%), 281 (8%), 244 (32%), 219 (8%), 199 (9%), 158 (9%), 131 (23%), 130 (100%), 109 (57%), 105 (27%), 97 (16%);

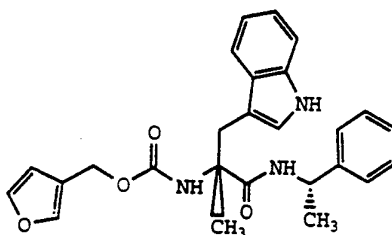
Analysis calculated for $\text{C}_{28}\text{H}_{28}\text{N}_3\text{O}_3\text{F}$:

C, 71.02; H, 5.96; N, 8.87%.

20 Found: C, 71.16; H, 6.01; N, 8.87%.

EXAMPLE 48

3-Furanylmethyl [R-(R*,S*)]-[1-(1H-indol-3-ylmethyl)-1-methyl-2-oxo-2-[(1-phenylethyl)amino]ethyl]carbamate



Step 1

See Method for Example 42. Product
 35 chromatographed using 14% EtOAc/Hexane then

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crystallized from EtOAc to give pure product

(1.87 mg, 71%); mp 56.5-57.5°C;

IR (film): 1766 (CO, carbonate), 1617, 1594, 1525, 1348 (NO₂), 1214, 1161, 863 cm⁻¹;

5 NMR (CDCl₃): δ 5.18 (2H, s, PhCH₂); 6.51 (1H, d, J = 1.1 Hz, furan C₄-H); 7.37 (2H, d, J = 9.2 Hz, CH meta to NO₂); 7.45 (1H, s, furan C₂ or C₅-H); 7.57 (1H, s, furan C₂ or C₅-H); 8.27 (2H, d, J = 9.2 Hz, CH ortho to NO₂);

10 Analysis calculated for C₁₂H₉NO₆:

C, 54.76; H, 3.45; N, 5.32%.

Found: C, 54.68; H, 3.45; N, 5.32%.

Step 2

15 See Method for Example 42 except used 158 mg (0.6 mmol) of carbonate. Crude product chromatographed using normal phase silica with 1% MeOH

n-dichloromethane as eluent then crystallized from ether to give product (164 mg, 74%); mp 126-128°C;

20 $[\alpha]_D^{21} = +4.9^\circ$ (c = 1, MeOH);

IR (film): 3332 (br, NH), 1709 (CO, urethane), 1652 (CO, amide), 1495, 1456, 1247, 1066, 1020, 874, 742 cm⁻¹;

25 NMR (CDCl₃): δ 1.32 (3H, d, J = 6.9 Hz, CHCH₃); 1.61 (3H, s, CCH₃); 3.25 (1H, d, J = 14.7 Hz, one of CH₂ indole); 3.45 (1H, d, J = 14.8 Hz, one of CH₂ indole); 4.93 (2H, s, CH₂O); 5.02 (1H, p, J = 7.2 Hz, NHCHCH₃); 5.32 (1H, s, OCONH); 6.30-6.40 (1H, m, CHNH); 6.37 (1H, s, furan C₄-H); 6.81 (1H, d, J = 2.2 Hz, indole C₂H); 30 7.05-7.35 (9H, m, aromatics); 7.43 (1H, s, furan CH); 7.58 (1H, d, J = 7.8 Hz, indole C₄-H); 8.02 (1H, s, indole NH);

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MS m/e (CI⁺): 446 (M⁺+1, 7%), 445 (2%), 402 (12%), 316 (11%), 304 (26%), 253 (12%), 244 (6%), 199 (8%), 191 (10%), 131 (23%), 130 (100%), 105 (51%), 81 (34%);

Analysis calculated for C₂₆H₂₇N₃O₄:

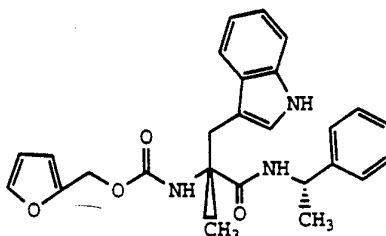
5 C, 70.10; H, 6.11; N, 9.43%.

Found: C, 70.13; H, 6.13; N, 9.46%.

EXAMPLE 49

10 2-Furanylmethyl [R.(R*,S*)]-[1-(1H-indol-3-ylmethyl)-
1-methyl-2-oxo-2-[(1-phenylethyl)amino]ethyl]carbamate

15



Step 1

20 See Method for Example 42, however, product was unstable and no pure sample was obtained. Used in the next step after chromatography on normal phase silica using 12.5% EtOAc/Hexane estimated purity >90%;

25 NMR (CDCl₃): δ 5.26 (2H, s, CH₂O); 6.37-6.45 (1H, m, H₄ on ring); 6.54 (1H, d, J = 3.2 Hz, H₃ on ring); 7.38 (2H, d, J = 9.2 Hz, H meta to NO₂ Group); 7.43-7.50 (1H, m, H₅ on ring); 8.27 (2H, d, J = 9.1 Hz, H ortho to NO₂ group);

30 Step 2

See Method for Example 42 except used 158 mg (0.6 mmol) of carbonate. Crude product chromatographed on normal phase silica using 1% MeOH/CH₂Cl₂ then crystallized from ether to give product (95 mg, 43%);

35 mp 133-140.5°C;
[α]_D²¹ = +9.0° (c = 0.5, MeOH);

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IR (film): 3331 (br, NH), 1713 (CO, urethane), 1652 (CO, amide), 1495, 1248, 1068, 742 cm^{-1} ;

NMR (CDCl_3): δ 1.33 (3H, d, J = 6.9 Hz, CHCH_3); 1.61 (3H, s, CCH_3); 3.24 (1H, d, J = 14.7 Hz, one the CH_2 indole); 3.46 (1H, d, J = 14.8 Hz, one of CH_2 indole); 4.95-5.10 (3H, m, CH_2O and CONHCH); 5.31 (1H, s, OCONH); 6.30-6.40 (3H, m, CONHCH , furan C_3 and C_4 -H); 6.80 (1H, d, J = 7.2 Hz, indole C_2 -H); 7.05-7.35 (8H, m, aromatics); 7.38 (1H, s, furan C_5 -H); 7.57 (1H, d, J = 8.1 Hz, indole C_4 -H); 7.99 (1H, s, indole NH);

MS m/e (CI^+ : 446 ($\text{M}^+ + 1$, 23%), 445 (M^+ , 11%), 402 (66%), 348 (16%), 316 (16%), 304 (82%), 253 (22%), 244 (24%), 191 (36%), 130 (100%), 105 (88%), 81 (49%);

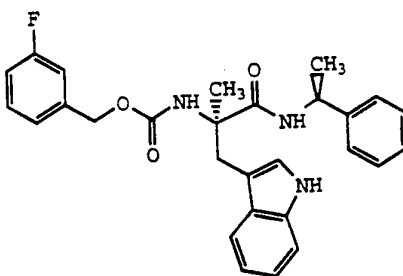
Analysis calculated for $\text{C}_{26}\text{H}_{27}\text{N}_3\text{O}_4$:

C, 70.10; H, 6.11; N, 9.43%.

Found: C, 70.09; H, 6.16; N, 9.37%.

EXAMPLE 50

(3-Fluorophenyl)methyl [R-(R*,S*)]-[1-(1H-indol-3-ylmethyl)-1-methyl-2-oxo-2-[(1-phenylethyl)amino]ethyl]carbamate



To a stirred solution of 3-fluorobenzyl alcohol (189 mg, 1.5 mmol) and triphosgene (178 mg, 0.6 mmol) under an atmosphere of N_2 at 0°C (ice bath) in CH_2Cl_2 (10 mL, anhydrous) was added a solution of pyridine (119 mg, 1.5 mmol) in CH_2Cl_2 (2 mL, anhydrous). IR recorded after 5 and 30 minutes indicated no change with chloroformate at 1776 cm^{-1} . Solvent removed under

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vacuum at 30°C using a 20% NaOH trap for excess phosgene, added EtOAc (20 mL), and filtered of pyridine hydrochloride. Removed solvent under reduced pressure and added about half of chloroformate to a stirred

5 solution of α -metryptophanyl-1-phenethyl amide (160 mg, 0.5 mmol) and pyridine (40 mg, 0.5 mmol) in THF (20 mL, anhydrous). Precipitate formed immediately and after 5 minutes H_2 indicated no starting amine remaining. Removed solvent under reduced pressure and added 50 mL

10 of EtOAc. Organic phase washed successively with 10% citric acid solution (2 x 30 mL), H_2O (30 mL), saturated $NaHCO_3$ (2 x 30 mL), H_2O (2 x 30 mL), brine (30 mL), then dried over $MgSO_4$. Product recrystallized from ether to give pure product (0.2 g, 84%); mp

15 109-112.5°C;
[α] $_D^{21^\circ C}$ = +8.5° (c = 1, MeOH);
IR (film): 3334 (br, NH str), 1717 (CO, urethane), 1653 (CO, amide); 1592, 1491, 1456, 1256, 1070, 744 cm^{-1} ;

20 NMR ($CDCl_3$): δ 1.29 (3H, d, J = 6.9 Hz, CH_3CH); 1.63 (3H, s, CH_3C); 3.27 (1H, d, J = 14.8 Hz, one of CH_2 indole); 3.46 (1H, d, J = 14.6 Hz, one of CH_2 indole); 4.95-5.05 (1H, m, $NHCHCH_3$); 5.05 (2H, s, CH_2O); 5.46 (1H, s, $CONH$); 6.29 (1H, d, J = 7.3 Hz, $CONHCH$); 6.81

25 (1H, s, indole C_2-H); 6.95-7.30 (11H, m, aromatics); 7.34 (1H, d, J = 8.0 Hz, indole C_7-H); 7.58 (1H, d, J = 7.9 Hz, indole C_4-H); 8.01 (1H, s, indole NH);
MS m/e (CI^+): 475 (M^+ , 2.27%), 474 (M^+H , 85%); 473 (M^+ , 13%); 353 (12%); 348 (14%); 348 (14%); 344 (28%);

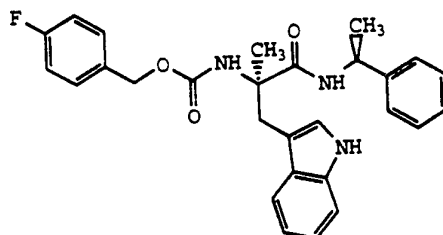
30 305 (16%); 304 (67%); 281 (29%); 244 (23%); 199 (14%); 131 (44%); 130 (100%);
Analysis calculated for $C_{28}H_{28}N_3O_3F$:
C, 71.02; H, 5.96; N, 8.87%.
Found: C, 71.01; H, 6.00; N, 8.87%.

35

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EXAMPLE 51

(4-Fluorophenyl)methyl [R-(R*,S*)]-[1-(1H-indol-3-ylmethyl)-1-methyl-2-oxo-2-[(1-phenylethyl)amino]ethyl]carbamate

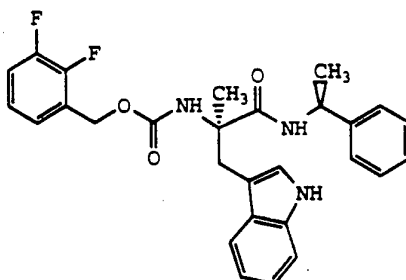


See Method for Example 50. Crystallization from ether gave pure product (191 mg, 81%); mp 101-111°C; $[\alpha]_D^{21} = +7.9$ (c = 0.5, MeOH); IR (film): 3327 (br, NH str), 1716 (CO, urethane), 1653 (CO, amide), 1511, 1457, 1225, 1071, 825, 743 cm^{-1} ; NMR (CDCl_3): δ 1.29 (3H, d, $J = 6.9$ Hz, CH_3CH); 1.62 (3H, s, CH_3C); 3.26 (1H, d, $J = 14.8$ Hz, one of CH_2 indole); 3.46 (1H, d, $J = 14.8$ Hz, one of CH_2 indole); 4.95-5.05 (1H, m, CONCHCH_3); 5.02 (2H, s, CH_2O); 5.39 (1H, s, OCONH); 6.25-6.35 (1H, br.d, CONHCH); 6.80 (1H, s, indole $\text{C}_2\text{-H}$); 6.95-7.30 (11H, m, aromatics); 7.34 (1H, d, $J = 7.8$ Hz, indole $\text{C}_7\text{-H}$); 7.58 (1H, d, $J = 7.9$ Hz, indole $\text{C}_4\text{-H}$); 7.99 (1H, s, indole NH); MS m/e (CI^+): 475 ($\text{M}^+ + 2$, 22%), 474 ($\text{M}^+ + \text{H}$, 68%), 473 (M^+ , 10%), 430 (35%), 348 (29%), 344 (31%), 305 (22%), 304 (83%), 281 (23%), 244 (36%), 131 (60%), 130 (100%); Analysis calculated for $\text{C}_{28}\text{H}_{28}\text{N}_3\text{O}_3\text{F}$: C, 71.02; H, 5.96; N, 8.87%. Found: C, 70.80; H, 5.93; N, 8.69%.

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EXAMPLE 52

(2,3-Difluorophenyl)methyl [R-(R*,S*)]-[1-(1H-indol-3-methyl)-1-methyl-2-oxo-[(1-phenylethyl)amino]ethyl]-carbamate



See method for Example 50. Crude product chromatographed using 2% MeOH/CH₂Cl₂ the crystallized from ether to give pure product (232 mg, 94%);

mp 96-102°C;

$[\alpha]_D^{21} = +6.7^\circ$ (c = 0.5, MeOH);

IR (film): 3336 (br, NH str), 1716 (CO, urethane), 1652 (CO, amide), 1492, 1457, 1288, 1250, 1069, 741 cm⁻¹;

NMR (CDCl₃): δ 1.29 (3H, d, $J = 6.9$ Hz, CH₃CH); 1.60 (3H, s, CCH₃); 3.27 (1H, d, $J = 14.7$ Hz, one of CH₂ indole); 3.46 (1H, d, $J = 14.6$ Hz, one of CH₂ indole); 4.95-5.05 (1H, m, NHCHCH₃); 5.13 (1H, d, $J = 13.0$ Hz, one of CH₂O); 5.18 (1H, d, $J = 13.4$ Hz, one of CH₂O); 5.49 (1H, s, OCONH); 6.29 (1H, d, $J = 7.2$ Hz, NHCH); 6.84 (1H, s, indole C₂H); 6.95-7.35 (11H, m, aromatics); 7.58 (1H, d, $J = 7.7$ Hz, indole C₄-H); 8.10 (1H, s, indole NH);

MS m/e (CI⁺): 493 (M⁺+2, 10%), 492 (M⁺+1, 4%), 491 (M⁺, 5%), 371 (11%), 348 (19%), 305 (17%), 304 (54%), 299 (18%), 244 (22%), 199 (12%), 144 (40%), 130 (98%), 127 (100%), 105 (78%);

Analysis calculated for C₂₈H₂₇N₃O₃F₂:

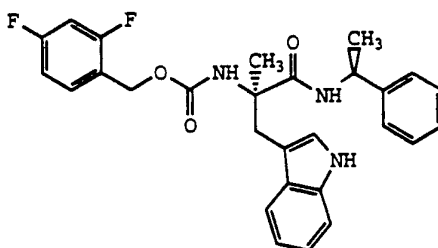
C, 68.42; H, 5.54; N, 8.55%.

Found: C, 68.43; H, 5.64; N, 8.51%.

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EXAMPLE 53

(2,4-Difluorophenyl)methyl [R-(R*,S*)]-[1-(1H-indol-3-ylmethyl)-1-methyl-2-oxo-2-[(1-phenylethyl)amino]-ethyl]carbamate



See Method for Example 50. Crude product chromatographed using 2% MeOH/CH₂Cl₂ then crystallized from ether to give pure product (240 mg, 98%);

mp 77-87°C;

$[\alpha]_D^{21} = +5.6$ (c = 1, MeOH);

IR (film): 3332 (br, NH str), 1713 (CO, urethane), 1651 (CO, amide), 1507, 1250, 1140, 1101, 1071, 742 cm⁻¹;

NMR (CDCl₃): δ 1.29 (3H, d, J = 6.9 Hz, CH₃CH); 1.03 (3H, s, CCH₃); 3.27 (1H, d, J = 14.7 Hz, one of CH₂ indole); 3.46 (1H, d, J = 14.9 Hz, one of CH₂ indole); 4.95-5.05 (1H, m, CHCH₃); 5.09 (2H, s, CH₂O); 5.43 (1H, s, OCONH); 6.23-6.33 (1H, br.d, CONHCH); 6.75-6.90 (3H, m, aromatics); 7.05-7.35 (9H, m, aromatics); 7.58 (1H, d, J = 7.8 Hz, indole C₄-H); 8.01 (1H, s, indole NH); MS m/e (CI⁺): 493 (M⁺+2, 11%), 492 (M⁺+1, 40%), 491 (M⁺, 7%), 448 (12%), 361 (26%), 348 (15%), 304 (56%), 299 (15%), 244 (33%), 199 (14%), 144 (36%), 131 (45%), 130 (100%), 127 (93%), 105 (70%);

Analysis calculated for C₂₈H₂₇N₃O₃F₂:

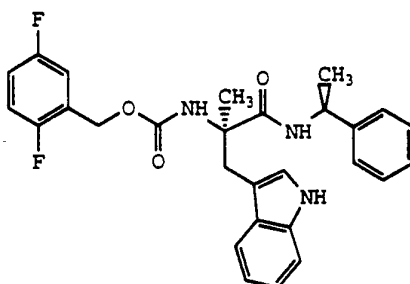
C, 68.42; H, 5.54; N, 8.55%.

Found: C, 68.66; H, 5.63; N, 8.45%.

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EXAMPLE 54

(2,5-Difluorophenyl)methyl [R-(R*,S*)]-[1-(1H-indol-3-ylmethyl)-1-methyl-2-oxo-2-[(1-phenylethyl)amino]-ethyl]carbamate



See Method for Example 50. Crystallization from ether gave pure product (229 mg, 95%); mp 121-122°C; $[\alpha]_D^{21} = +6.0$ ($c = 0.5$, MeOH);

IR (film): 3336 (br, NH str), 1721 (CO, urethane), 1656 (CO, amide), 1496, 1457, 1246, 1191, 1144, 1072, 909, 741 cm^{-1} ;

NMR (CDCl_3): δ 1.29 (3H, d, $J = 6.9$ Hz, CH_3CH); 1.64 (3H, s, CCH_3); 3.28 (1H, d, $J = 14.7$ Hz, one of CH_2 indole); 3.47 (1H, d, $J = 14.0$ Hz, one of CH_2 indole); 4.95-5.05 (1H, m, NHCHCH_3); 5.08 and 5.14 (each 1H, each d, each one of CH_2O , $J = 13.4$ Hz); 5.51 (1H, s, OCONH); 6.28 (1H, d, $J = 7.6$ Hz, CONHCH); 6.85 (1H, d, $J = 2.1$ Hz, indole C_2H); 6.90-7.33 (10H, m, aromatics); 7.34 (1H, d, $J = 8.0$ Hz, indole $\text{C}_7\text{-H}$); 7.58 (1H, d, $J = 7.8$ Hz, indole $\text{C}_4\text{-H}$); 8.05 (1H, s, indole NH);

MS m/e (CI^+): 493 ($\text{M}^+ + 2$, 14%), 492 ($\text{M}^+ + 1$, 55%), 491 (M^+ , 6%), 362 (12%), 348 (31%), 347 (17%), 304 (39%), 244 (40%), 131 (50%), 130 (100%), 127 (65%), 105 (66%);

Analysis calculated for $\text{C}_{28}\text{H}_{27}\text{N}_3\text{O}_3\text{F}_2$:

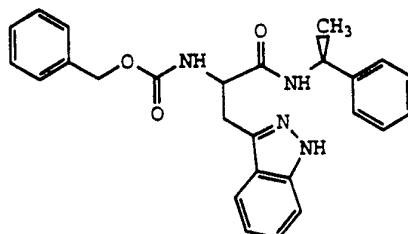
C, 68.42; H, 5.54; N, 8.55%.

Found: C, 68.17; H, 5.46; N, 8.35%.

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EXAMPLE 55

Phenylmethyl [R-(R*,S*)] and [S-(R*,R*)]-
[1-(1H-indazol-3-ylmethyl)-2-oxo-2-[(1-phenylethyl)-
amino]ethyl]carbamate



Step 1: N-Benzyloxycarbonyltryptazan

A mixture of tryptazan (PD 018111) (0.09 g, 0.44 mmol), sodium hydrogen carbonate (0.13 g, 1.55 mmol), dibenzylidencarbonate (0.18 g, 0.63 mmol), water (5 mL), and dioxan (5 mL) was stirred at room temperature overnight. The mixture was diluted with water, washed twice with ether, acidified with 1N hydrochloric acid, and extracted with ethyl acetate. The combined extracts were washed with water, dried over MgSO_4 , filtered, and evaporated to dryness. Recrystallization from ethyl acetate/hexane gave colorless crystals (0.12 g).

Step 2: Phenylmethyl [R-(R*,S*)] and [S-(R*,R*)]-
[1-(1H-indazol-3-ylmethyl)-2-oxo-
2-[(1-phenylethyl)amino]ethyl]carbamate

To a solution of N-benzyloxycarbonyl tryptazan (0.12 g, 0.35 mmol) in ethyl acetate (20 mL) was added hydroxybenzotriazole hydrate (0.058 g, 0.38 mmol) followed by dicyclohexylcarbodiimide (0.075 g, 0.36 mmol). After stirring at room temperature for 3 hours, the mixture was filtered and (S)- α -methylbenzylamine (0.055 g, 0.45 mmol) in ethyl acetate (5 mL) was added to the filtrate. After stirring at room temperature overnight, the reaction mixture was

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washed with saturated sodium bicarbonate solution, 1N hydrochloric acid, and water. The solution was then dried over magnesium sulphate, filtered, and evaporated to dryness. The residue was purified by reverse phase chromatography eluting with methanol/water mixtures to give the title compound (0.070 g, 45%); mp 116-120°C; NMR (300 MHz, CDCl₃): δ 1.23 (3H, d, J = 6.9 Hz); 3.32 (1H, dd, J = 15.0, 7.3 Hz); 3.59 (1H, ddd, J = 15.0, 9.7, and 4.8 Hz); 4.70-4.80 (1H, m); 4.85-4.95 (1H, m); 5.11 (2H, s); 6.14 (0.5H d, J = 7.4 Hz); 6.20 (0.5H, d, J = 7.1 Hz); 6.60-6.85 (1H, m); 6.90-7.40 (14H, m); 7.70-7.80 (1H, m);

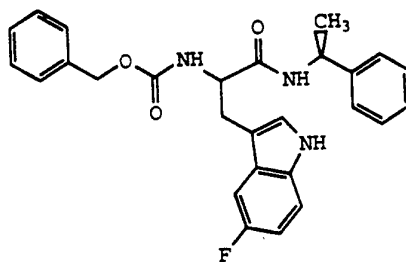
Analysis calculated for C₂₆H₂₆N₄O₃:

C, 70.57; H, 5.92; N, 12.66%.

Found: C, 70.41; H, 5.97; N, 12.60%.

EXAMPLE 56

Phenylmethyl [R-(R*,S*)] and [S-(R*,R*)]-[1-[(5-fluoro-1H-indol-3-yl)methyl]-2-oxo-2-[(1-phenylethyl)amino]ethyl]carbamate



Step 1: N-Benzylloxycarbonyl-5-fluoro-RS-tryptophan

Dibenzyliddicarbonate (0.39 g, 3.1 mmol) was dissolved in dioxan (15 mL) and added to a stirred suspension of 5-fluoro tryptophan (0.58 g, 2.6 mmol) and sodium bicarbonate (0.67 g, 8.0 mmol) in water (15 mL). After stirring at room temperature overnight, the reaction mixture was diluted with water and washed with ether twice, acidified with 1N hydrochloric acid, and extracted three times with ethyl acetate. The

-114-

combined extracts were washed with water, dried MgSO_4 , sulphate, filtered, and evaporated. Recrystallization from ethyl acetate and hexane gave colorless crystals (0.75 g, 81%); mp 126-128°C;

5 NMR (300 MHz, DMSO-d_6): δ 2.96 (1H, dd, J = 14.4 and 9.6 Hz); 3.14 (1H, dd, J = 14.5 and 4.4 Hz); 4.15-4.25 (1H, m); 4.97 (2H, s); 6.90 (1H, dt, J = 9.2 and 2.5 Hz); 7.10-7.35 (8H, m); 7.55 (1H, d, J = 8.1 Hz); 10.94 (1H, s); 12.6 (1H, bs);

10 Analysis calculated for $\text{C}_{19}\text{H}_{17}\text{FN}_2\text{O}_4$:

C, 64.04; H, 4.81; N, 7.86.

Found: C, 64.02; H, 4.80; N, 7.84.

Step 2: Phenylmethyl [R-(R*,S*)] and [S-(R*,R*)]-
15 [1-[(5-fluoro-1H-indol-3-yl)methyl]-2-oxo-
2-[(1-phenylethyl)amino]ethyl]carbamate

To a solution of N-benzyloxycarbonyl-5-fluoro-tryptophan (0.15 g, 0.42 mmol) in ethyl acetate (25 mL) was added 1-hydroxybenzotriazole hydrate (0.066 g, 0.43 mmol) followed by dicyclohexylcarbodiimide (0.089 g, 0.43 mmol). After stirring at room temperature for 2 hours, the mixture was filtered and to the filtrate was added a solution of (S)- α -methylbenzylamine (0.065 g, 0.54 mmol) in ethyl acetate (5 mL). After stirring at room temperature for 48 hours, the solution was washed with saturated sodium bicarbonate solution, 1N hydrochloric acid solution, and water. After drying over magnesium sulphate, the solution was filtered, dried, and evaporated. The residue was purified by reverse phase chromatography to give the title compound (0.15 g, 78%); mp 152-155°C; NMR (300 MHz, CDCl_3): δ 1.18 (1.5H, d, J = 6.9 Hz); 1.32 (1.5H, d, J = 6.9 Hz); 3.00-3.15 (1H, m); 3.20-3.35 (1H, m); 4.35-4.50 (1H, m); 4.90-5.05 (1H, m); 5.10 (2H, s); 5.35-5.50 (1H, m); 5.70-5.80 (1H, m);

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6.78 (0.5H, d); 6.90-7.05 (3.5H, m); 7.20-7.35 (10H, m); 7.80 (0.5H, s); 8.02 (0.5H, s);

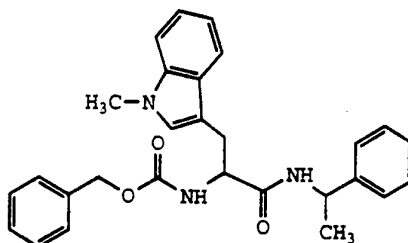
Analysis calculated for $C_{27}H_{26}FN_3O_3$:

C, 70.57; H, 5.70; N, 9.14%.

5 Found: C, 70.67; H, 5.67; N, 9.09%.

EXAMPLE 57

Phenylmethyl [1-(1-methyl-1H-indol-3-ylmethyl)-2-oxo-
2-[(1-phenylethyl)amino]ethyl]carbamate

Step 1: CBZ-1-methyl-DL-tryptophan

1-Methyl-DL-tryptophan was suspended in H_2O /dioxan (20 mL) and $NaHCO_3$ (0.072 g, 8 mmol) added. A solution of dibenzylidicarbonate (1.37 g, 4.8 mmol) was added and the reaction was stirred at room temperature overnight. The solution was diluted with water then washed with ether. The aqueous was then acidified to pH 1 with concentrated HCl and extracted with ethylacetate. The combined organic extracts were washed with water, dried over $MgSO_4$, and the solvent removed in vacuo. The brown oil obtained was purified by reverse phase chromatography (0.800 g, 65%); mp 58-60°C;

$[\alpha]_D^{20} = 0$ (c = 0.25, MeOH);

30 IR (film): 1716 (urethane CO), 1507 cm^{-1} (amide II);

NMR ($DMSO-d_6$): δ 2.99 (1H, dxd, $J = 14.7, 9.5$ Hz, one of βCH_2); 3.16 (1H, dxd, $J = 14.7$ and 4.5 Hz, one of βCH_2); 3.71 (3H, s, NCH_3); 4.32 (1H, m, αCH); 4.97 (2H, s, CH_2Ph); 7.01-7.65 (11H, m, aromatic protons, urethane NH); 12.65 (1H, s, br, CO_2H);

35 MS m/e (CI): 353 MH^+ ;

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Analysis calculated for $C_{20}H_{20}N_2O_4$:

C, 68.17; H, 5.72; N, 7.95%.

Found: C, 67.80; H, 5.86; N, 8.19%.

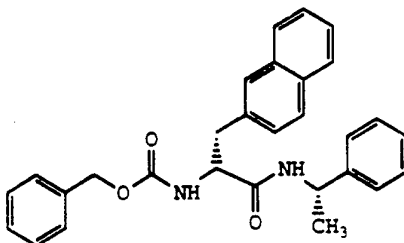
5 Step 2: CBZ-1-Methyl-DL-tryptophan-(+)-
 α -methylbenzylamine

 CBZ-1-methyl-DL-tryptophan (0.39 g, 1.2 mmol),
HBTU (0.91 g, 1.2 mmol), and diisopropylethylamine
 (0.42 mL, 2.4 mmol) were dissolved in DCM (3 mL) and
10 the solution stirred for 10 minutes at room
 temperature. The (+)- α -methylbenzylamine (0.15 mL,
 1.2 mmol) was added and the reaction was stirred for a
 further 4 hours. The solvent was removed in vacuo and
 the resulting residue redissolved in ethylacetate. The
15 organic was washed with 5% HCl, 5% NaHCO₃, water, and
 brine. The organic layer was then dried over MgSO₄ and
 the solvent removed in vacuo. The crude material was
 purified by medium pressure chromatography, ethyl-
 acetate/hexane (0.076 g, 14%); mp 69.5-71.8°C;
20 $[\alpha]_D^{20} = 0$ (c = 0.25, MeOH);
 IR (film): 1712 (urethane CO), 1687 (urethane CO),
 1652 (amide I), 1548 cm⁻¹ (amide II);
 NMR (DMSO-d₆): δ 1.23, 1.34 (3H, 2xd, J = 6.9 and
 7.5 Hz, CH₃); 2.84-3.19 (2H, m, β CH₂); 3.66; 3.71 (3H,
25 2xs, N-CH₃); 4.32-4.37 (1H, m, CH); 4.86-4.97 (3H, m,
 PhCH₂, CH); 6.87-7.66 (16H, m, Ph x 2, indole
 aromatics, urethane NH); 8.32-8.41 (1H, 2xd, J = 7.7
 and 7.9 Hz, amide NH);
 MS m/e (CI): 456.3 MH⁺;
30 Analysis calculated for $C_{28}H_{29}N_3O_3$:
 C, 73.82; H, 6.42; N, 9.22%.
 Found: C, 73.89; H, 6.57; N, 8.95%.

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EXAMPLE 58

Phenylmethyl [R-(R*, S*)]-[1-(2-naphthalenylmethyl)-
2-oxo-2-[(1-phenylmethyl)amino]ethyl]carbamate



Step 1: CBZ-D-3-(1-naphthyl)alanine

See Method for CBZ-1-methyl-DL-tryptophan in Example 57 (0.17 g, 22%);

IR (film): 1709 (urethane CO), 1532 cm^{-1} (amide II);

NMR (DMSO-d_6): δ 2.97-3.23 (2H, m, βCH_2); 4.32 (1H, m, αCH); 4.94 (2H, s, PhCH_2); 7.21-7.89 (13H, m, aromatics, urethane NH).

Step 2: CBZ-D-3-(2-naphthyl)alanine-3-(-)- α -methyl-benzylamine

See Method as for the 1-methyl-DL-tryptophan derivative (0.081 g, 14%); mp 100.2-102.7°C;

$[\alpha]_D^{20} = -26^\circ$ ($c = 0.25$, MeOH);

IR (film): 1709 (urethane CO), 1656 (amide I), 1537 cm^{-1} (amide II);

NMR (DMSO-d_6): δ 1.24 (3H, d, $J = 7.0$ Hz, CH_3); 2.97 (1H, dxd, $J = 13.4$ and 9.9 Hz, one of βCH_2); 3.13 (1H, dxd, $J = 13.4$ and 5.0 Hz, one of βCH_2); 4.42 (1H, m, αH , methylbenzylamine); 4.89 (3H, m, PhCH_2 , αCH); 7.23-7.48 (14H, m, naphthyl $\text{H}_{3,6,7}$, Phx_2 , urethane NH); 7.84 (4H, m, naphthyl $\text{H}_{1,4,5,8}$); 8.38 (1H, d, $J = 8.0$ Hz, amide NH);

MS m/e (CI): 453 MH^+ ;

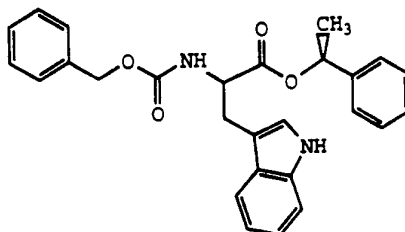
Analysis calculated for $\text{C}_{29}\text{H}_{28}\text{N}_2\text{O}_3$:

C, 76.34; H, 6.41; N, 6.36%.

Found: C, 76.74; H, 6.22; N, 6.06%.

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EXAMPLE 59

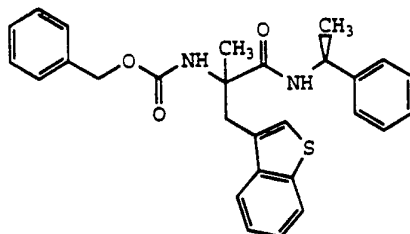
1-Phenylethyl N-[(phenylmethoxy)carbonyl]-DL-tryptophan

- 5
- 10 To a solution of N-benzyloxycarbonyl-RS-tryptophan (1.07 g, 3.16 mmol), (S)-sec-phenethyl alcohol (0.39 g, 3.19 mmol) and dimethylaminopyridine (0.04 g, 0.33 mmol) in ethyl acetate (60 mL) was added
- 15 dicyclohexylcarbodiimide (0.65 g, 3.16 mmol). After stirring at room temperature overnight, the mixture was filtered and evaporated to dryness. Purification by column chromatography eluting with 2% ethyl acetate in dichloromethane gave a colorless gum (1.1 g, 79%);
- 20 NMR (300 MHz, CDCl₃): δ 1.41 and 1.49 (3H, two d, J = 6.5 Hz); 3.10-3.30 (2H, m); 4.70-4.80 (1H, m); 5.00-5.15 (2H, m); 5.20-5.35 (1H, m); 5.80-5.95 (1H, two m); 6.49 and 6.89 (1H, two s); 7.00-7.35 (13H, m); 7.42 (0.5H, d, J = 8.0 Hz); 7.55-7.60 (0.5H, m); 7.81-7.94 (1H, two s);
- 25 Analysis calculated for C₂₇H₂₆N₂O₄:
C, 73.29; H, 5.92; N, 6.33%.
Found: C, 73.03; H, 6.01; N, 6.21%.

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EXAMPLE 60

Phenylmethyl [1-(benzo[b]thien-3-ylmethyl)-1-methyl-2-oxo-2-[(1-phenylethyl)amino]ethyl]carbamate



Step 1: Methyl N-CBZ- α -methyl-3-benzothiophenylalanine

A solution of methyl α -methyl-3-benzothiophenylalanine (Horwell, et al., WO9204025 A1. March 19, 1992) (0.5 g, 2.0 mmol), sodium hydrogen carbonate (0.50 g, 6.00 mmol), dibenzylidencarbonate (0.7 g, 2.4 mmol), water (10 mL), and dioxan (10 mL) was stirred at room temperature overnight. The reaction mixture was diluted with water and ether. The organic phase was separated, washed with water, dried over MgSO_4 , filtered, and evaporated to dryness. Purification by column chromatography eluting with 2% ethyl acetate in dichloromethane gave an oil (0.6 g, 78%);

NMR (300 MHz, CDCl_3): δ 1.68 (3H, s); 3.48 (1H, d, $J = 14.5$ Hz); 3.60-3.75 (4H, m); 5.05-5.20 (2H, m); 5.53 (1H, bs); 6.94 (1H, s); 7.20-7.40 (7H, m); 7.65-7.75 (1H, m); 7.80-7.85 (1H, m);

Analysis calculated for $\text{C}_{21}\text{H}_{21}\text{NO}_4\text{S}$:

C, 65.78; H, 5.52; N, 3.65%.

Found: C, 65.85; H, 5.50; N, 3.49%.

Step 2: N-CBZ- α -methyl-3-benzothiophenylalanine

A solution of methyl N-CBZ- α -methyl-3-benzothiophenylalanine (0.6 g, 1.57 mmol), lithium hydroxide hydrate (0.14 g, 3.33 mmol) in water (20 mL), and dioxan (20 mL) was stirred at room temperature overnight. The reaction mixture was diluted with

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water, washed with ether, acidified with 1N hydrochloric acid, and extracted with ethyl acetate three times. The combined extracts were washed with water, dried over magnesium sulphate, filtered, and evaporated to dryness. Crystallization from ether/hexane gave colorless crystals 0.48 g (83%); mp 133-135°C; NMR (300 MHz, CDCl₃): δ 1.28 (3H, s); 3.27 (1H, d, J = 14.4 Hz); 3.59 (1H, d, J = 14.4 Hz); 5.02 (1H, d, J = 12.6 Hz); 5.08 (1H, d, J = 12.3 Hz); 7.25-7.40 (8H, m); 7.75 (1H, d, J = 7.9 Hz); 7.90-8.00 (1H, m), 12.6 (1H, s); Analysis calculated for C₂₀H₁₉NO₄S: C, 65.02; H, 5.15; N, 3.79%. Found: C, 64.99; H, 5.15; N, 3.80%.

Step 3: Phenylmethyl [1-(benzo[b]thien-3-ylmethyl)-1-methyl-2-oxo-2-(1-phenylethyl)amino]ethyl-carbamate

To a solution of N-CBZ- α -methyl-3-benzothiophenyl-alanine (0.12 g, 0.33 mmol) in ethyl acetate (10 mL) was added hydroxybenzotriazole hydrate (0.055 g, 0.36 mmol) and followed by dicyclohexylcarbodiimide (0.072 g, 0.35 mmol). After stirring at room temperature for 15 minutes, the mixture was filtered and (S)-sec-phenylethylamine (0.051 g, 0.42 mmol) in ethyl acetate was added to the filtrate. After stirring at room temperature overnight, the mixture was diluted with ethyl acetate and washed with saturated sodium hydrogen carbonate solution, 1N hydrochloric acid solution and water. The solution was dried over magnesium sulphate, filtered, and evaporated to dryness. Purification by column chromatography eluting with dichloromethane/ethyl acetate 98:2 and crystallization from ether gave colorless crystals (0.09 g, 58%); mp 147-150°C;

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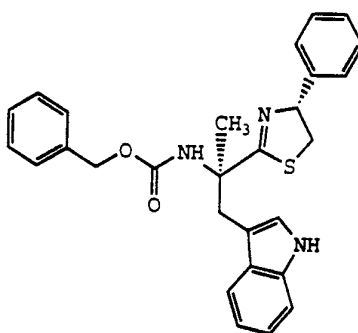
NMR (300 MHz, DMSO- d_6): δ 1.20-1.40 (6H, m); 3.30-3.60 (2H, m); 4.85-4.95 (1H, m); 5.05 (2H, s); 7.00-7.40 (14H, m); 7.75-7.90 (1H, m); 7.90-7.95 (1H, m); 8.0 and 8.1 (1H, two d).

5

EXAMPLE 61

Phenylmethyl [R-(R*,R*)]-[1-(4,5-dihydro-4-phenyl-2-thiazoly-1)-2-(1H-indol-3-yl)-1-methylethyl]carbamate

10



15

A solution of Z- α -Me-R-tryphophanyl-R-phenyl-glycinol (0.14 g, 0.30 mmol) in toluene (20 mL) was treated with Lawesson's reagent (0.2 g, 0.5 mmol) and the mixture heated at reflux for 90 minutes. The crude reaction mixture was loaded onto a silica gel column and eluted with CH_2Cl_2 , then Et_2O . Further purification was then carried out using reverse phase silica gel and 85% MeOH in H_2O as eluant to give the product as a white foam (0.08 g, 57%); mp 64-66°C; $[\alpha]_D^{20} = -3^\circ$ ($c = 0.25$, MeOH);

20

IR (film): 3391, 1715, 1617, 1496, 1456 cm^{-1} ;

NMR (DMSO- d_6): δ 1.41 (3H, s); 2.94 (1H, br.t); 3.30 (1H, obscured by H_2O); 3.54 (1H, d, $J = 13.9$ Hz); 3.71 (1H, br.t); 5.09 (2H, m); 5.46 (1H, m); 6.92 (1H, t, $J = 7.1$ Hz); 7.00-7.39 (13H, m); 7.53 (1H, d, $J = 7.8$ Hz); 7.58 (1H, br.s); 10.92 (1H, br.s);

30

Analysis calculated for $C_{28}H_{27}N_3O_2S \cdot 0.25H_2O$:

C, 70.93; H, 5.85; N, 8.86%.

35

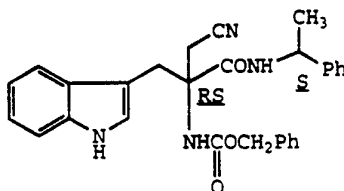
Found: C, 70.93; H, 5.73; N, 8.84%.

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EXAMPLE 62

(See Scheme X)

Phenylmethyl [1-(cyanomethyl)-1-(1H-indol-3-ylmethyl)-
2-oxo-2-[(1-phenylethyl)amino]-ethyl]carbamate

Step 1

RS-Tryptophanmethylester (2.03 g, 9.30 mmol) was stirred and dissolved in formic acid (15 mL) at room temperature. To this was added acetic anhydride (4.4 mL, 46.5 mmol) in one portion and the mixture stirred for 2.5 hours. The solution was poured into water (100 mL) and the mixture neutralized by the addition of Na₂CO₃. The product was extracted into EtOAc (2 x 100 mL) and the combined extracts washed with saturated NaHCO₃ solution (50 mL) and once with brine (50 mL). The EtOAc solution was dried over MgSO₄, filtered, and the solvent removed in vacuo to give the product as a syrup. This was crystallized from 50% EtOAc/50% n-hexane as a white solid (1.55 g, 68%); mp 113-119°C;

IR (film): 3370, 2920, 1740, 1672, and 1212 cm⁻¹;

NMR (CDCl₃): δ 3.29-3.41 (2H, m, CH₂ indole); 3.71 (3H, s, CO₂CH₃); 5.00-5.05 (1H, m, CH₂CH); 6.13 (1H, b, NHCHO); 6.98 (1H, s, indole-H₂); 7.09-7.21 (2H, m, indole-H₅H₆); 7.35 (1H, d, J = 8.0 Hz indole-H₇); 7.53 (1H, d, J = 7.8 Hz, indole-H₄); 8.14 (1H, s, NHCHO); 8.20 (1H, b, indole-NH).

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Step 2

N-Formyl-RS-tryptophanmethylester (1.50 g, 6.09 mmol) was stirred and dissolved in anhydrous DMF (20 mL) and cooled in an ice bath. 4-Dimethylamino-
5 pyridine (0.075g, 0.61 mmol) was added followed by dropwise addition of ditertbutyldicarbonate (1.33 g, 6.09 mmol) in anhydrous DMF (20 mL) added over 1 hour. The cold solution was stirred for 18 hours with slow rewarming to room temperature. The mixture was poured
10 into water (300 mL) and extracted with Et₂O (3 x 100 mL). The combined Et₂O extracts were washed with water (3 x 100 mL), dried over MgSO₄, filtered and the solvent removed in vacuo. The residue was purified by chromatography on silica using 50% n-hexane/50% EtOAc
15 as eluant giving the product as a white solid (1.71 g, 81%); mp 61-62°C; IR (film): 3306, 2979, 1733, 1688, 1454, 1371, and 1158 cm⁻¹;

20 NMR (CDCl₃): δ 1.66 (9H, s, $\text{COC}(\text{CH}_3)_3$); 3.20-3.34 (2H, m, CH_2 indole); 3.71 (3H, s, CO_2CH_3); 4.98-5.04 (1H, m, $\text{CH}_2\text{CHCO}_2\text{CH}_3$); 6.32 (1H, d, $J = 7.4$ Hz, NHCHO); 7.20-7.33 (2H, m, indole-H₅H₆); 7.39 (1H, s, indole-H₂); 7.48 (1H, d, $J = 7.9$ Hz, indole-H₄); 8.09 (1H, d, $J = 8.1$ Hz, indole-H₇); 8.18 (1H, s, NHCHO).

Step 3

BOC-N-formyl-RS-tryptophanmethylester (3.25 g, 9.38 mmol) was stirred and dissolved in CH₂Cl₂ (75 mL) and cooled in an ice bath. Et₃N (7.84 mL, 56.28 mmol) was added followed by a solution of triphosgene (1.02 g, 3.44 mmol) in CH₂Cl₂ (25 mL) added dropwise
30 over 45 minutes. The cold solution was stirred for 3 hours with slow rewarming to room temperature. The CH₂Cl₂ solution was then washed with 5% citric acid solution (3 x 25 mL), saturated NaHCO₃ solution (25 mL)
35

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and brine (25 mL), dried over MgSO_4 , filtered, and the solvent removed in vacuo. The residue was purified by chromatography on silica using 67% n-hexane/33% EtOAc as eluant giving the product as an off-white solid

5 (2.26 g, 73%); mp 90-91°C;

IR (film): 2980, 2149, 1760, 1733, 1454, 1372, 1157, and 1088 cm^{-1} ;

10 NMR (CDCl_3): δ 1.67 (9H, s, $\text{COC}(\text{CH}_3)_3$); 3.28 (1H, dd,

$\text{J} = 14.7$ and 8.0 Hz, CHH indole); 3.41 (1H, dd, $\text{J} = 14.7$ and 4.9 Hz, CHH indole); 3.79 (3H, s, CO_2CH_3); 4.54-4.58 (1H, m, $\text{CH}_2\text{CHCO}_2\text{CH}_3$); 7.23-7.36 (2H, m, indole- H_5H_6); 7.50 (1H, d, $\text{J} = 7.8$ Hz, indole- H_4); 15 7.59 (1H, s, indole- H_2); 8.16 (1H, d, $\text{J} = 8.2$ Hz, indole- H_7).

Step 4

20 1,3-Dimethyl-3,4,5-tetrahydro-2(1H)-pyridinidinone (DMPU) (0.121 mL, 1.0 mmol) was added to a stirred solution of the isonitrile (0.328 g, 1.0 mmol) in anhydrous THF (10 mL) at -78°C. To this was added lithiumhexamethyldisilazide (1.1 mL, 1.0 mmol, 1.1 mmol) and the mixture stirred for 30 minutes.

25 Bromoacetonitrile (0.077 mL, 1.1 mmol) was added and the mixture stirred for 1 hour at -78°C and then at room temperature for 1.5 hours. The mixture was poured into water (25 mL) and extracted with Et_2O (2 x 25 mL), the combined extracts washed once with brine (25 mL),

30 the Et_2O dried over MgSO_4 , filtered, and the solvent removed in vacuo. The residue was purified by chromatography on silica using 75% n-hexane/25% EtOAc as eluant giving the product as a white solid (0.315 g, 86%); mp 92-93°C;

35 IR (film): 2981, 1737, 1454, 1371, 1259, and 1156 cm^{-1} ;

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NMR (CDCl₃): δ 1.68 (9H, s, CO₂C(CH₃)₃); 2.98 (1H, d, J = 16.7 Hz, indole CHH); 3.09 (1H, d, J = 16.8 Hz indole CHH); 3.47 (2H, d, J = 3.7 Hz, CH₂CN); 3.76 (3H, s, CO₂CH₃); 7.24-7.37 (2H, m, indole-H₅H₆); 7.51 (1H, d, J = 7.6 Hz, indole-H₄); 7.62 (1H, s, indole-H₂); 8.15 (1H, d, J = 8.1 Hz, indole-H₇);

Analysis calculated for C₂₀H₂₁N₃O₄:

C, 65.38; H, 5.76; N, 11.44%.

Found: C, 65.23; H, 5.90; N, 11.36%.

Step 5

4.7 M HCl in 1,4-dioxan (1.0 mL, 4.7 mmol) was added to a stirred solution of the isonitrile (0.413 g, 1.12 mmol) in EtOAc (10 mL) cooled to 5°C. To this mixture was added water (1.0 mL) and the solution stirred at room temperature for 1 hour. The solvents were removed in vacuo and the residual solid partitioned between saturated NaHCO₃ solution (10 mL) and EtOAc (2 x 25 mL). The combined EtOAc extracts were washed once with brine (25 mL), dried over MgSO₄, filtered, and the solvent removed in vacuo. The residue was purified by chromatography on silica using 50% n-hexane/50% EtOAc as eluant giving the product as a syrup (0.301 g, 75%).

IR (film): 3380, 2979, 2256, 1734, 1454, 1370, 1258, 1157 cm⁻¹;

NMR (CDCl₃): δ 1.67 (9H, s, NCOC(CH₃)₃); 1.88 (2H, bs, NH₂); 2.74 (1H, d, J = 16.5 Hz, CHHCN); 2.89 (1H, d, J = 16.4 Hz, CHHCN); 3.12 (1H, d, J = 14.3 Hz, indole CHH); 3.25 (1H, d, J = 14.2 Hz, indole CHH); 3.69 (3H, s, CO₂CH₃); 7.22-7.35 (2H, m, indole-H₅H₆); 7.46 (1H, s, indole-H₂); 7.52 (1H, d, J = 7.6 Hz, indole-H₄); 8.13 (1H, d, J 8.1 Hz, indole-H₇);

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Analysis calculated for $C_{19}H_{23}N_3O_4 \cdot 3H_2O$:

C, 63.85; H, 6.49; N, 11.76%.

Found: C, 63.82; H, 6.64; N, 11.49%.

5 Step 6

The amine (0.561 g, 1.57 mmol) was stirred and dissolved in 1,4-dioxan (10 mL) and water (0.5 mL) added. Na_2CO_3 (0.832 g, 7.85 mmol) was added followed by benzylchloroformate (0.448 mL, 3.14 mmol) and the reaction stirred at room temperature for 1 hour. The 1,4-dioxan was removed in vacuo and the residue partitioned between EtOAc (50 mL) and brine (2 x 25 mL). The EtOAc solution was dried over MgSO_4 , filtered, and the solvent removed in vacuo. The residue was purified by chromatography on silica using 67% n-hexane/33% EtOAc as eluant to give the product as a syrup (0.662 g, 86%); IR (film): 3342, 2929, 2253, 1732, 1454, 1372, 1156, 1089 cm^{-1} ;

20 NMR (CDCl₃): δ 1.66 (9H, s, COC(CH₃)₃); 3.24-3.34 (2H, m, CH₂CN); 3.47-3.62 (2H, m, CH₂ indole); 3.67 (3H, s, CO₂CH₃); 5.14 (2H, s, PHCH₂OCO); 5.78 (1H, s, NHCOO);
25 7.15-7.20 (1H, m, indole); 7.28-7.43 (12H, m, Ar); 8.10 (1H, d, J = 8.4 Hz, indole-H₇);

Analysis calculated for $C_{27}H_{29}N_3O_6$:

C, 65.97; H, 5.95; N, 8.55%.

Found: C, 65.72; H, 6.01; N, 8.29%

30

Step 7

The BOC protected ester (0.119 g, 0.24 mmol) was stirred and dissolved in CH_2Cl_2 (2 mL) at room temperature. Trifluoroacetic acid (1.0 mL) was added and the mixture stirred at room temperature for 2 hours. The solvents were removed in vacuo to give

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the product as a syrup which formed a foam out of Et₂O (0.078 g, 87%);

IR (film): 3358, 2254, 1718, 1457 cm⁻¹;

NMR (CDCl₃): δ 3.27 (1H, d, J = 6.2 Hz, CHHCN); 3.32
5 (1H, d, J = 8.8 Hz, CHHCN); 3.53-3.63 (2H, m, CH₂
indole); 3.70 (3H, s, CO₂CH₃); 5.11 (1H, d,
J = 12.1 Hz, OCHHPh); 5.21 (1H, d, J = 12.1 Hz,
OCHHPh); 5.87 (1H, s, NHCOO); 7.22-7.45 (10H, m,
indole, C₆H₅); 8.17 (1H, d, J = 8.2 Hz, indole-NH);

10

Step 8

LiOH-H₂O (0.040 g, 0.95 mmol) was added to a stirred solution of the methylester (0.070 g, 0.19 mmol) in THF:H₂O (4 mL, 3:1 mixture) at room
15 temperature. The mixture was stirred at room temperature for 16 hours and the THF removed in vacuo. The residue was diluted with water (10 mL) and extracted once with Et₂O (10 mL). The aqueous solution was made pH 4 with 5% citric acid solution and the
20 product extracted into EtOAc (3 x 10 mL). The combined EtOAc extracts were dried over MgSO₄, filtered, and the solvent removed in vacuo giving the product as a foam (0.045 g, 65%);

IR (film): 3401, 2586, 1712 cm⁻¹;

25 NMR (CDCl₃): δ 3.25-3.37 (3H, m, CH₂CN, CHH indole); 3.54-3.59 (1H, m, CHH indole); 5.05 (1H, d, J = 12.3 Hz, OCHHPh); 5.14 (1H, d, J = 12.1 Hz, OCHHPh); 5.76 (1H, b, NHCOO); 6.89 (1H, s, indole-H₂); 7.02-7.16 (2H, m, indole-H₅H₆); 7.28-7.31 (6H, m, indole, C₆H₅); 7.58 (1H, d, J = 7.7 Hz, indole), 8.24
30 (1H, s, indole-NH);

Step 9

N,N'-dicyclohexylcarbodiimide (0.028 g, 0.138 mmol) was added to a stirred solution of the acid (0.045 g, 0.125 mmol) and 1-hydroxybenzotriazole

35

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monohydrate (0.023 g, 0.150 mmol) in EtOAc (2 mL). The mixture was stirred for 2 hours at room temperature and the N,N'-dicyclohexylurea filtered off. A solution of (S)-(-)- α -methylbenzylamine (0.023 g, 0.188 mmol) in EtOAc (0.5 mL) was added and the mixture stirred at room temperature for 21 hours. The mixture was filtered and diluted with EtOAc (25 mL) and the EtOAc solution washed with 5% citric acid solution (2 x 10 mL), once with saturated NaHCO₃ solution (10 mL), and once with brine (10 mL). The EtOAc solution was dried over MgSO₄, filtered, and solvent removed in vacuo. The residue was purified by chromatography on silica using 67% n-hexane/33% EtOAc as eluant giving the product as a white amorphous solid (0.023 g, 40%);

IR (film): 3337, 3033, 2931, 2251, 1717, 1656, 1496, 1257 cm⁻¹;

NMR (CDCl₃): δ 0.98 (1.5H, d, J = 6.7 Hz, 0.5 CH₃); 1.29 (1.5H, d, J = 7.4 Hz, 0.5 CH₃); 3.16-3.57 (4H, m, indole CH₂, CH₂CN); 4.82-4.95 (1H, m, PhCHNHCO); 5.01-5.19 (2H, m, CH₂Ph); 5.55 (1H, d, J = 8.9 Hz, NHCOO); 6.03 (0.5H, d, J = 7.3 Hz, 0.5 CONH); 6.12 (0.5H, d, J = 7.7 Hz, 0.5 CONH); 6.56 (0.5H, s, 0.5 indole-H₂); 6.97-7.37 (13.5H, m, Ar); 7.54-7.61 (1H, m, Ar); 7.98 and 8.29 (1H, two s, indole-NH).

Analysis calculated for C₂₉H₂₈N₄O₃:

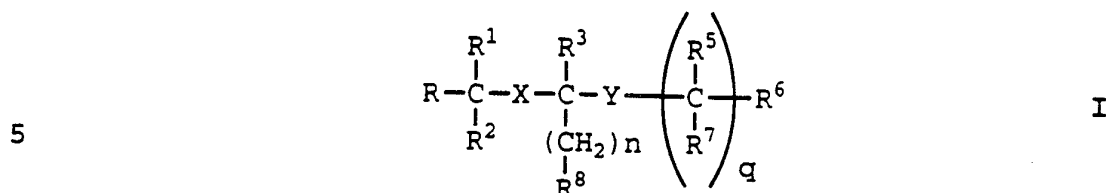
C, 72.48; H, 5.87; N, 11.66%.

Found: C, 72.29; H, 5.97; N, 11.48%.

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CLAIMS

1. A compound of formula



or a pharmaceutically acceptable salt thereof
wherein

R is phenyl,

10 pyridine,
 thiophene,
 furan,
 naphthalene,
 indole,

15 benzofuran, or
 benzothiophene each unsubstituted,
 mono-, di-, or trisubstituted by

 alkyl,
 hydroxy,
20 alkoxy,
 NO₂,
 halogen,
 NH₂, or
 CF₃;

25 R¹ and R² are each independently hydrogen or alkyl
 of from 1 to 4 atoms;

R and R², when joined by a bond, can form a ring;

30 X is $-\text{O}-\overset{\text{O}}{\parallel}{\text{C}}-\text{NR}^{11}$ wherein R¹¹ is hydrogen or alkyl of
 from 1 to 3 carbon atoms;

R³ is hydrogen or (CH₂)_mR¹³ where m is an integer
of from 1 to 6 and R¹³ is H, CN, NH₂, N(CH₃)₂, or
NHCOCH₃;

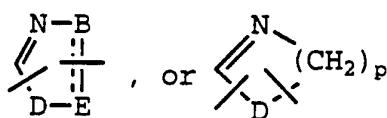
35 n is an integer of from 1 to 2;

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R^8 is phenyl,
 pyridine,
 thiophene,
 furan,
 40 naphthalene,
 indole,
 benzofuran, or
 benzothiophene each unsubstituted, or
 mono-, di-, or trisubstituted by
 45 alkyl,
 hydroxy,
 alkoxy,
 NO_2 ,
 halogen,
 50 NH_2 , or
 CF_3 ;

Y is $\begin{array}{c} O \\ || \\ -C-N- \\ | \\ R^4 \end{array}$ wherein R^4 is hydrogen or alkyl of from
 55 1 to 3 carbon atoms,

$-CO_2-$,
 $-COCH_2-$,
 $-CH_2O-$,
 $-CH_2NH-$,
 60 $-CH=CH-$,
 $-CH_2CH_2-$,
 $-CHOHCH_2-$,



wherein B is nitrogen,

CH, CH_2 , oxygen, or sulfur, D is
 nitrogen, oxygen, or sulfur, E is
 70 nitrogen, CH, CH_2 , p is an integer of
 from 3 to 4, and the dotted line
 indicates a double or single bond;

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R⁵ and R⁷ are each independently hydrogen or alkyl
of from 1 to 4 carbon atoms;

75 q is an integer of from 0 to 1; and
R⁶ is phenyl,

pyridine,
thiophene,
furan,
80 naphthalene,
indole,
benzofuran, or
benzothiophene each unsubstituted, or
mono-, di-, or trisubstituted by
85 alkyl,
hydroxy,
alkoxy,
NO₂,
halogen,
90 NH₂, or
CF₃;

straight alkyl of from 1 to 8 carbons, branched
alkyl of from 3 to 8 carbons, cycloalkyl of from
5 to 8 carbons, or heterocycloalkyl.

2. A compound according to Claim 1 wherein

R is pyridine,
thiophene,
furan,
5 naphthalene,
indole,
benzofuran, or
benzothiophene each unsubstituted, mono-,
di-, trisubstituted by
10 alkyl,
hydroxy,
alkoxy,
NO₂,

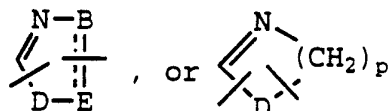
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- halogen,
 15 NH_2 , or
 CF_3 ;
- R^1 and R^2 are each independently hydrogen or alkyl
 of from 1 to 4 atoms;
 R and R^2 , when joined by a bond, can form a ring;
- 20 X is $-\text{O}-\overset{\text{O}}{\parallel}{\text{C}}-\text{NR}^{11}$ wherein R^{11} is hydrogen or alkyl of
 from 1 to 3 carbon atoms;
 R^3 is hydrogen or $(\text{CH}_2)_m\text{R}^{13}$ where m is an integer
 25 of from 1 to 6 and R^{13} is H , CN , NH_2 , $\text{N}(\text{CH}_3)_2$, or
 NHCOCH_3 ;
 n is an integer of from 1 to 2;
 R^8 is phenyl,
 pyridine,
 30 thiophene,
 furan,
 naphthalene,
 indole,
 benzofuran, or
 35 benzothiophene each unsubstituted, or
 mono-, di-, or trisubstituted by
 alkyl,
 hydroxy,
 alkoxy,
 40 NO_2 ,
 halogen,
 NH_2 , or
 CF_3 ;
- 45 Y is $-\overset{\text{O}}{\parallel}{\text{C}}-\overset{\text{R}^4}{\mid}{\text{N}}-$ wherein R^4 is hydrogen or alkyl of from
 1 to 3 carbon atoms,
 $-\text{CO}_2-$,
 $-\text{COCH}_2-$,
 50 $-\text{CH}_2\text{O}-$,
 $-\text{CH}_2\text{NH}-$,

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-CH=CH-,
 -CH₂CH₂-,
 -CHOHCH₂-,

55



60

wherein B is nitrogen,

CH, CH₂, oxygen, or sulfur, D is
 nitrogen, oxygen, or sulfur, E is
 nitrogen, CH, CH₂, p is an integer of
 from 3 to 4, and the dotted line
 indicates a double or single bond;

65

R⁵ and R⁷ are each independently hydrogen or alkyl
 of from 1 to 4 carbon atoms;

q is an integer of from 0 to 1; and

R⁶ is phenyl,

70

pyridine,
 thiophene,
 furan,
 naphthalene,
 indole,
 benzofuran, or

75

benzothiophene each unsubstituted, or
 mono-, di-, or trisubstituted by

alkyl,
 hydroxy,
 alkoxy,
 NO₂,
 halogen,
 NH₂, or
 CF₃;

80

straight alkyl of from 1 to 8 carbons, branched
 alkyl of from 3 to 8 carbons, cycloalkyl of from
 5 to 8 carbons, or heterocycloalkyl.

85

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3. A compound according to Claim 1 wherein

R is phenyl,

pyridyl,

thiophene,

furan,

5 naphthalene,

indole each unsubstituted, or

mono- or disubstituted by alkyl of 1 to

3 carbons, methoxy, ethoxy, chlorine,

fluorine, NH_2 , or CF_3 ;

10 R^1 and R^2 are each independently selected from hydrogen and methyl;

X is $\begin{array}{c} \text{O} \\ \parallel \\ -\text{OC}-\text{NR}^{11} \end{array}$ wherein R^{11} is hydrogen or methyl;

15 R^3 is hydrogen or $(\text{CH}_2)_m\text{R}^{13}$ where m is an integer of from 1 to 6 and R^{13} is H, CN, NH_2 , $\text{N}(\text{CH}_3)_2$ or NHCOCH_3 ;

n is 1;

R^8 is phenyl,

20 naphthyl,

indole, or

benzothiophene;

25 Y is $\begin{array}{c} \text{O} \quad \text{R}^4 \\ \parallel \quad | \\ -\text{C}-\text{N}- \end{array}$ wherein R^4 is hydrogen or methyl, $-\text{CO}_2-$,



wherein B is CH, CH_2 , D is sulfur, and E is CH, CH_2 ;

30 R^5 and R^7 are each independently hydrogen or methyl;

q is an integer of from 0 to 1, and

R^6 is phenyl,

substituted phenyl, or

cyclohexyl.

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4. A compound according to Claim 1 wherein

R is phenyl,

thiophene

furan each unsubstituted, or mono- or

5 disubstituted by alkyl of 1 to 3 carbons,

methoxy, ethoxy, chlorine, fluorine, NH_2

or CF_3 ;

R_1 and R_2 are each independently hydrogen or

methyl;

10

X is $\text{-O}-\overset{\text{O}}{\parallel}{\text{C}}-\text{NH}$;

R^3 is hydrogen or methyl;

n is 1;

15

R^8 is indole;

Y is $\text{-}\overset{\text{O}}{\parallel}{\text{C}}-\text{NH}-$ or $\text{C}-\overset{\text{O}}{\parallel}{\text{NCH}_3}-$

R^5 and R^7 are each independently hydrogen or

methyl;

q is 1;

R^6 is phenyl,

substituted phenyl, or

cyclohexyl.

5. A compound selected from:

phenylmethyl (S)-[1-(1H-indol-3-ylmethyl)-
2-[methyl(phenylmethyl)amino]-2-oxoethyl]-
carbamate;

5

phenylmethyl [R-(R*S*)]-[1-(1H-indol-
3-ylmethyl)-2-oxo-2-[(1-phenylethyl)amino]ethyl]-
carbamate

phenylmethyl [S-R*,R*]-[1-(1H-indol-
3-ylmethyl)-2-oxo-2-[(1-phenylethyl)amino]-ethyl]-
carbamate;

10

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- phenylmethyl [S-(R*,R*)] - [1-(1H-indol-3-ylmethyl)-1-methyl-2-oxo-2-[(1-phenylethyl)-amino]ethyl] carbamate;
- 15 phenylmethyl [S-(R*,R*)] - [1-(1H-indol-3-ylmethyl)-2-oxo-2-[(1-phenylethyl)amino]ethyl]-methyl] carbamate;
- phenylmethyl [S-(R*,S*)] - [1-(1H-indol-3-ylmethyl)-2-oxo-2-[(1-phenylethyl)amino]ethyl]-methyl carbamate;
- 20 phenylmethyl (S) - [1-(1H-indol-3-ylmethyl)-2-[methyl(phenylmethyl)amino]-2-oxoethyl]-carbamate;
- phenylmethyl (S) - [2-[[[(4-chlorophenyl)-methyl]amino]1-(1H-indol-3-ylmethyl)-2-oxoethyl]-methyl carbamate; and
- 25 phenylmethyl (S) - [1-(1H-indol-3-ylmethyl)-2-oxo-2-[[[4-(trifluoromethyl)phenyl]methyl]-amino]ethyl]methyl carbamate.
6. A compound named phenylmethyl [R-(R*,S*)] - [1-(1H-indol-3-ylmethyl)-1-methyl-2-oxo-2-[(1-phenylethyl)amino]ethyl] carbamate.
7. A compound named (4-methoxyphenyl) methyl [R-(R*,S*)] - [1-(1H-indol-3-ylmethyl)-1-methyl-2-oxo-2-[(1-phenylethyl)amino]ethyl] carbamate.
8. A compound named (4-methylphenyl)methyl [R-(R*,S*)] - [1-(1H-indol-3-ylmethyl)-1-methyl-2-oxo-2-[(1-phenylethyl)amino]ethyl] carbamate.
9. A compound named (4-chlorophenyl)methyl [R-(R*,S*)] - [1-(1H-indol-3-ylmethyl)-1-methyl-2-oxo-2-[(1-phenylethyl)amino]ethyl] carbamate.

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10. A compound named phenylmethyl [R-(R*,R*)]-
[2-[(1-cyclohexylethyl)amino]-1-(1H-indol-
3-ylmethyl)-1-methyl-2-oxoethyl] carbamate.
11. A compound named phenylmethyl [R-(R*,S*)]-[1-
(1H-indol-3-ylmethyl)-2-oxo-2-[(1-phenylethyl)
amino]ethyl] carbamate.
12. A compound selected from:
- methyl N-[(phenylmethoxy)carbonyl]-,
[3,5-bis(trifluoromethyl)phenyl]-L-tryptophan;
phenylmethyl [1-(1H-indol-3-ylmethyl)-
1-methyl-2-[[1-(4-methylphenyl)ethyl]amino]-
2-oxoethyl] carbamate;
phenylmethyl [1-(1H-indol-3-ylmethyl)-
1-methyl-2-[[1-(4-methylphenyl)ethyl]amino]-
2-oxoethyl] carbamate;
- phenylmethyl [R-(R*, R*)]-(2-[(1-cyclo-
hexylethyl)amino]-1-(1H-indol-3-ylmethyl)-
1-methyl-2-oxoethyl] carbamate;
- phenylmethyl (R,RS)-[2-[[1-[3,5-
bis(trifluoromethyl)phenyl]ethyl]amino]-1-
(1H-indol-3-ylmethyl)-1-methyl-
2-oxoethyl] carbamate;
- phenylmethyl (R,RS)-[1-(1H-indol-3-ylmethyl)-
2-[[1-(4-methoxyphenyl)ethyl]amino]-1-methyl-
2-oxoethyl] carbamate;
- (3-Fluorophenyl)methyl [R-(R*,S*)]-
[1-(1H-indol-3-ylmethyl)-1-methyl-2-oxo-
2-[(1-phenylethyl)amino]ethyl] carbamate;
- (4-Fluorophenyl)methyl [R-(R*,S*)]-[1-
(1H-indol-3-ylmethyl)-1-methyl-2-oxo-
2-[(1-phenylethyl)amino]ethyl] carbamate;
- (2,3-Difluorophenyl)methyl [R-(R*,S*)]-
[1-(1H-indol-3-methyl)-1-methyl-2-oxo-
[(1-phenylethyl)amino]ethyl] carbamate;

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- 30 (2,4-Difluorophenyl)methyl [R-(R*,S*)]-
[1-(1H-indol-3-ylmethyl)-1-methyl-2-oxo-
2-[(1-phenylethyl)amino]ethyl] carbamate;
(2,5-Difluorophenyl)methyl [R-(R*,S*)]-
[1-(1H-indol-3-ylmethyl)-1-methyl-2-oxo-
2-[(1-phenylethyl)amino]ethyl] carbamate;
- 35 phenylmethyl [R-(R*,S*)] and [S-(R*,R*)]-
[1-(1H-indazol-3-ylmethyl)-2-oxo-2-[(1-phenyl-
ethyl)amino]ethyl] carbamate;
phenylmethyl [R-(R*,S*)] and [S-(R*,R*)]-
[1-[(5-fluoro-1H-indol-3-yl)methyl]-2-oxo-
40 2-[(1-phenylethyl)amino]ethyl] carbamate;
phenylmethyl [1-(1-methyl-1H-indol-
3-ylmethyl)-2-oxo-2-[(1-phenylethyl)amino]-
ethyl] carbamate;
- 45 phenylmethyl [R-(R*, S*)]-[1-(2-naphthalenyl-
methyl-2-oxo-2-[(1-phenylmethyl)amino]ethyl]-
carbamate;
phenylmethyl [1-(benzo[b]thien-3-ylmethyl)-
1-methyl-2-oxo-2-[(1-phenylethyl)amino]ethyl]-
carbamate;
- 50 phenylmethyl [R-(R*,R*)]-[1-(4,5-dihydro-
4-phenyl-2-thiazolyl)-2-(1H-indol-3-yl)-1-methyl-
ethyl] carbamate;
13. A compound named 4-Pyridinylmethyl [1-(1H-indol-
3-ylmethyl)-1-methyl-2-oxo-2-[(1-phenylethyl)-
amino] carbamate.
14. A compound named 3-Thienylmethyl [R-(R*,S*)]-[1-
(1H-indol-3-ylmethyl)-1-methyl-2-oxo-2-[(1-phenyl-
ethyl)amino]ethyl] carbamate.
15. A compound named 2-Thienylmethyl [R-(R*,S*)]-
[1-(1H-indol-3-ylmethyl)-1-methyl-2-oxo-
2-[(1-phenylethyl)amino]ethyl] carbamate.

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16. A compound named 2,3-Dihydro-1H-inden-3-yl-
[R- (R*,S*)] - [1-(1H-indol-3-ylmethyl)-1-methyl-
2-oxo-2-[(phenylethyl)amino]ethyl] carbamate.
17. A compound named 2-Naphthalenylmethyl [R- (R*,S*)] -
[1-(1H-indol-3-ylmethyl)-1-methyl-2-oxo-
2-[(1-phenylethyl)amino]ethyl] carbamate.
18. A compound named 2,3-Dihydro-1H-inden-2-yl
[1-(1H-indol-3-ylmethyl)-1-methyl-2-oxo-
2-[(1-phenylethyl)amino]ethyl] carbamate.
19. A compound named (2-Fluorophenyl)methyl-
[R- (R*,S*)] - [1-(1H-indol-3-ylmethyl)-1-methyl-
2-oxo-[1-phenylethyl)amino]ethyl] carbamate.
20. A compound named 3-Furanylmethyl [R- (R*,S*)] -
[1-(1H-indol-3-ylmethyl)-1-methyl-2-oxo-2-
[(1-phenylethyl)amino]ethyl] carbamate.
21. A compound named 2-Furanylmethyl [R, (R*,S*)] -
[1-(1H-indol-3-ylmethyl)-1-methyl-2-oxo-2-
[(1-phenylethyl)amino]ethyl] carbamate.
22. A pharmaceutical composition comprising an amount
of a compound according to Claim 1 effective to
treat respiratory disorders in a mammal suffering
therefrom, and a pharmaceutically acceptable
carrier.
23. A method for treating respiratory disorders in a
mammal comprising administering a therapeutically
effective amount of a compound according to
Claim 1.

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24. A pharmaceutical composition comprising an amount of a compound according to Claim 1 effective to treat asthma in a mammal suffering therefrom, and a pharmaceutically acceptable carrier.
25. A method for treating asthma in a mammal comprising administering a therapeutically effective amount of a compound according to Claim 1.
26. A pharmaceutical composition comprising an amount of a compound according to Claim 1 effective to treat inflammation in a mammal suffering therefrom, and a pharmaceutically acceptable carrier.
27. A method for treating inflammation in a mammal comprising administering a therapeutically effective amount of a compound according to Claim 1.
28. A pharmaceutical composition comprising an amount of a compound according to Claim 1 effective to treat arthritis in a mammal suffering therefrom, and a pharmaceutically acceptable carrier.
29. A method for treating arthritis in a mammal comprising administering a therapeutically effective amount of a compound according to Claim 1.
30. A pharmaceutical composition comprising an amount of a compound according to Claim 1 effective to treat gastrointestinal disorders in a mammal suffering therefrom, and a pharmaceutically acceptable carrier.

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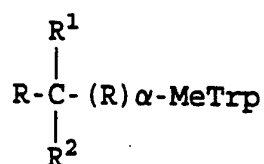
31. A method for treating gastrointestinal disorders in a mammal comprising administering a therapeutically effective amount of a compound according to Claim 1.
32. A pharmaceutical composition comprising an amount of a compound according to Claim 1 effective to treat ophthalmic diseases in a mammal suffering therefrom, and a pharmaceutically acceptable carrier.
- 5
33. A method for treating ophthalmic diseases in a mammal comprising administering a therapeutically effective amount of a compound according to Claim 1.
34. A pharmaceutical composition comprising an amount of a compound according to Claim 1 effective to treat allergies in a mammal suffering therefrom, and a pharmaceutically acceptable carrier.
35. A method for treating allergies in a mammal comprising administering a therapeutically effective amount of a compound according to Claim 1.
36. A pharmaceutical composition comprising an amount of a compound according to Claim 1 effective to treat diseases of the central nervous system in a mammal suffering therefrom, and a pharmaceutically acceptable carrier.
- 5
37. A method for treating diseases of the central nervous system in a mammal comprising administering a therapeutically effective amount of a compound according to Claim 1.

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38. A pharmaceutical composition comprising an amount of a compound according to Claim 1 effective to treat migraine in a mammal suffering therefrom, and a pharmaceutically acceptable carrier.
39. A method for treating migraine in a mammal comprising administering a therapeutically effective amount of a compound according to Claim 1.
40. A pharmaceutical composition comprising an amount of a compound according to Claim 1 effective to treat inflammatory pain or neurogenic inflammation in a mammal suffering therefrom, and a
5 pharmaceutically acceptable carrier.
41. A method for treating inflammatory pain or neurogenic inflammation in a mammal comprising administration of therapeutically effective amounts of a compound according to Claim 1.
42. A pharmaceutical composition comprising an amount of a compound according to Claim 1 effective to treat rheumatoid arthritis in a mammal suffering therefrom, and a pharmaceutically acceptable
5 carrier.
43. A method for treating rheumatoid arthritis in a mammal comprising administration of therapeutically effective amounts of a compound according to Claim 1.

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- 5 44. A pharmaceutical composition comprising an amount of a compound according to Claim 1 effective to treat atherosclerosis in a mammal suffering therefrom, and a pharmaceutically acceptable carrier.
45. A method for treating atherosclerosis in a mammal comprising administration of therapeutically effective amounts of a compound according to Claim 1.
- 5 46. A pharmaceutical composition comprising an amount of a compound according to Claim 1 effective to treat tumor cell growth in a mammal suffering therefrom, and a pharmaceutically acceptable carrier.
47. A method for treating tumor cell growth in a mammal comprising administration of therapeutically effective amounts of a compound according to Claim 1.
48. A diagnostic useful in imaging NK_1 receptors in vivo.
49. A compound selected from the group consisting of:
(R) -Trp (S) -NHCH(CH₃) -phenyl,
(R) - α -MeTrp (S) -NHCH(CH₃) -phenyl, and
(S) -Trp N(CH₃)CH₂ -phenyl.
50. A compound of formula



wherein R, R^1 , and R^2 are as defined in Claim 1.

INTERNATIONAL SEARCH REPORT

Int. onal Application No

PCT/US 93/07552

A. CLASSIFICATION OF SUBJECT MATTER

IPC 5 C07D209/20 C07C271/22 A61K31/40 C07D401/12 C07D409/12
 C07D405/12 C07D231/56 C07D333/60 C07D417/12

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 5 C07D C07C A61K

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 394 989 (FUJISAWA PHARMACEUTICAL CO., LTD.) 31 October 1990 see claims ---	1,22
A	EP,A,0 443 132 (FUJISAWA PHARMACEUTICAL CO., LTD.) 28 August 1991 see claims ---	1,22
A	EP,A,0 428 434 (SANOFI S.A.) 22 May 1991 see claims ---	1,22
P,X	WO,A,93 01169 (MERCK SHARP & DOHME LTD.) 21 January 1993 see claims -----	1,22

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
 E earlier document but published on or after the international filing date
 L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
 O document referring to an oral disclosure, use, exhibition or other means
 P document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
 X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
 Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
 & document member of the same patent family

Date of the actual completion of the international search

26 November 1993

Date of mailing of the international search report

29.12.93

Name and mailing address of the ISA

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Authorized officer

Van Bijlen, H

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 93/07552

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

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims **. are directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
** Claims 23,25,27,29,31,33,35,37,39,41,43,45 and 47
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
The structural formula of claim 50 is meaningless as it can not be found out at which position the * - group is attached to the α -MeTrp moiety

Claim 50 has not been searched
$$\begin{array}{c} * \\ | \\ R - C - (R) \\ | \\ R_2 \end{array}$$
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 93/07552

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0394989	31-10-90	JP-A- 3027399 US-A- 5164372	05-02-91 17-11-92
EP-A-0443132	28-08-91	AU-B- 640185 AU-A- 6801090 CN-A- 1064080 JP-A- 4210996	19-08-93 27-06-91 02-09-92 03-08-92
EP-A-0428434	22-05-91	FR-A- 2654100 FR-A- 2663329 AU-A- 6583890 CA-A- 2029275 JP-A- 3206086	10-05-91 20-12-91 23-05-91 07-05-91 09-09-91
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