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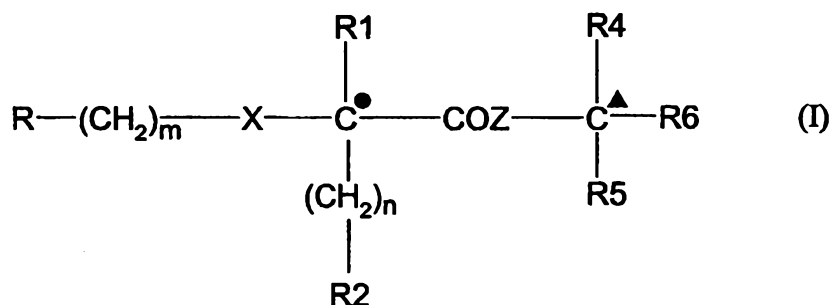
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(54) Title: NON PEPTIDE TACHYKININ RECEPTOR ANTAGONISTS



(57) Abstract: Compounds of Formula (I) are specific tachykinin receptor antagonists where R, m, X, R1, R2, n, Y, R3, R4, R5, and R6 are as described in the specification. The compounds are useful agents for treating conditions associated with aberrant neo-vascularization such as rheumatoid arthritis, atherosclerosis and tumour cell growth.

NON PEPTIDE TACHYKININ RECEPTOR ANTAGONISTS

5

BACKGROUND OF THE INVENTION

The mammalian tachykinins are a family of small peptides which share the common C-terminal sequence Phe-X-Gly-Leu-Met-NH₂ (Nakanishi S., *Physiol Rev.*, 67:117, 1987). It is now well established that substance P, neurokinin A (NKA) and neurokinin B (NKB) 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.*, 18:149, 1991). Substance P displays the highest affinity for the NK₁ receptor, whereas NKA and NKB bind preferentially to the NK₂ and NK₃ receptors, respectively. 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.*, 14:123, 1991).

In the years since 1991, a number of high-affinity nonpeptide tachykinin receptor antagonists have been reported (*IDrugs*, Vol.1, No.1, p. 73-91, 1998).

A wealth of evidence supports the involvement of tachykinin neuropeptides in a variety of biological activities including pain transmission, neuronal excitation, secretion of saliva, angiogenesis, vasodilation, smooth muscle contraction, bronchoconstriction, activation of the immune system and neurogenic inflammation (Pernow B, *Pharmacol. Rev.* 35:85, 1983).

Accordingly, compounds capable of antagonising the effects of substance P at NK₁ receptors may be useful in treating or preventing a variety of CNS disorders including pain (inflammatory, surgical and neuropathic), anxiety, panic, depression, major depression with anxiety, schizophrenia, neuralgia, stress, sexual dysfunction, bipolar disorders, movement disorders, cognitive disorders and addiction disorders; inflammatory diseases such as arthritis, asthma, bronchitis, chronic obstructive pulmonary disease (COPD) and psoriasis;

gastrointestinal disorders including 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 scleroderma and emesis.

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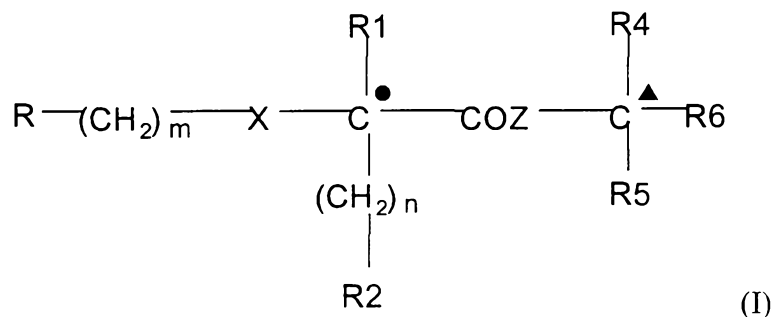
SUMMARY OF THE INVENTION

The invention provides tachykinin receptor antagonists; the compounds have proved to be highly selective and functional tachykinin receptor antagonists.

10

These compounds are unique in the substitution at the C[●] carbon.

Compounds of the invention are those of Formula (I):



or a pharmaceutically acceptable salt thereof wherein R, m, X, R₁, R₂, n, Y, R₃, R₄, R₅ and R₆ are as described below:

15

● and ▲ indicate all stereoisomers;

R is phenyl,
 pyridyl,
 thienyl,
 furyl,
 quinolyl
 isoquinolyl
 naphthyl,
 benzofuryl,

20

benzo[1,3]dioxole

benzothienyl or,

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

alkyl,

hydroxy,

alkoxy,

halogen,

CF₃ or

OCF₃;

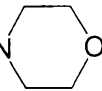
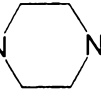
m is an integer from 1 to 3;

X is NR₈ or NHCONH where R₈ is H or alkyl of 1 to 3 carbon atoms;

R₁ is (CH₂)_pY where p is 0 to 3 and Y is OH, OCH₃, F, CF₃, CO₂H, N(CH₃)₂, NHCH₃, NH₂, COCF₃, COCH₃ or NO₂;

n is an integer from 1 to 2;

R₂ is naphthyl or indolyl unsubstituted or N-substituted with hydroxy, alkyl,

CH₂N(CH₃)₂, CH₂N  or CH₂N  N— ;
formyl, CH₂OH,

Z is NR₃ or O, where R₃ is H or C₁-C₄ alkyl;

R₄ and R₅ are each independently hydrogen, or (CH₂)_pR₇ where:

p is an integer of 1 to 3, and

R₇ is H, CH₃, CN, OH, OCH₃, CO₂CH₃, NH₂, NHCH₃, or N(CH₃)₂;

R₆ is phenyl,

pyridyl,

thienyl,

furyl,

pyrrolyl,

pyrazolyl,

imidazolyl,

quinolyl,

isoquinolyl,

naphthyl,

indolyl,
benzofuryl,
benzothiophenyl,
benzimidazolyl, or
5 benzoxazolyl, wherein each of the foregoing is unsubstituted, mono-, di-
or trisubstituted by alkyl,

hydroxy,

alkoxy,

halogen,

10 CF_3 ,

NO_2 ,

$\text{N}(\text{CH}_3)_2$,

OCF_3 ,

SONH_2 ,

15 NH_2 ,

CONH_2 ,

CO_2CH_3 or

CO_2H ,

or R6 is:

20 straight alkyl of from 1 to 3 carbons,

branched alkyl of from 3 to 8 carbons,

cycloalkyl of from 5 to 8 carbons or

heterocycloalkyl,

each of which can be substituted with up to one or two substituents

25 selected from

OH ,

CO_2H ,

$\text{N}(\text{CH}_3)_2$,

NHCH_3 and

30 CH_3 ; or

R5 and R6, when joined by a bond, can form a ring.

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

● is R or S, and ▲ is R or S;

-R is phenyl,

pyridyl,

thienyl,

furyl,

quinolyl

isoquinolyl

benzofuryl,

benzo[1,3]dioxole

benzothienyl or

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

alkyl,

hydroxy,

alkoxy,

halogen,

CF₃ or

OCF₃;

m is an integer from 1 to 3;

X is NR₈ or NHCONH where R₈ is H or alkyl of 1 to 3 carbon atoms;

R₁ is (CH₂)_pY where p is 0 to 3 and Y is OH, F, CF₃, OCH₃, CO₂H, N(CH₃)₂, NHCH₃, NH₂, COCF₃, COCH₃ or NO₂;

n is an integer from 1 to 2;

R₂ is naphthyl or indolyl unsubstituted or N-substituted with hydroxy, alkyl,

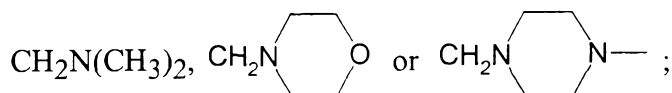
formyl, CH₂OH,

Z is NR₃ or O, where R₃ is H or CH₃;

R₄ and R₅ are each independently hydrogen, CH₃ or CH₂OH;

R₆ is phenyl,

pyridyl,



thienyl,
furyl,
pyrrolyl,
cyclohexyl or
5 benzimidazolyl,
wherein each of the foregoing is unsubstituted, mono-, di- or
trisubstituted by

alkyl,

hydroxy,

10 alkoxy,

halogen,

CF₃,

NO₂, or

15 N(CH₃)₂.

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

● is R or S, and ▲ is R or S;

R is phenyl,

20 pyridyl,

thienyl,

furyl,

benzofuryl,

benzo[1,3]dioxole

25 benzothienyl or

benzimidazolyl,

each unsubstituted, mono-, di- or trisubstituted by

alkyl,

hydroxy,

30 alkoxy,

halogen,

CF₃ or

OCF₃;

m is an integer from 1 to 3;

X is NR₈ or NHCONH where R₈ is H or alkyl of 1 to 3 carbon atoms;

5 R₁ is (CH₂)_pY where p is 0 to 3 and Y is OH, OCH₃, F, CF₃, CO₂H, N(CH₃)₂, NHCH₃, NH₂, COCF₃, COCH₃ or NO₂;

n is an integer from 1 to 2;

R₂ is indolyl unsubstituted or N-substituted with alkyl or formyl;

Z is NR₃ or O, where R₃ is H or CH₃;

10 R₄ and R₅ are each independently hydrogen, CH₃, or CH₂OH;

R₆ is phenyl,

pyridyl,

thienyl,

furyl,

15 pyrrolyl,

cyclohexyl or

benzimidazolyl,

each unsubstituted, mono-, di- or trisubstituted by

alkyl,

20 hydroxy,

alkoxy,

halogen,

CF₃,

NO₂ or

25 N(CH₃)₂.

Most preferred compounds of the invention are:

2-[(Benzofuran-2-ylmethyl)-amino]-3-(1*H*-indol-3-yl)-2-methoxymethyl-N-(1-phenyl-ethyl)-propionamide [S-(R*,R*)];

30 2-[(Benzofuran-2-ylmethyl)-amino]-2-dimethylaminomethyl-3-(1*H*-indol-3-yl)-N-(1-phenyl-ethyl)-propionamide (S,S);

2-[(Benzofuran-2-ylmethyl)-amino]-2-hydroxymethyl-3-(1*H*-indol-3-yl)-N-(1-phenyl-ethyl)-propionamide [S-(R*,R*)];

2-(3-Benzofuran-2-ylmethyl-ureido)-2-hydroxymethyl-3-(1*H*-indol-3-yl)-N-(1-phenyl-ethyl)-propionamide [S-(R*,R*)];

5 2-(3-Benzofuran-2-ylmethyl-ureido)-3-(1*H*-indol-3-yl)-2-methoxymethyl-N-(1-phenyl-ethyl)-propionamide [S-(R*,R*)];

(R)-C-[(Benzofuran-2-ylmethyl)-amino]-dimethylamino-C-(1-hydroxymethyl-1*H*-indol-3-ylmethyl)-N-((S)-1-phenyl-ethyl)-propionamide;

10 (R)-C-[(Benzofuran-2-ylmethyl)-amino]-dimethylamino-C-(1-dimethylaminomethyl-1*H*-indol-3-ylmethyl)-N-((S)-1-phenyl-ethyl)-propionamide.

15 The invention additionally provides pharmaceutical formulations comprising a compound of Formula I admixed with a pharmaceutically acceptable carrier, diluent or excipient therefor.

The invention also provides a method for antagonizing NK₁ receptors in a mammal in need of treatment comprising administering to a mammal an effective amount of a compound of Formula I.

20 The invention further provides a method for treating or preventing a variety of CNS disorders including pain (inflammatory, surgical and neuropathic), anxiety, panic, depression, major depression with anxiety, schizophrenia, neuralgia, stress, sexual dysfunction, bipolar disorders, movement disorders, cognitive disorders, obesity and addiction disorders; inflammatory diseases such as arthritis, asthma, bronchitis, chronic obstructive pulmonary disease (COPD) and psoriasis; gastrointestinal disorders including colitis, Crohn's disease, irritable
25 bowel syndrome and satiety; allergic responses such as eczema and rhinitis; vascular disorders such as angina and migraine; neuropathological disorders including scleroderma and emesis comprising administering to a mammal in need of treatment an effective amount of a compound of Formula I.

30

The compounds of the invention, NK₁ receptor antagonists, being useful as anti-angiogenic agents, the invention further provides a method for treating or

preventing conditions associated with aberrant neovascularization such as rheumatoid arthritis, atherosclerosis and tumour cell growth, which comprises administering to a mammal in need of treatment an effective amount of a compound of Formula I.

5 The invention further provides agents for imaging NK₁ receptors in vivo in conditions such as ulcerative colitis and Crohn's disease.

The invention further provides the use of a compound of Claim 1 for the preparation of a medicament intended for preventing or treating CNS disorders such as pain (inflammatory, surgical and neuropathic), anxiety, panic,
10 depression, major depression with anxiety, schizophrenia, neuralgia, stress, sexual dysfunction, bipolar disorders, movement disorders, cognitive disorders, obesity and addiction disorders; inflammatory diseases such as arthritis, asthma, bronchitis, chronic obstructive pulmonary disease (COPD) and psoriasis; gastrointestinal disorders including colitis, Crohn's disease, irritable bowel
15 syndrome and satiety; allergic responses such as eczema and rhinitis; vascular disorders such as angina and migraine; neuropathological disorders including scleroderma and emesis; conditions associated with aberrant neovascularization such as rheumatoid arthritis, atherosclerosis and tumour cell growth.

20 This invention also concerns a process for the preparation of ((S)-2-benzylideneamino)-3-(1H-indol-3-yl)-propionic acid methyl ester which comprises reacting (S)-tryptophan methyl ester with benzaldehyde and recovering the desired product.

The present invention also further concerns a process for the preparation of α -
25 dimethylaminomethyltryptophan methyl ester, wherein ((S)-2-benzylidene-amino)-3-(1H-indol-3-yl)-propionic acid methyl ester is reacted with 1-dimethylaminomethylbenzotriazole to give racemic α -dimethylaminomethyltryptophan methyl ester.

The present invention also discloses a process wherein the racemic methyl ester
30 obtained is separated into the (R)- and (S)-enantiomers.

Another embodiment of the present invention is the preparation of 2-
[(Benzofuran-2-ylmethyl)-amino]-2-dimethylaminomethyl-3-(1*H*-indol-3-yl)-*N*-
(1-phenyl-ethyl)-propionamide (S,S) wherein (S)-2-[(Benzofuran-2-ylmethyl)-
amino]-2-dimethylaminomethyl-3-(1*H*-indol-3-yl)-propionic acid *bis*-
5 hydrochloride is reacted with (S)-alpha-methylbenzylamine.

A further embodiment of this invention is the preparation of (R)-*C*-
[(Benzofuran-2-ylmethyl)-amino]-dimethylamino-*C*-(1-hydroxymethyl-1*H*-
indol-3-ylmethyl)-*N*-((S)-1-phenyl-ethyl)-propionamide wherein 2-
10 [(Benzofuran-2-ylmethyl)-amino]-2-dimethylaminomethyl-3-(1*H*-indol-3-yl)-*N*-
(1-phenyl-ethyl)-propionamide (S,S) is reacted with potassium
hexamethyldisilazide and formaldehyde.

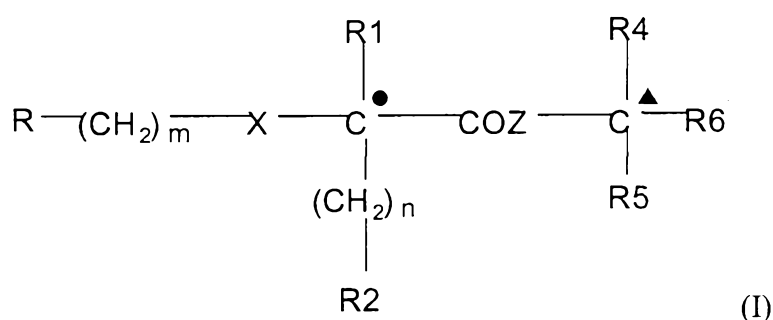
The invention also concerns the preparation of (R)-*C*-[(Benzofuran-2-ylmethyl)-
15 amino]-dimethylamino-*C*-(1-dimethylaminomethyl-1*H*-indol-3-ylmethyl)-*N*-
((S)-1-phenyl-ethyl)-propionamide wherein 2-[(Benzofuran-2-ylmethyl)-amino]-
2-dimethylaminomethyl-3-(1*H*-indol-3-yl)-*N*-(1-phenyl-ethyl)-propionamide
(S,S) is reacted with lithium hexamethyldisilazide and Eschenmoser's salt.

BRIEF DESCRIPTION OF FIGURES

Figure 1 shows the evaluation of the compound of Example 2 in the carrageenan-
induced hypersensitivity model in the guinea-pig.

DETAILED DESCRIPTION OF THE INVENTION

30 The invention provides tachykinin receptor antagonists; the compounds have
proved to be highly selective and functional tachykinin receptor antagonists.
These compounds are unique in the substitution at the C[●] carbon.
Compounds of the invention are those of Formula (I):



or a pharmaceutically acceptable salt thereof wherein R, m, X, R1, R2, n, Y, R3, R4, R5 and R6 are as described below:

● and ▲ indicate all stereoisomers;

- 5 R is phenyl,
pyridyl,
thienyl,
furyl,
quinolyl
10 isoquinolyl
naphthyl,
benzofuryl,
benzo[1,3]dioxole
benzothienyl or,
15 benzimidazolyl, each unsubstituted, mono-, di- or trisubstituted by
alkyl,
hydroxy,
alkoxy,
halogen,
20 CF₃ or
OCF₃;

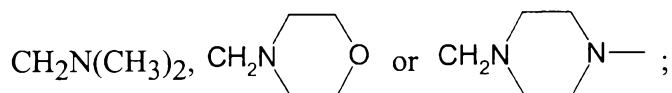
m is an integer from 1 to 3;

X is NR₈ or NHCONH where R₈ is H or alkyl of 1 to 3 carbon atoms;

R1 is $(\text{CH}_2)_p\text{Y}$ where p is 0 to 3 and Y is OH, OCH_3 , F, CF_3 , CO_2H , $\text{N}(\text{CH}_3)_2$, NHCH_3 , NH_2 , COCF_3 , COCH_3 or NO_2 ;

n is an integer from 1 to 2;

R2 is naphthyl or indolyl unsubstituted or N-substituted with hydroxy, alkyl,



formyl, CH_2OH ,

Z is NR_3 or O, where R3 is H or $\text{C}_1\text{-C}_4$ alkyl;

R4 and R5 are each independently hydrogen, or $(\text{CH}_2)_p\text{R}_7$ where:

p is an integer of 1 to 3, and

R7 is H, CH_3 , CN, OH, OCH_3 , CO_2CH_3 , NH_2 , NHCH_3 , or $\text{N}(\text{CH}_3)_2$;

R6 is phenyl,

pyridyl,

thienyl,

furyl,

pyrrolyl,

pyrazolyl,

imidazolyl,

quinolyl,

isoquinolyl,

naphthyl,

indolyl,

benzofuryl,

benzothiophenyl,

benzimidazolyl, or

benzoxazolyl, wherein each of the foregoing is unsubstituted, mono-, di-

or trisubstituted by alkyl,

hydroxy,

alkoxy,

halogen,

CF_3 ,

NO_2 ,

$\text{N}(\text{CH}_3)_2$,

OCF_3 ,

SONH_2 ,

NH_2 ,

CONH_2 ,

CO_2CH_3 or

CO_2H ,

or R6 is:

straight alkyl of from 1 to 3 carbons,

branched alkyl of from 3 to 8 carbons,

cycloalkyl of from 5 to 8 carbons or

heterocycloalkyl,

each of which can be substituted with up to one or two substituents

selected from

OH ,

CO_2H ,

$\text{N}(\text{CH}_3)_2$,

NHCH_3 and

CH_3 ; or

R5 and R6, when joined by a bond, can form a ring.

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

● is R or S, and ▲ is R or S;

-R is phenyl,

pyridyl,

thienyl,

furyl,

quinolyl

isoquinolyl

benzofuryl,

benzo[1,3]dioxole

benzothienyl or

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

alkyl,

5 hydroxy,

alkoxy,

halogen,

CF₃ or

OCF₃;

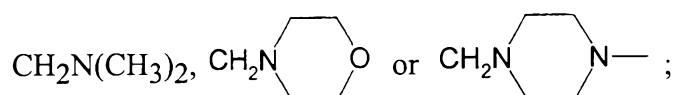
10 m is an integer from 1 to 3;

X is NR₈ or NHCONH where R₈ is H or alkyl of 1 to 3 carbon atoms;

R₁ is (CH₂)_pY where p is 0 to 3 and Y is OH, F, CF₃, OCH₃, CO₂H, N(CH₃)₂, NHCH₃, NH₂, COCF₃, COCH₃ or NO₂;

n is an integer from 1 to 2;

15 R₂ is naphthyl or indolyl unsubstituted or N-substituted with hydroxy, alkyl,



formyl, CH₂OH,

Z is NR₃ or O, where R₃ is H or CH₃;

R₄ and R₅ are each independently hydrogen, CH₃ or CH₂OH;

R₆ is phenyl,

20 pyridyl,

thienyl,

furyl,

pyrrolyl,

cyclohexyl or

25 benzimidazolyl,

wherein each of the foregoing is unsubstituted, mono-, di- or trisubstituted by

alkyl,

hydroxy,

30 alkoxy,

halogen,
CF₃,
NO₂, or
N(CH₃)₂.

5

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

● is R or S, and ▲ is R or S;

R is phenyl,

10

pyridyl,

thienyl,

furyl,

benzofuryl,

benzo[1,3]dioxole

15

benzothienyl or

benzimidazolyl,

each unsubstituted, mono-, di- or trisubstituted by

alkyl,

hydroxy,

20

alkoxy,

halogen,

CF₃ or

OCF₃;

m is an integer from 1 to 3;

25

X is NR₈ or NHCONH where R₈ is H or alkyl of 1 to 3 carbon atoms;

R₁ is (CH₂)_pY where p is 0 to 3 and Y is OH, OCH₃, F, CF₃, CO₂H, N(CH₃)₂, NHCH₃, NH₂, COCF₃, COCH₃ or NO₂;

n is an integer from 1 to 2;

R₂ is indolyl unsubstituted or N-substituted with alkyl or formyl;

30

Z is NR₃ or O, where R₃ is H or CH₃;

R₄ and R₅ are each independently hydrogen, CH₃, or CH₂OH;

R₆ is phenyl,

pyridyl,
thienyl,
furyl,
pyrrolyl,
5 cyclohexyl or
benzimidazolyl,
each unsubstituted, mono-, di- or trisubstituted by
alkyl,
hydroxy,
10 alkoxy,
halogen,
CF₃ ,
NO₂ or
N(CH₃)₂.

15 Most preferred compounds of the invention are:

2-[(Benzofuran-2-ylmethyl)-amino]-3-(1*H*-indol-3-yl)-2-methoxymethyl-N-(1-phenyl-ethyl)-propionamide [S-(R*,R*)];

2-[(Benzofuran-2-ylmethyl)-amino]-2-dimethylaminomethyl-3-(1*H*-indol-3-yl)-
20 N-(1-phenyl-ethyl)-propionamide (S,S);

2-[(Benzofuran-2-ylmethyl)-amino]-2-hydroxymethyl-3-(1*H*-indol-3-yl)-N-(1-phenyl-ethyl)-propionamide [S-(R*,R*)];

2-(3-Benzofuran-2-ylmethyl-ureido)-2-hydroxymethyl-3-(1*H*-indol-3-yl)-N-(1-phenyl-ethyl)-propionamide [S-(R*,R*)];

25 2-(3-Benzofuran-2-ylmethyl-ureido)-3-(1*H*-indol-3-yl)-2-methoxymethyl-N-(1-phenyl-ethyl)-propionamide [S-(R*,R*)];

(R)-C-[(Benzofuran-2-ylmethyl)-amino]-dimethylamino-C-(1-hydroxymethyl-1*H*-indol-3-ylmethyl)-N-((S)-1-phenyl-ethyl)-propionamide;

(R)-C-[(Benzofuran-2-ylmethyl)-amino]-dimethylamino-C-(1-dimethylaminomethyl-1*H*-indol-3-ylmethyl)-N-((S)-1-phenyl-ethyl)-
30 propionamide.

The present invention also concerns prodrugs of a compound of Formula I such as would be contemplated by to one skilled in the art (see Bundgaard et al., Acta Pharma Suec., 1987; 24: 233-246.) for example a suitable moiety may be attached to a nitrogen of the linker X, to the nitrogen of the Z linker, or that of an indolyl radical of R2 when R2 is an indolyl radical.

The invention additionally provides pharmaceutical formulations comprising a compound of Formula I admixed with a pharmaceutically acceptable carrier, diluent or excipient therefor.

The invention also provides a method for antagonizing NK₁ receptors in a mammal in need of treatment comprising administering to a mammal an effective amount of a compound of Formula I.

The invention further provides a method for treating or preventing a variety of CNS disorders including pain (inflammatory, surgical and neuropathic), anxiety, panic, depression, major depression with anxiety, schizophrenia, neuralgia, stress, sexual dysfunction, bipolar disorders, movement disorders, cognitive disorders, obesity and addiction disorders; inflammatory diseases such as arthritis, asthma, bronchitis, chronic obstructive pulmonary disease (COPD) and psoriasis; gastrointestinal disorders including 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 scleroderma and emesis comprising administering to a mammal in need of treatment an effective amount of a compound of Formula I.

The compounds of the invention, NK₁ receptor antagonists, being useful as anti-angiogenic agents, the invention further provides a method for treating or preventing conditions associated with aberrant neovascularization such as rheumatoid arthritis, atherosclerosis and tumour cell growth, which comprises administering to a mammal in need of treatment an effective amount of a compound of Formula I.

The invention further provides agents for imaging NK₁ receptors in vivo in conditions such as ulcerative colitis and Crohn's disease.

The invention further provides the use of a compound of formula 1 for the preparation of a medicament intended for preventing or treating CNS disorders such as pain (inflammatory, surgical and neuropathic), anxiety, panic, depression, major depression with anxiety, schizophrenia, neuralgia, stress, sexual dysfunction, bipolar disorders, movement disorders, cognitive disorders, obesity and addiction disorders; inflammatory diseases such as arthritis, asthma, bronchitis, chronic obstructive pulmonary disease (COPD) and psoriasis; gastrointestinal disorders including 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 scleroderma and emesis; conditions associated with aberrant neovascularization such as rheumatoid arthritis, atherosclerosis and tumour cell growth.

Throughout this application, the following abbreviations have the meanings listed below:

CBZ	carbobenzoxo
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
DCC	1,3-dicyclohexyl carbodiimide
DIPEA	<i>N,N</i> -diisopropylethylamine
DMAP	<i>N,N</i> -dimethyl-4-amino pyridine
DMF	<i>N,N</i> -dimethylformamide
DMPU	<i>N,N'</i> -dimethyl- <i>N,N'</i> -propylene urea
HBTU	<i>O</i> -benzotriazol-1-yl- <i>N,N,N',N'</i> -tetramethyluronium hexafluorophosphate
HRMS	high resolution mass spectrometry
LHMDS	lithium hexamethyl disilazide
Met	methionine
PEI	poly(ethylene imine)
Sar	sarcosine
s.c.	subcutaneous

SEM-Cl	2-(trimethylsilyl)ethoxymethyl chloride
RT	room temperature
TBAF	tetrabutylammonium fluoride
TFA	trifluoroacetic acid
5 THF	tetrahydrofuran
TIPS	triisopropylsilyl
Tris	tris(hydroxymethyl)aminomethane
Trp	tryptophan

10 The compounds of Formula I are further defined as follows.

The term "alkyl" means a straight or branched hydrocarbon having from one to 12 carbon atoms and includes, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, secbutyl, tert-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, undecyl, dodecyl, and the like unless stated specifically otherwise.

15 The term "cycloalkyl" means a saturated hydrocarbon ring which contains from 3 to 12 carbon atoms, for example cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl except as otherwise stated.

The term "alkoxy" means an alkyl as described above attached through an oxygen atom.

20 The term "halogen" is chlorine, bromine, fluorine or iodine.

The ring formed by joining R5 and R6 is from 4 to 6 atoms total and is unsubstituted.

25 The compounds of Formula I are capable of forming pharmaceutically acceptable acid addition salts. All of these forms are within the scope of the present invention.

30 Pharmaceutically acceptable acid addition salts of the compound of Formula I include salts derived from nontoxic inorganic acids such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydroiodic, hydrofluoric, phosphorous, and the like as well as the salts derived from nontoxic organic acids, such as the aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanolic acids, hydroxy-alkanoic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc. Such salts thus include sulfate,

pyrosulfate, bisulfate sulfite, bisulfite, nitrate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, fluoride, acetate, trifluoroacetate, propionate, caprylate, isobutyrate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, mandalate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, phthalate, benzenesulfonate, toluenesulfonate, phenylacetate, citrate, lactate, tartrate, methanesulfonate, and the like. Also contemplated are salts of amino acids such as arginate and the like. For example, see Berge S.M., *et al.*, Pharmaceutical Salts, J. Pharm. Sci., 66:1-19 (1977) incorporated herein by reference.

The acid addition salts of said basic compounds are prepared by contacting the free base form with a sufficient amount of the desired acid to produce the salt in the conventional manner. Preferably, a compound of Formula I can be converted to an acidic salt by treating an aqueous solution of the desired acid, such that the resulting pH is less than four. The solution can be passed through a C18 cartridge to absorb the compound, washed with copious amounts of water, the compound eluted with a polar organic solvent such as, for example methanol acetonitrile, aqueous mixtures thereof, and the like, and isolated by concentrating under reduced pressure followed by lyophilisation. The free base form may be regenerated by contacting the salt form with a base and isolating the free base in the conventional manner. The free base forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free base for the purpose of the present invention.

Certain of the compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms, including hydrated forms are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention.

Certain of the compounds of the present invention possess one or more chiral centres and each centre may exist in the R (D) or S (L) configuration. The present invention includes all enantiomeric and epimeric forms as well as the appropriate mixtures thereof.

The compounds of the present invention can be prepared and administered in a wide variety of oral and parenteral dosage forms. Thus, the compounds of the present invention can be administered by injection, that is intravenously, intramuscularly, intracutaneously, subcutaneously, intraduodenally, or intraperitoneally. In addition, the compounds of the present invention can be administered by inhalation, for example intranasally. Additionally, the compounds of the present invention can be administered transdermally. It will be obvious to those skilled in the art that the following dosage forms may comprise as the active component, either a compound of Formula I or a corresponding pharmaceutically acceptable salt of the compound of Formula I.

For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, pills, tablets, capsules, cachets, suppositories and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavouring agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is 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.

The powders and tablets preferably contain from 5% or 10% to about 70% of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound 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 and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogeneous mixture is then poured into convenient sized moulds, allowed to cool, and the thereby to solidify.

Liquid form preparations include solutions, suspensions and emulsions, for example, water or water propylene glycol solutions. For parenteral injection liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavours, stabilising and thickening agents as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose sodium carboxymethylcellulose, and other well-known suspending agents.

Also included are solid form preparations that are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavours, stabilisers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilising agents and the like.

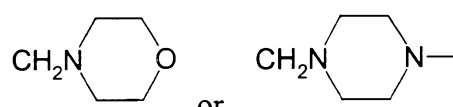
The pharmaceutical preparation is preferably in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampules. Also, the unit dosage form can be a capsule, tablet, cachet or lozenge itself, or it can be the appropriate number of any of these in packaged form.

The quantity of active component in a unit dose preparation may be varied or adjusted from 0.1 mg to 200 mg preferably 0.5 mg to 100 mg according to the

particular application and the potency of the active component. The composition can, if desired also contain other compatible therapeutic agents.

In therapeutic use, the highly selective and competitive antagonists of the NK₁ receptor and compounds of this invention are administered at the initial dosage of about 0.01 mg to about 500 mg/kg daily. A daily dose range of about 0.01 mg to about 100 mg/kg is preferred. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated and the compound being employed. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller doses which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day, if desired.

The compounds of Formula I or Intermediates for their synthesis and particularly compounds for which R₂ is an indolyl unsubstituted or N-substituted with hydroxy, alkyl, formyl, CH₂OH, CH₂N(CH₃)₂,

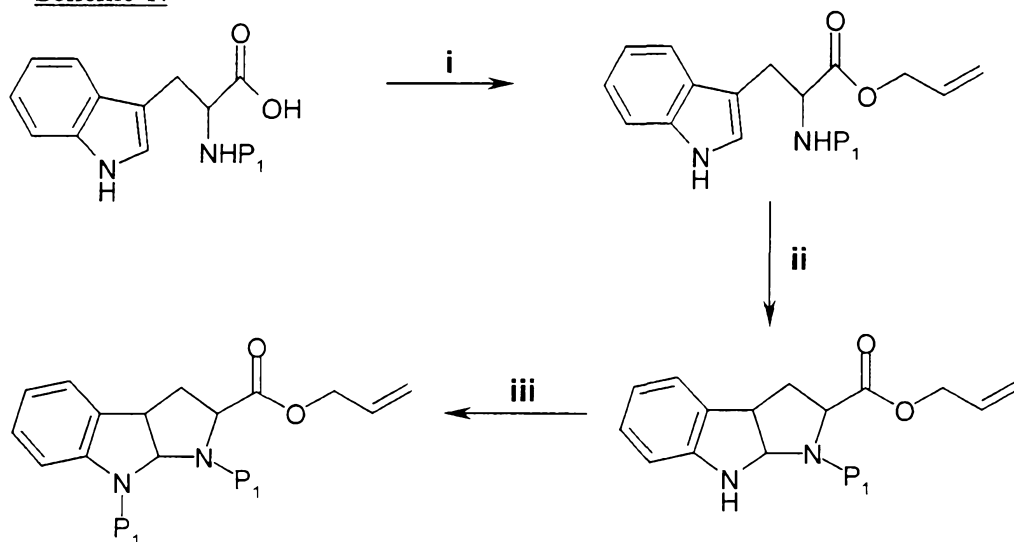
 or , can be prepared by any several synthetic processes well known to those skilled in the art of organic chemistry.

The synthesis can be carried out on racemic reactants, to provide invention compounds in racemic form, which can then be resolved by conventional methods, if desired. Alternatively, the invention compounds can be prepared in optically active form by using enantiomeric reactants and asymmetric reactions.

A process for the obtention of an Intermediate for the synthesis of a compound of the present invention is the process of scheme 1.

Scheme 1 describes the synthesis of the tricyclic Intermediate 1, which is one of the possible key Intermediates in the synthesis of compounds of the invention and particularly the compounds of Examples 1 to 7.

Scheme 1:



Intermediate 1

where P₁ is an *N*-protecting group such as benzyloxy carbonyl, alkyloxy carbonyl (eg, Methyl, Ethyl, halogenated alkyl), arylsulfonyl (eg toluyl, phenyl), alkylsulfonyl (Methyl, Ethyl), RCO-.

5

i) Allyl alcohol, DCC, DMAP, CH₂Cl₂, 89 %

ii) TFA, 52 %

iii) P₁-Cl, Na₂CO₃ (aq), dioxan, 92 %

10

In this synthesis:

- in step i) the allyl ester of P₁-Trp is formed using DCC and DMAP;
- in step ii) the compound obtained is then cyclised using TFA; and
- in step iii) the indole nitrogen is then protected with a second protecting group.

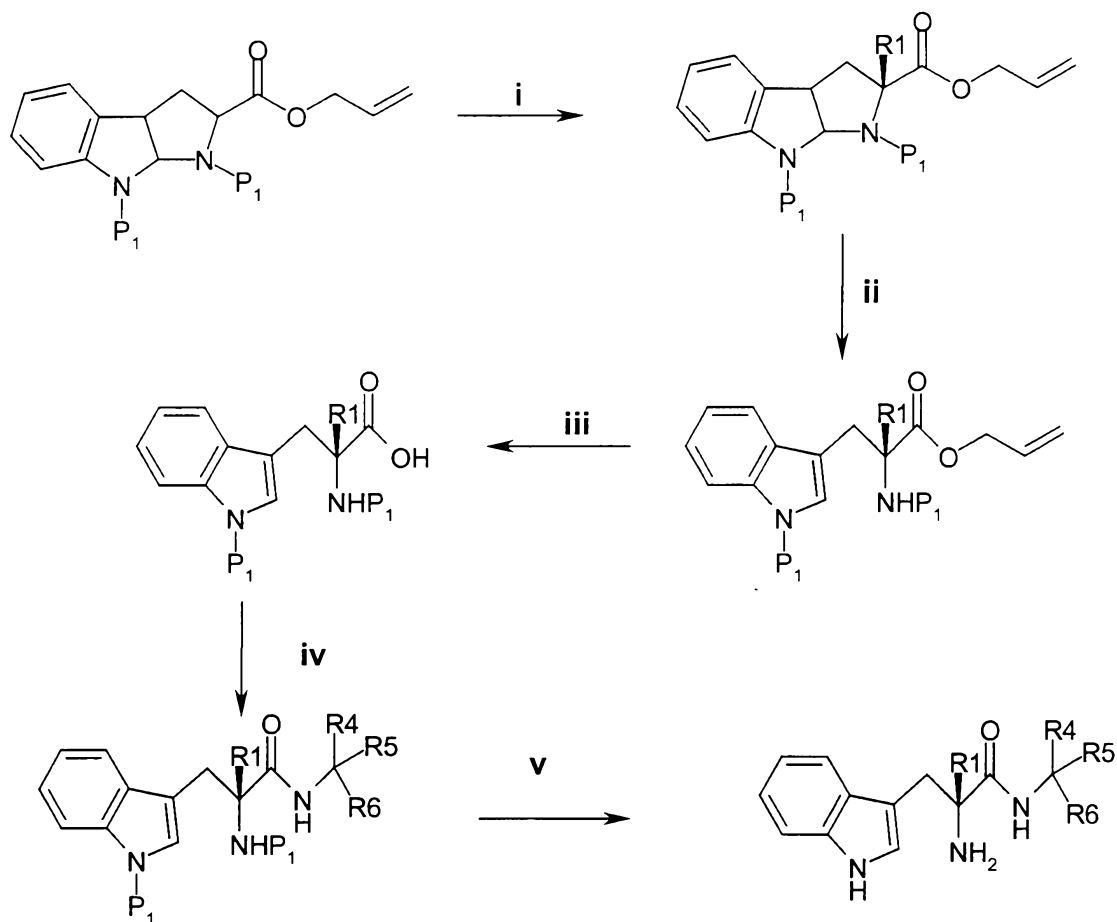
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In a preferred embodiment of the present invention P₁ is a benzyloxy carbonyl group.

Other Intermediates useful in the synthesis of compounds of the present invention can be obtained as shown in scheme 2.

20

Scheme 2:



wherein R₁, R₄, R₅, R₆ and P₁ are as defined previously.

5

In this synthesis:

- In step i) the tricyclic Intermediate 1 is asymmetrically alkylated;
- In step ii) the product obtained is then ring opened for instance using TFA;
- In step iii) the allyl ester is removed;
- In step iv) the acid obtained is coupled with the appropriate amine; and
- In step v) the N-terminal protecting groups are removed to yield the desired Intermediates.

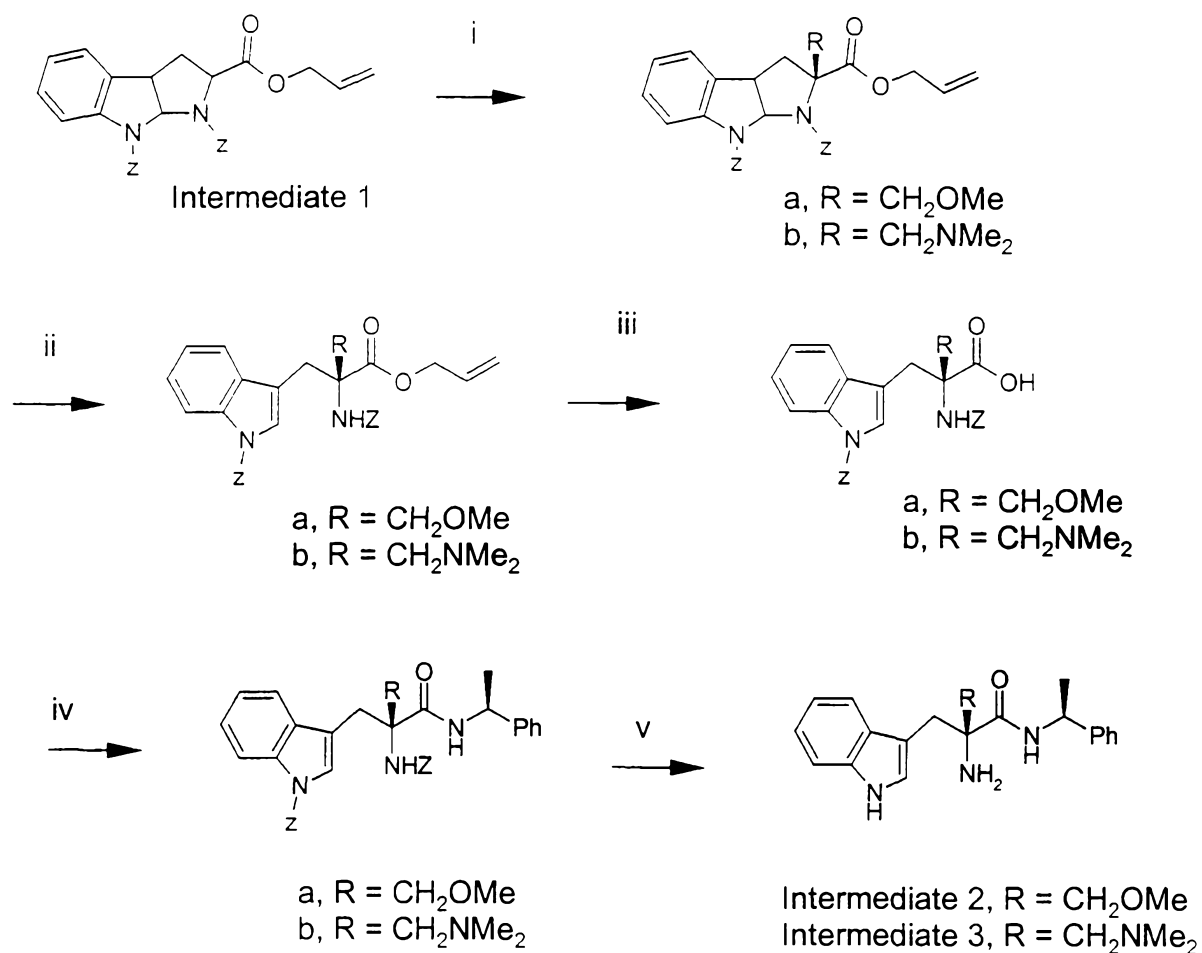
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Scheme 2.1 below exemplifies the synthesis of Intermediates 2 and 3.

In this synthesis:

- the tricyclic Intermediate 1 is asymmetrically alkylated;
- the product obtained is then ring opened using TFA;
- the allyl ester is then removed and
- the acid obtained is coupled with alpha-methylbenzylamine using HBTU activation;
- Intermediates 2 and 3 are then formed by removal of the benzyloxy carbonyl N-terminal protecting group with palladium hydroxide on carbon.

Scheme 2.1:



5

wherein Z is an *N*-protecting group such as benzyloxy carbonyl, alkyloxy carbonyl (eg, Methyl, Ethyl, halogenated alkyl), arylsulfonyl (eg toluyl, phenyl), alkylsulfonyl (Methyl, Ethyl), RCO-.

10

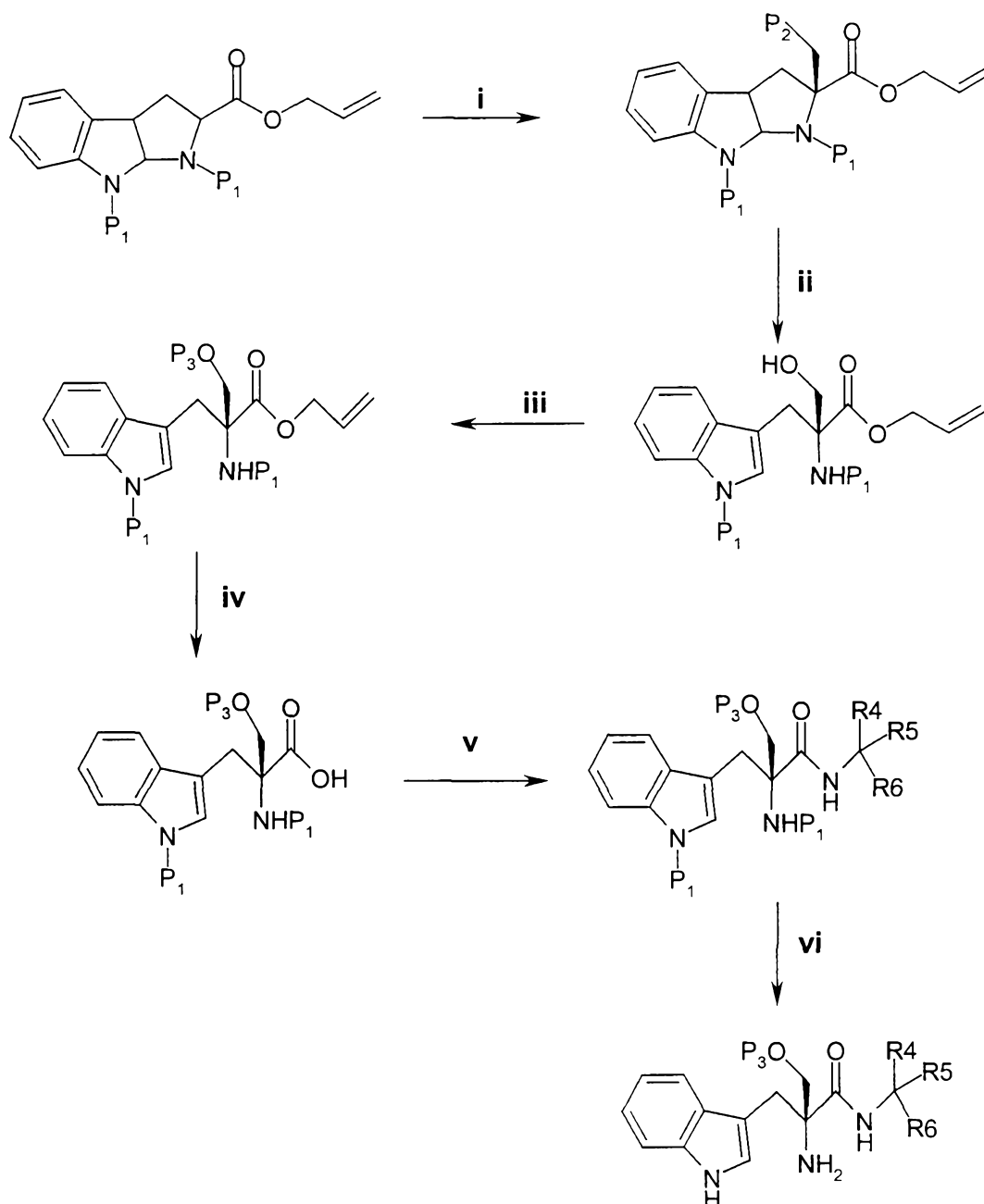
- i) LHMDS, RX, DMPU, THF
- ii) TFA, CH₂Cl₂ or H₂SO₄, MeOH, H₂O
- iii) Pd(PPh₃)₄, morpholine, THF
- iv) amine, HBTU, DIPEA, DMF
- v) Pd(OH)₂/C, EtOH

15

In a preferred embodiment of this invention Z is a benzyloxy carbonyl group.

Further Intermediates useful in the synthesis of compounds of the invention can be obtained as shown in scheme 3.

Scheme 3:



wherein P_1 , R_4 , R_5 , R_6 are as defined previously and wherein P_2 and P_3 are protecting groups, P_2 being SEM, P_3 being TIPS, TBS, TBDMS, or DPS or an ether group such as MOM, THP.

In this synthesis:

- In step i) a protected hydroxyl function is introduced;
- In step ii) the ring is opened and the protecting group on the hydroxy function is removed;
- 5 -In step iii) the hydroxy moiety is protected with an appropriate protecting group;
- In step iv) the allyl ester is removed;
- In step v) the acid is coupled with the appropriate amine;
- In step vi) the desired Intermediate is obtained by removing the N-terminal
- 10 protecting groups.

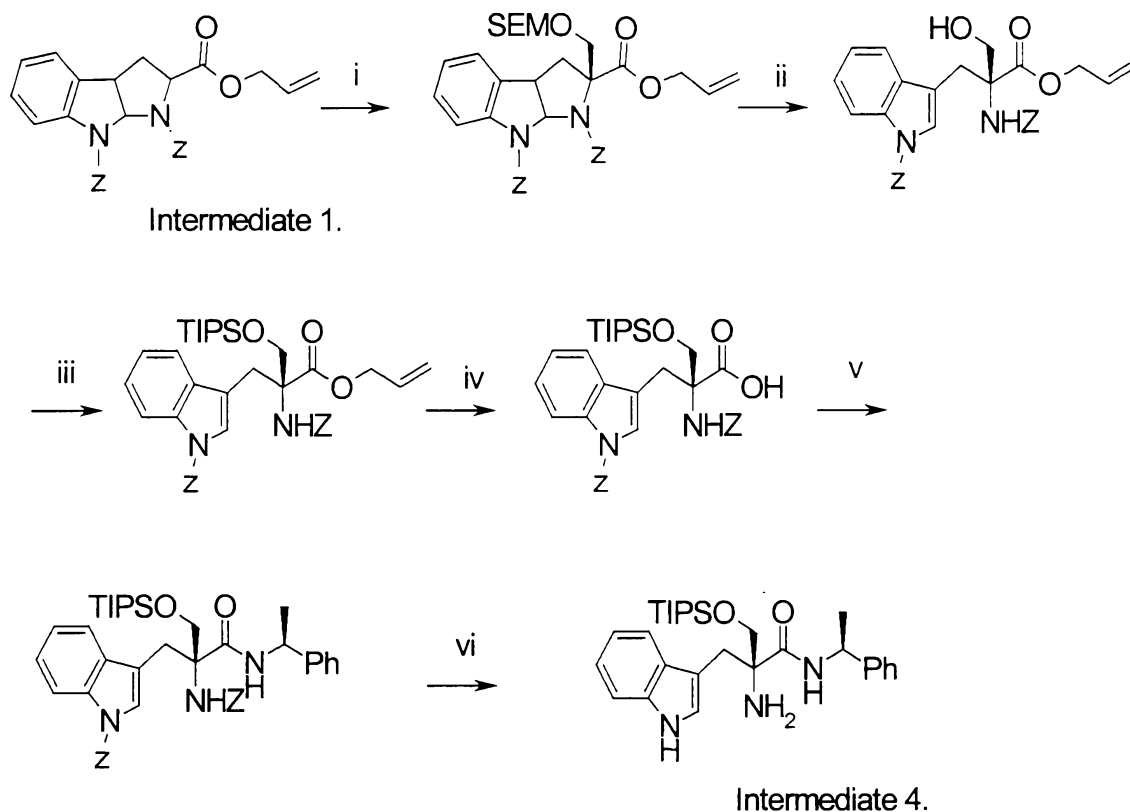
In a preferred embodiment of the present invention P2 is SEM and P3 is TIPS.

Scheme 3.1 belows exemplifies the synthesis of Intermediate 4.

In this process:

- the protected hydroxyl function is introduced by reaction of Intermediate 1 with LHMDs followed by SEM-Cl;
- the ring is opened and the protecting group is removed using TFA in
- 20 dichloromethane;
- the hydroxyl moiety is then protected with a TIPS group by TIPS-Cl in DMF;
- the allyl ester is then removed and
- the acid is coupled with alpha-methylbenzylamine using HBTU activation.
- Intermediate 4 is then formed by removal of the benzyloxycarbonyl N-terminal
- 25 protecting group with palladium hydroxide on carbon.

Scheme 3.1:



wherein Z is an *N*-protecting group such as benzyloxy carbonyl, alkyloxy carbonyl (eg, Methyl, Ethyl, halogenated alkyl), arylsufonyl (eg toluyl, phenyl), alkylsulfonyl (Methyl, Ethyl), RCO-.

i) LHMDS, SEM-Cl, THF

ii) TFA, CH₂Cl₂

iii) Imidazole, TIPS-Cl, CH₂Cl₂

iv) Pd(PPh₃)₄, morpholine, THF

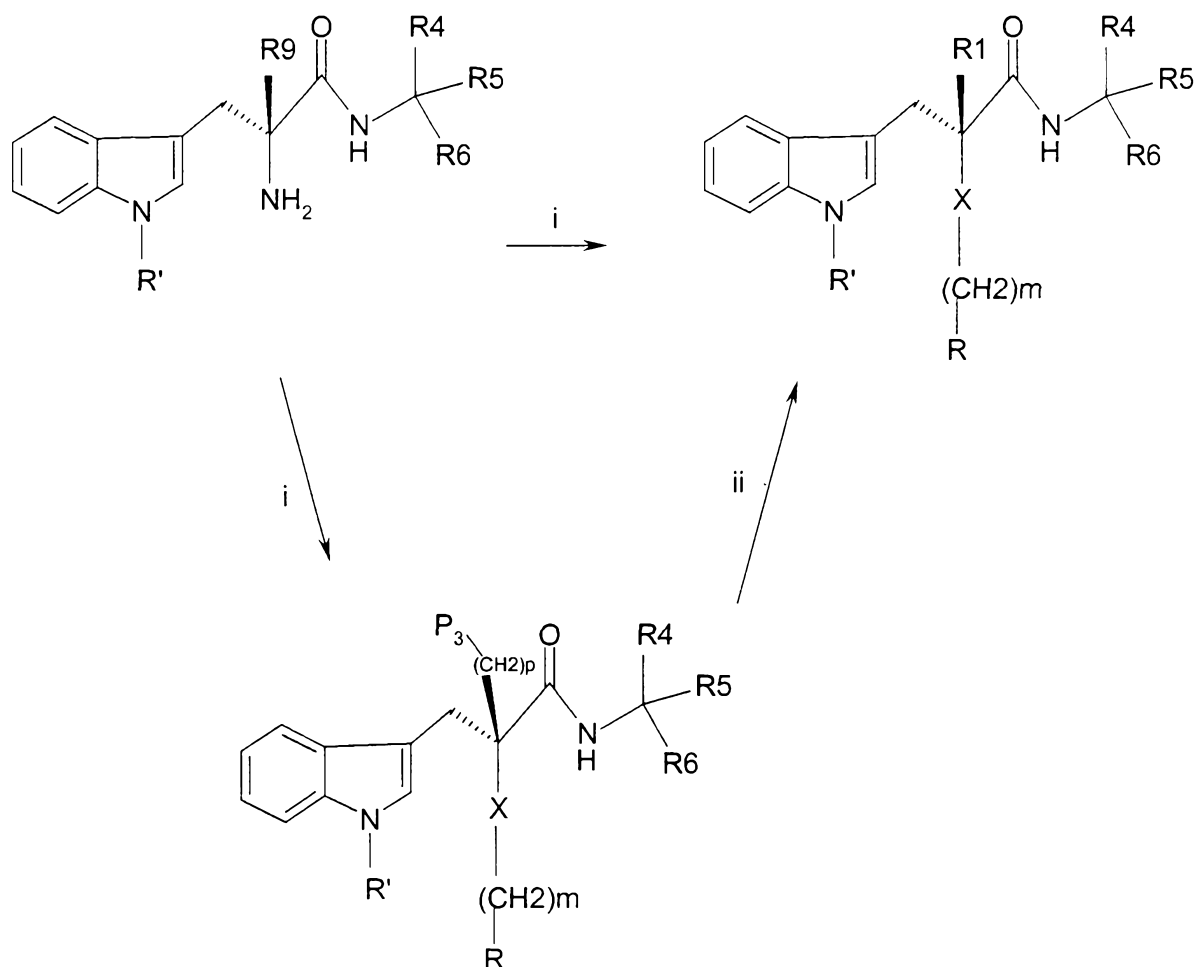
v) amine, HBTU, DIPEA, DMF

vi) Pd(OH)₂ /C, EtOH

In a preferred embodiment of the present invention Z is a benzyloxy carbonyl group.

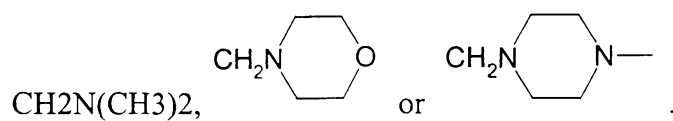
A process for the synthesis of compounds of the present invention is as shown in scheme 4.

Scheme 4:



5

wherein R9 is R1 as defined above or (CH₂)_p P₃ wherein p is an integer from 0 to 3 and P₃ is as defined above; wherein R, m, R₄, R₅ and R₆ are as defined above, and wherein R' is hydroxy, alkyl, formyl, CH₂OH,



10

-Step i) of this process requires reduction of the amino group into a secondary amine.

-Step ii) is required only when R⁹ is (CH₂)_p P3. In this second step the protecting group is removed by conventional methods known to the skilled person.

5 Very most preferred compounds are compounds wherein R is benzofuryl.

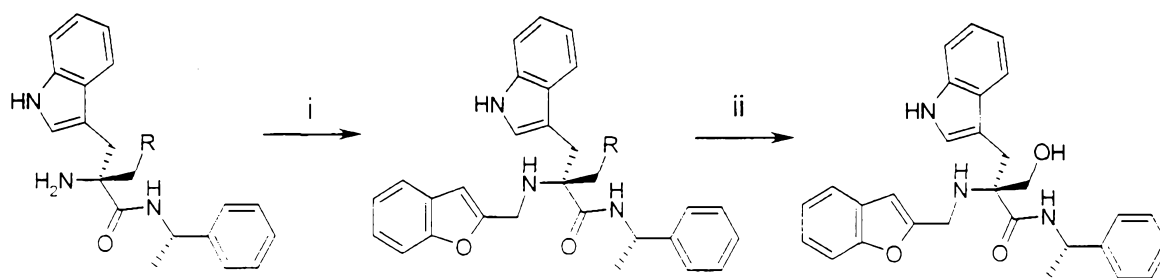
Scheme 4.1 outlines below the synthesis of the compounds of Examples 1, 2 and 3.

10 Examples 1 and 2 are prepared from a reductive amination of benzofuran-2-carboxaldehyde with Intermediates 2 and 3 respectively and sodium triacetoxy borohydride in 1,2-dichloroethane.

Example 3 is prepared in an analogous manner with an additional step to remove the TIPS protection using TBAF in tetrahydrofuran.

15

Scheme 4.1:



Intermediate 4, R = TIPS
Intermediate 2, R = OMe
Intermediate 3, R = NMe₂

a), R = TIPS
Example 1, R = OMe
Example 2, R = NMe₂

Example 3

i) Benzofuran-2-carboxaldehyde, NaBH(OAc)₃, (CH₂Cl)₂

ii) TBAF, THF

20

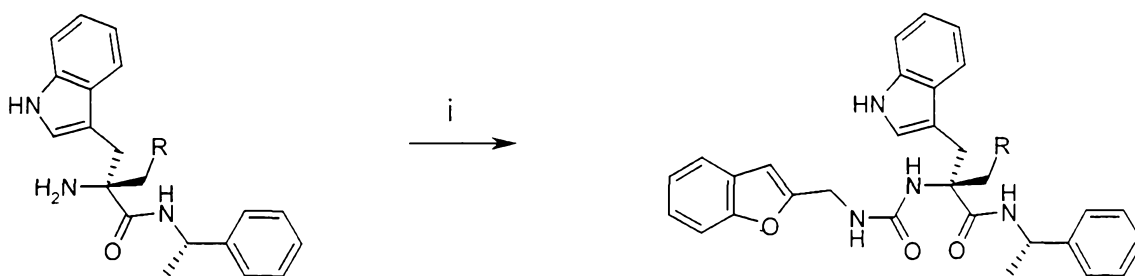
Scheme 4.2 below exemplifies the synthesis of the compounds of Examples 4 and 5.

Example 4 is prepared by reaction of Intermediate 2 with (2-benzofuranyl)methylisocyanate in tetrahydrofuran.

Example 5 is prepared in an analogous manner with an additional step to remove the TIPS protection using TBAF in tetrahydrofuran.

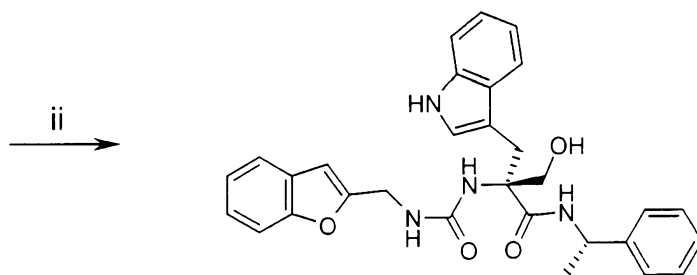
Scheme 4.2:

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Intermediate 4, R = TIPS
Intermediate 2, R = OMe

a) , R = TIPSO
Example 4, R = OMe



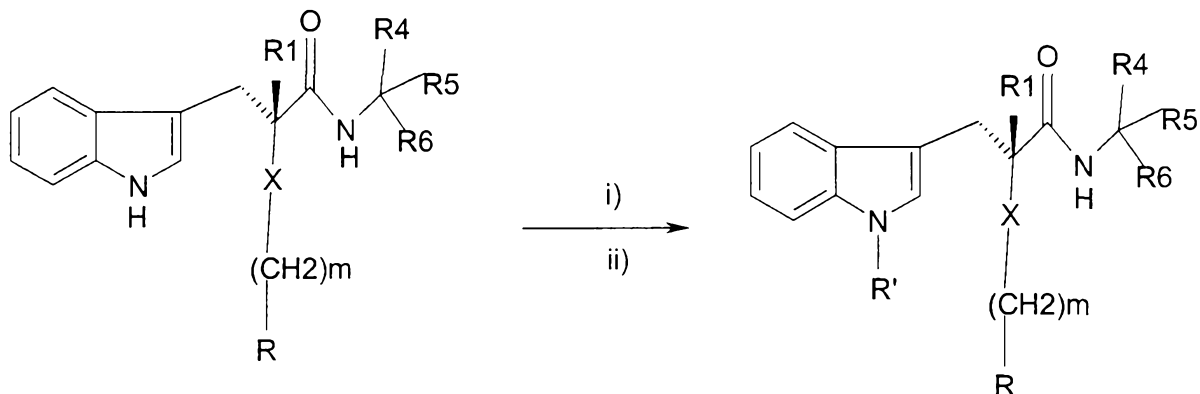
Example 5.

i) (2-benzofuran)methyl isocyanate, THF

ii) TBAF, THF

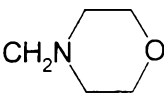
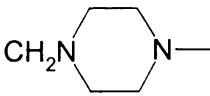
Another process of the invention can be used to introduce a substituent on the N atom of the indolyl group of R2, scheme 5.

Scheme 5:



5

wherein R1, R4, R5, R6, R and m are as defined above, R' being hydroxy, alkyl,

formyl, CH₂OH, CH₂N(CH₃)₂,  or  .

In this synthesis:

10

-in step i) reaction with potassium hexamethyldisilazide takes place.

-in step ii) reaction with formaldehyde or Eschenmoser's salt takes place.

Those two reactions could also be combined as in Scheme 2.1 (above) into one 'step' e.g. LHMDs, RX, THF.

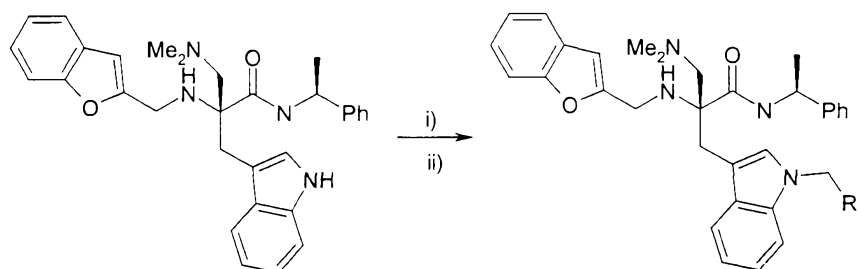
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Scheme 5.1 below exemplifies the synthesis of the compounds of Examples 6 and 7.

20

Example 6 is prepared by reaction of Example 2 with potassium hexamethyldisilazide and formaldehyde in THF at -78 °C.

Example 7 is prepared in an analogous manner but with Eschenmoser's salt in place of the formaldehyde.

Scheme 5.1:

Example 6, $\text{R} = \text{OH}$
Example 7, $\text{R} = \text{N}(\text{CH}_3)_2$

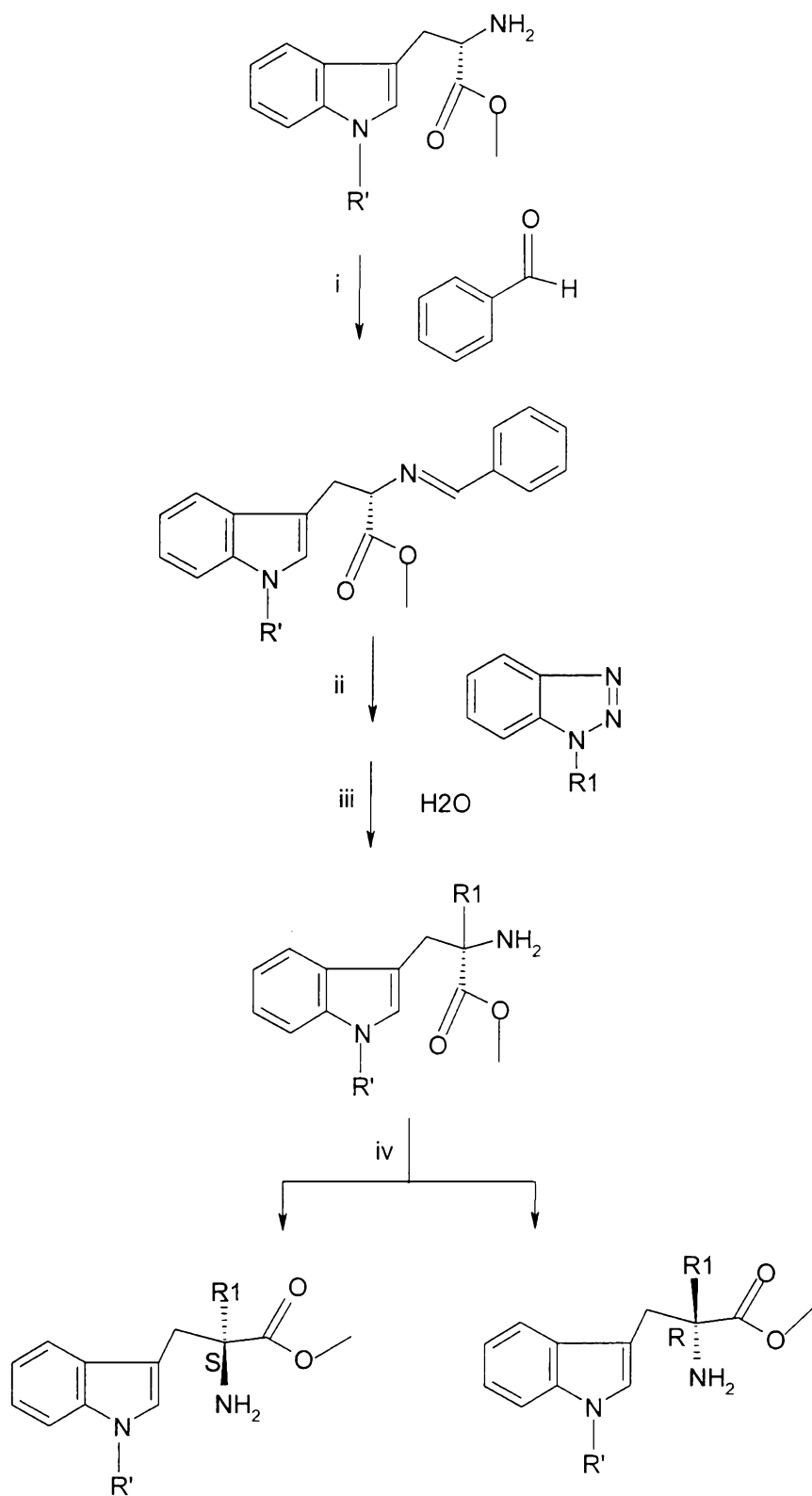
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- i) Potassium hexamethyldisilazide, Example 2, THF (-78°C)
- ii) formaldehyde or Eschenmoser's salt

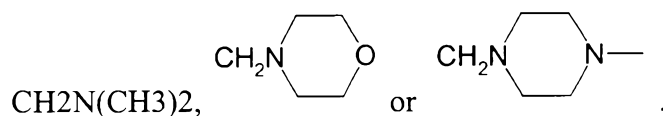
Alternative Intermediates useful in the synthesis of compounds of the invention can be obtained as shown in scheme 6.

10

Scheme 6:



wherein R1 is as described previously and R' is hydroxy, alkyl, formyl, CH₂OH,



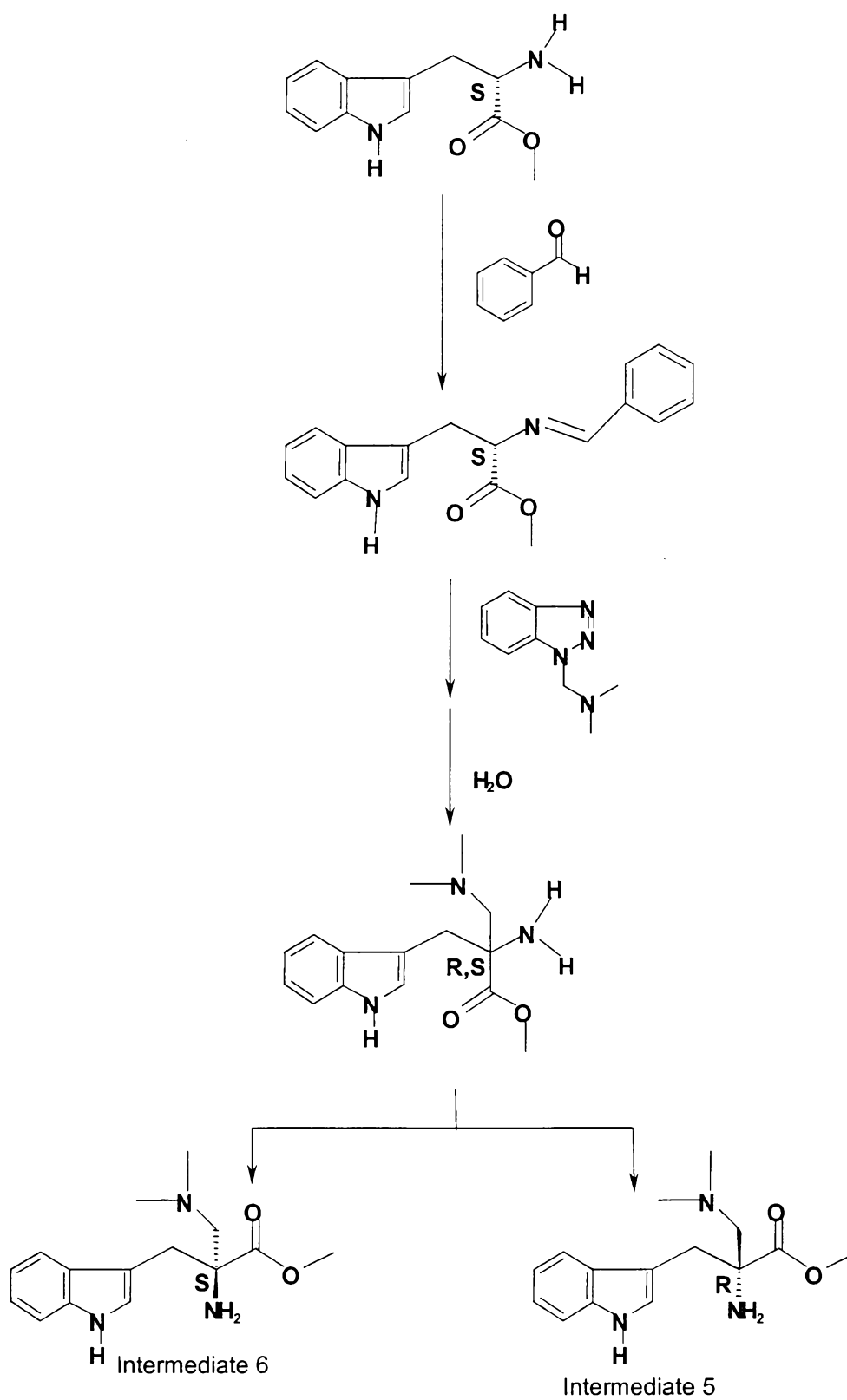
In this synthesis:

- 5 -In step i) reaction with benzaldehyde takes place. This is an imine formation where the water by-product is removed with a dehydrating reagent (eg MgSO₄), molecular sieves or azeotropic removal (Dean-Stark trap).
- In step ii) an alpha aminoalkylation takes place;
- In step iii) the hydrolysis of the benzylimine takes place:
- 10 -In step iv) the racemate is separated in the two corresponding diastereoisomers chiral HPLC phase.

The racemate could also be separated in the two corresponding diastereoisomers by crystallisation after reaction with a chiral acid.

- 15 Scheme 6.1 below exemplifies the synthesis of Intermediate 6.

Scheme 6.1:



Ways were sought to prepare α -dimethylaminomethyltryptophan methyl ester without the use of protective group chemistry contrary to literature references, the desired α -aminoalkylation with 1-dimethylaminomethylbenzotriazole, starting from the Schiff's base ((S)-2-benzylideneamino)-3-(1H-indol-3-yl)-propionic acid methyl ester), could be achieved.

It was very surprising that α -dimethylaminomethyltryptophan can only be esterified in conventional manner with extreme difficulty.

Surprisingly, we have now found that ((S)-2-benzylidene-amino)-3-(1H-indol-3-yl)-propionic acid methyl ester (Schiff's base), which can be prepared in one synthesis step from the cheap (S)-tryptophan methyl ester ((S)-Trp-OMe), can, by reaction with 1-dimethylaminomethylbenzotriazole, be converted into racemic α -dimethylaminomethyltryptophan methyl ester without using protection group chemistry.

It is known that N-(α -aminoalkyl)-benzotriazole derivatives, which can be prepared very easily from benzotriazole, an aldehyde and a primary or secondary amine, can be used as aminoalkylation reagents (see A. Katritzky et al., Tetrahedron, 46, No. 24, 8153-8160/1990).

The preparation of 1-dimethylaminomethylbenzotriazole has been described by J.H. Bruckhalter et al. (J.A.C.S., 74, 3868-3369/1952).

B.E. Love and B.T. Nguyer (Synlett, 1123, October, 1998) have described the reaction of 1-methylaminomethylbenzotriazole and indole. As main reaction, there hereby takes place an aminoalkylation on the indole nitrogen atom, an aminoalkylation on the 3-position only taking place as a secondary reaction.

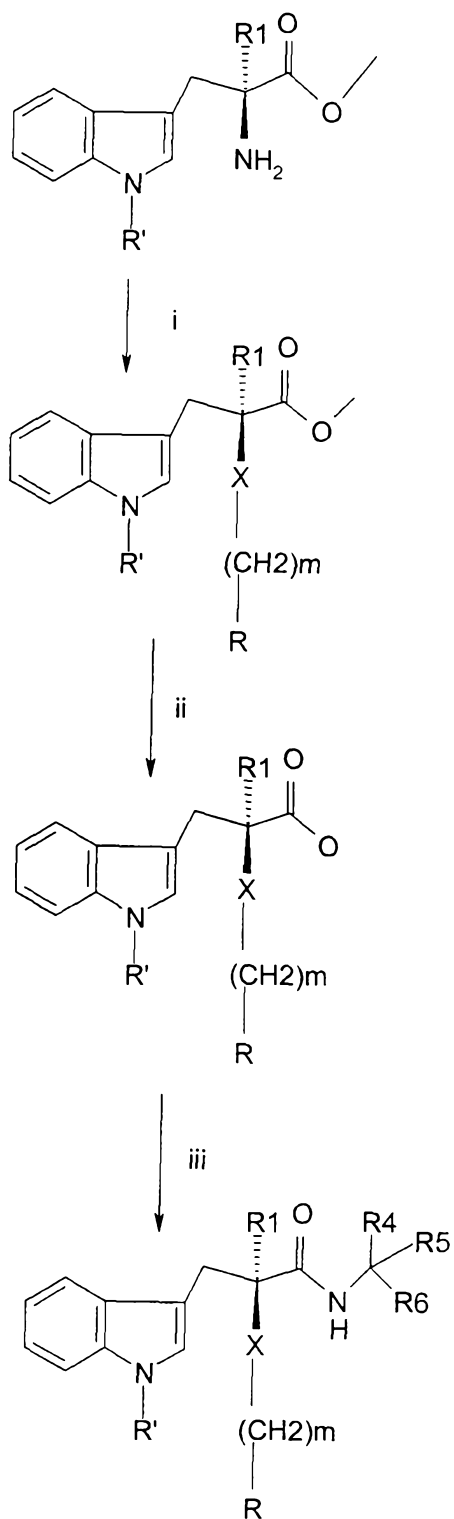
Surprisingly, in the case of the tryptophan derivative (Schiff's base) used in the case of the present invention, this aminoalkylation reaction with 1-dimethylaminomethyl-benzotriazole only takes place on the α -C atom. In contradistinction to the above-mentioned literature references, an alkylation on the indole nitrogen atom was not observed.

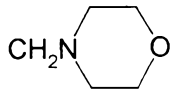
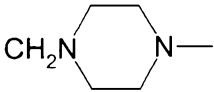
Furthermore, we have found that the racemic α -dimethylaminomethyltryptophan methyl ester cannot be separated into the enantiomers either enzymatically or

after formation of diastereomeric salts. It was even more surprising that the two enantiomers, i.e. the (S)-enantiomer and the (R)-enantiomer, can be separated on a preparative scale on a chiral HPLC phase.

5 The racemic α -dimethylaminomethyltryptophan methyl ester can then be further reacted in the usual way with a second chiral component to give a diastereomeric mixture which can be separated by crystallisation into the two diastereomeric compounds.

10 Further compounds of the invention can be obtained by an alternative process as follows, scheme 7.

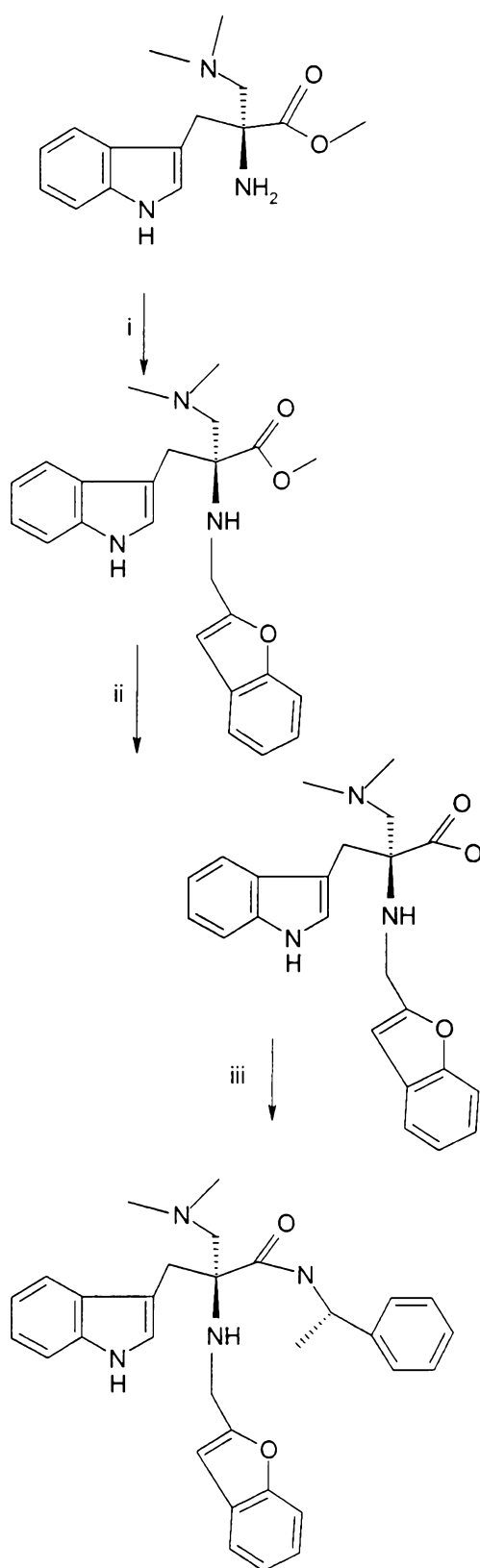
Scheme 7:

wherein R' is hydroxy, alkyl, formyl, CH₂OH, CH₂N(CH₃)₂,  or  and wherein R₁, m, R, R₄, R₅, R₆ are as described previously.

In this synthesis:

- 5 -In step i) the amino group is reduced into a secondary amine.
-In step ii) the methyl ester is hydrolysed with a base (LiOH, NaOH, KOH) in an appropriate solvent system
-In step iii) the acid is coupled with the appropriate amine.
- 10 Scheme 7.1 below exemplifies the alternative synthesis of the compound of Example 2.

Scheme 7.1:



- i) benzofuran-2-carbaldehyde, sodium triacetoxyborohydride, $(\text{CH}_2\text{Cl})_2$
- ii) NaOH, 1,4-dioxan/water.
- iii) HBTU, amine, DIPEA, DMF.

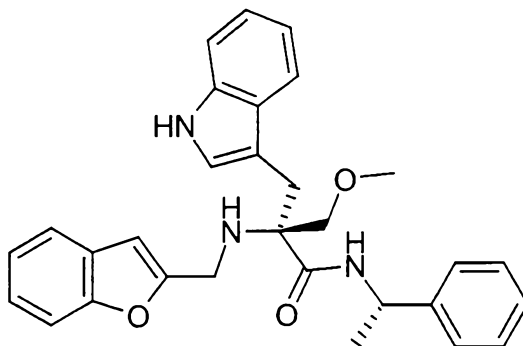
5 The compounds of Examples 6 and 7 can be obtained from the compound of example 2 synthesised said process, through the process outlined in scheme 5.1.

The present invention is further illustrated, but in no case limited, by the figures and the examples below.

EXAMPLES

EXAMPLE 1

2-[(Benzofuran-2-ylmethyl)-amino]-3-(1*H*-indol-3-yl)-2-methoxymethyl-N-(1-phenyl-ethyl)-propionamide [S-(R*,R*)]



Step 1

A solution of (*R*)-*N*-CBZ-tryptophan (1.00 g, 29.6 mmol), *N*, *N*'-dicyclohexylcarbodiimide (640 mg, 31.1 mmol), *N*, *N*-dimethyl-4-aminopyridine (36 mg, 2.96 mmol) and dichloromethane (10 ml) was stirred for 10 min, then allyl alcohol (0.22 ml, 32.5 mmol) was added. After 30 min the mixture was filtered and the solvent removed *in vacuo*. The products was purified by chromatography (33 % EtOAc in heptane) to yield a clear oil which solidified on standing. Recrystallisation (EtOAc/heptane) gave an amorphous solid (1.00 g, 89 %);

mp 83-85 °C;

δ_{H} 3.32 (2H, d, IndCH₂, *J* 5.2 Hz), 4.56 (2H, bs, CH₂O), 4.74 (1H, dt, α -H, *J* 7.8, 7.8 Hz), 5.11 (2H, m, CH₂O), 5.20-5.32 (3H, m, NH, =CH₂), 5.82 (1H, m, CH), 6.96 (1H, d, arom, *J* 2.0 Hz), 7.08 (1H, t, arom, *J* 7.4 Hz), 7.18 (1H, d, arom, *J* 7.2 Hz), 7.34 (6H, m, arom), 7.52 (1H, d, arom, *J* 8.0 Hz), 8.04 (1H, bs, NH);

ν_{max} 3410, 3361, 3060, 1713, 1512, 1205, 743 cm⁻¹;

m/z 378 (MH⁺, 18 %), 130 (100 %); Anal. calc. for C₂₂H₂₂N₂O₄ C 69.82, H 5.86, N 7.40 % found C 69.88, H 5.86, N 7.44 %; $[\alpha]_{\text{D}}^{20}$ (c = 0.75, MeOH): +14.5 °.

Step 2.

The ester (17.25 g, 45.6 mmol) was dissolved in trifluoroacetic acid (100 ml) and stirred at RT for 3 h. The mixture was concentrated (~ 50 ml) *in vacuo*, then added dropwise to a well stirred mixture of NaHCO₃ (15 %, 1 l) and

5 dichloromethane (500 ml). After the addition the organics were washed with saturated NaHCO₃, brine and dried (MgSO₄). The product was purified by chromatography (20-50 % Et₂O in heptane) to yield a clear oil (8.90 g, 52 %);

δ_{H} 2.64 (2H, m, CH₂), 3.83-4.25 (3H, m, CH, CH₂O), 4.58 (0.5H, dd, a-H, *J* 1.9, 8.3 Hz), 4.68 (0.5H, m, α -H), 4.75 (0.5H, bs, 0.5 NH), 5.05-5.26 (4.5H, m, CH₂O, =CH₂, 0.5 NH), 5.50 (1H, m, CH=), 5.60 (1H, t, CH, *J* 6.4 Hz), 6.58 (1H, m, arom), 6.67 (1H, m, arom), 7.01 (2H, m, arom), 7.28-7.40 (4H, m, arom), 7.41 (1H, m, arom);

10

ν_{max} 3400, 1702, 1416, 747 cm⁻¹;

m/z 378 (MH⁺, 90 %), 130 (100 %);

Anal. calc. for C₂₂H₂₂N₂O₄ C 69.82, H 5.86, N 7.40 % found C 69.54, H 5.85, N 7.79 %;

15

$[\alpha]_{\text{D}}^{20}$ (c = 1.62, MeOH): -144.9 °.

Step 3. Intermediate 1.

Benzyl chloroformate (8.01 g, 47.0 mmol, 6.7 ml) was added to a stirred mixture of the amine (8.90 g, 23.5 mmol), Na₂CO₃·10 H₂O (13.43 g, 47.0 mmol), 1,4-dioxan (100 ml) and water (10 ml) at 0 °C. The resulting mixture was allowed to warm to RT and stirred for 16 h. The solvent was removed *in vacuo* and the product extracted into EtOAc, the organics were washed with water, 10 % HCl, brine and dried (MgSO₄). The product was purified by chromatography (25 % EtOAc in heptane) to give a clear oil (10.39 g, 86 %);

20

25

δ_{H} 2.55 (1H, m, CH₂), 2.65 (1H, d, CHH, *J* 13.2 Hz), 3.85 (1H, dd, OCHH, *J* 5.2, 13.2 Hz), 4.01 (1H, t, CH, *J* 7.0 Hz), 4.12 (1H, m, OCHH), 4.69 (1H, t, α -H, *J* 8.0 Hz), 4.80-5.24 (6H, m, 2x CH₂O, =CH₂), 5.50 (1H, m, CH=), 6.51 (1H, d, CH, *J* 6.0 Hz), 6.98 (1H, t, arom, *J* 7.4 Hz), 7.10 (1H, m, arom), 7.19 (1H, t, arom, *J* 7.6 Hz), 7.27-7.38 (10H, m, arom), 7.63 (1H, bs, arom);

30

$\nu_{\max}$ 3065, 3033, 1716, 1483, 1416, 1266, 1173, 753 cm^{-1} ;

m/z 513 (MH^+ , 100);

$[\alpha]_{\text{D}}^{20}$ ($c = 0.11$, MeOH): + 2.6 °.

5 Step 4.

LHMDS (7.81 ml, 7.81 mmol, 1M in THF) was added to a solution of Intermediate 1 (2.00 g, 3.91 mmol), DMPU (0.47 ml, 3.91 mmol) in THF (30 ml) at -78 °C under dry N_2 . After 2 h at this temperature, iodomethyl methyl ether (1.34 g, 7.81 mmol) was added and the mixture allowed to warm to RT overnight. The solvent was removed *in vacuo* and the product extracted into EtOAc, washed with 10 % HCl, brine and dried (MgSO_4). Purification was achieved by chromatography (15-20 EtOAc in heptane) to leave a clear oil (1.66 g, 76 %);

15 δ_{H} 2.52 (1H, dd, CHH, J 1.2, 13.2 Hz), 2.82 (1H, dd, CHH, J 8.0, 13.6 Hz), 3.26 (3H, s, OCH_3), 3.58 (1H, d, CHHO, J 7.6 Hz), 3.78 (1H, dddd, OCHH, J 1.6, 1.6, 5.6, 13.2 Hz), 3.90 (1H, t, CH, J 7.0 Hz), 4.06 (1H, bs, CHHO), 4.17 (1H, dd, OCHH, J 5.6, 13.2 Hz), 4.96-5.16 (6H, m, 2x CH_2O , $=\text{CH}_2$), 5.38 (1H, m, $=\text{CH}$), 6.44 (1H, d, CH, J 6.0 Hz), 6.99 (1H, m, arom), 7.08 (1H, d, arom, J 7.2 Hz), 7.19 (1H, t, arom, J 7.6 Hz), 7.25-7.34 (10H, m, arom), 7.59 (1H, d, arom, J 8.0 Hz);

20 $\nu_{\max}$ 1717, 1483, 1412, 1335, 1274, 751 cm^{-1} ;

m/z 557 (MH^+ , 100 %);

Anal. calc. for $\text{C}_{32}\text{H}_{32}\text{N}_2\text{O}_7$ C 69.05, H 5.80, N 5.03 % found C 68.82, H 5.52, N 4.88 %;

25 $[\alpha]_{\text{D}}^{20}$ ($c = 0.75$, MeOH): + 9.6 °.

Step 5.

TFA (2 ml) was added to a solution of the above oil (1.66 g, 3.07 mmol) in dichloromethane (10 ml) and the resulting solution stirred at RT for 24 h. The solvent was removed and the residue diluted with EtOAc, the organics were washed with saturated NaHCO_3 , brine and dried (MgSO_4). The product was

30

purified by chromatography (15 % EtOAc in heptane) to yield a clear oil (1.19 g, 72 %);

δ_{H} 3.32 (3H, s, OCH₃), 3.24 (1H, d, IndCHH, *J* 14.4 Hz), 3.60 (1H, d, IndCHH, *J* 14.4 Hz), 3.77 (1H, d, CHHO, *J* 9.2 Hz), 4.13 (1H, d, CHHO, *J* 9.2 Hz), 4.49 (1H, dd, OCHH, *J* 4.8, 12.8 Hz), 4.61 (1H, dd, OCHH, *J* 5.2, 12.8 Hz), 5.09 (2H, s, CH₂O), 5.11 (1H, d, =CHH, *J* 10.8 Hz), 5.28 (1H, d, =CHH, *J* 17.2 Hz), 5.41 (2H, dd, CH₂O, *J* 12.0, 14.8 Hz), 5.75 (2H, m, =CH, NH), 7.14 (1H, t, arom, *J* 8.0 Hz), 7.28-7.47 (13H, m, arom), 8.15 (1H, bd, arom, *J* 6.4 Hz);

ν_{max} 3418, 3352, 1736, 1501, 1456, 1399, 1250, 1087, 749 cm⁻¹;

m/z 557 (MH⁺, 100 %); [α]_D²⁰ (c = 0.67, MeOH): + 13.0 °.

Step 6.

Tetrakis(triphenylphosphine)palladium (0) (50 mg, 43 μ mol) was added to a solution of the alpha substituted amino ester (1.14 g, 2.11 mmol) in THF (10 ml), after 5 min morpholine (1.84 g, 21.1 mmol) was added and the mixture stirred at RT for 30 min. EtOAc was added and the organics washed with 10 % HCl, brine and dried (MgSO₄). After removal of the solvent *in vacuo* a clear glass was obtained (1.11 g, 100 %);

δ_{H} 3.33 (1H, d, IndCHH, *J* 14.7 Hz), 3.37 (3H, s, OCH₃), 3.60 (1H, d, IndCHH, *J* 14.4 Hz), 3.84 (1H, d, CHHO, *J* 9.3 Hz), 3.99 (1H, d, CHHO, *J* 8.8 Hz), 5.09 (2H, s, CH₂O), 5.40 (2H, s, CH₂O), 5.71 (1H, s, NH), 7.14 (1H, t, arom, *J* 7.6 Hz), 7.27-7.52 (13H, m, arom), 8.18 (1H, dd, arom, *J* 6.8, 6.8 Hz);

ν_{max} 3411, 1732, 1456, 1399, 1250, 1086, 748 cm⁻¹;

m/z (MH⁺, 100 %);

HRMS for C₂₉H₂₉N₂O₇ requires 517.1975 found 499.187 (MH-H₂O⁺).

Step 7.

A mixture of the acid (1.01 g, 2.02 mmol), HBTU (766 mg, 2.02 mmol), DIPEA (0.70 ml, 2.02 mmol) in DMF (10 ml) was stirred at RT for 10 min then (*S*)-methylbenzylamine (244 mg, 2.02 mmol) and DIPEA (0.70 ml, 2.02 mmol) added and the resulting solution stirred for 8 h. The solvent was removed and

the product extracted into EtOAc, washed with 10 % HCl, 10 % K₂CO₃, brine and dried (MgSO₄). Purification by chromatography gave a clear glass which was recrystallised (EtOAc/heptane) to give a clear glass (1.04 g, 78 %);

5 δ_{H} 1.37 (3H, d, CHCH₃, *J* 6.8 Hz), 3.35 (3H, s, OCH₃), 3.39 (1H, d, IndCHH, *J* 15.2 Hz), 3.47 (1H, d, CHHO, *J* 9.2 Hz), 3.66 (1H, d, IndCHH, *J* 14.4 Hz), 4.16 (1H, d, CHHO, *J* 8.0 Hz), 4.98 (1H, m, CHCH₃), 5.03 (2H, bs, CH₂O), 5.40 (2H, bs, CH₂O), 6.02 (1H, bs, NH), 7.14-7.53 (20 H, m, arom, NH), 8.14 (1H, bs, arom);

10 ν_{max} 3350, 1732, 1653, 1488, 1455, 1398, 1249, 1084, 748 cm⁻¹;
m/z 620 (MH⁺, 100 %); Anal. calc. for C₃₇H₃₇N₃O₆: C 71.71, H 6.02, N 6.78 %

Found: C 71.85, H 6.04, N 6.59 %; $[\alpha]_{\text{D}}^{20}$ (c = 0.53, MeOH): -21.7 °.

Step 8. Intermediate 2.

15 A mixture of the amide (980 mg, 1.63 mmol), 10 % palladium hydroxide on carbon and methanol (20 ml) were hydrogenated at 50 psi (345 kPa) at 30 °C. After 90 min the mixture was filtered through Kieselguhr and upon removal of the solvent *in vacuo* to give a pink coloured foam (630 mg, quant.);

20 δ_{H} (DMSO-d₆) 1.36 (3H, d, CHCH₃, *J* 6.8 Hz), 3.26 (3H, s, OCH₃), 3.37 (2H, s, IndCH₂), 3.66 (1H, d, CHHO, *J* 10.0 Hz), 4.17 (1H, d, CHHO, *J* 10.0 Hz), 4.90 (1H, dq, CHCH₃, *J* 6.8, 6.8 Hz), 7.00-7.38 (8H, m, arom), 7.70 (1H, d, arom, *J* 7.6 Hz), 8.17 (3H, bs, NH, NH₂), 8.94 (1H, d, arom, *J* 7.6 Hz), 11.17 (1H, d, NH, *J* 1.2 Hz);

25 ν_{max} 3419, 3213, 3057, 1667, 1494, 1458, 1106, 746 cm⁻¹;
HRMS for C₂₁H₂₆N₃O₂ requires 352.2025 found 352.2025 (MH⁺);
Anal. calc. for C₂₁H₂₅N₃O₂·0.4 H₂O: C 70.33, H 7.25, N 11.72 %
Found: C 70.32, H 6.94, N 11.66 %;
 $[\alpha]_{\text{D}}^{19}$ (c = 0.66, MeOH): -9.2 °.

Step 9.

Benzofuran-2-carboxaldehyde (83 mg, 568 μmol), Intermediate 2 (200 mg, 406 μmol) and sodium triacetoxyborohydride (172 mg, 811 μmol) were stirred in 1,2-dichloroethane (2 ml) at RT for 16 h. The mixture was diluted with CH_2Cl_2 , washed with 0.5 M NaOH, brine and dried (MgSO_4). The product was purified by chromatography (5-15 % EtOAc in heptane) to yield a clear glass (60 mg, 44 %);

mp 50-53 $^{\circ}\text{C}$;

δ_{H} 1.45 (3H, d, CHCH_3 , J 6.8 Hz), 2.15 (1H, bs, NH), 3.15 (2H, dd, Ind CH_2 , J 14.6, 51.6 Hz), 3.39 (3H, s, OCH_3), 3.69 (2H, dd, CH_2O), J 9.6, 44.0 Hz), 3.92 (2H, dd, CH_2N , J 13.8, 67.6 Hz), 5.02 (1H, dq, CHCH_3 , J 7.6, 7.6 Hz), 6.49 (1H, s, arom), 6.59 (1H, s, NH, J 2.0 Hz), 7.03-7.27 (10H, m, arom), 7.39 (1H, m, arom), 7.50 (1H, m, arom), 7.57 (1H, d, arom, J 8.6 Hz), 7.77 (1H, d, arom, J 8.4 Hz), 7.85 (1H, s, NH);

ν_{max} 3338, 2925, 1659, 1512, 1455, 1106, 742 cm^{-1} ;

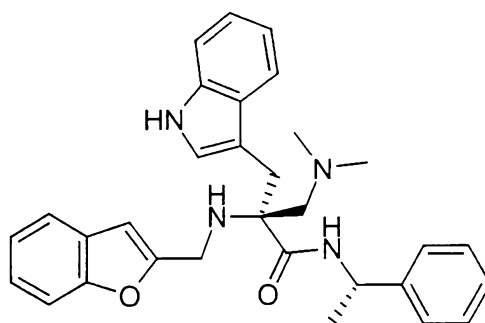
m/z 482 (MH^+ , 100 %);

Anal. calc. for $\text{C}_{30}\text{H}_{31}\text{N}_3\text{O}_3$ C 74.82, H 6.49, N 8.73 % found C 74.57, H 6.36, N 8.74 %; $[\alpha]_{\text{D}}^{19}$ ($c = 0.31$, MeOH): -37.7° .

EXAMPLE 2.

2-[(Benzofuran-2-ylmethyl)-amino]-2-dimethylaminomethyl-3-(1*H*-indol-3-yl)-*N*-(1-phenyl-ethyl)-propionamide (S,S)

5



Step 1.

10 Method as for Example 1, step 4 to give a clear oil (1.90g, 76 %);
 δ_{H} 2.23 (6H, s, 2x CH₃), 2.40 (1H, d, IndCHH, *J* 13.2 Hz), 2.66 (1H, d, CHHN, *J* 14.4 Hz); 3.00 (1H, dd, IndCHH, *J* 8.2, 13.4 Hz), 3.29 (1H, bs, CHHN), 3.69 (1H, dddd, OCHH, *J* 1.6, 2.9, 5.8, 13.3 Hz), 3.94 (1H, t, CH, *J* 7.0 Hz), 4.11 (1H, bs, CHHN), 4.93-5.33 (7H, m, 2x CH₂O, =CH, =CH₂), 6.40 (1H, d, CH, *J* 6.4 Hz), 6.99 (1H, t, arom, *J* 7.4 Hz), 7.06 (1H, d, arom, *J* 7.6 Hz), 7.18 (1H, t, arom, *J* 7.6 Hz), 7.26-7.37 (10H, m, arom), 7.58 (1H, bs, arom);
15 ν_{max} 2947, 1717, 1483, 1412, 1331, 1267, 1043, 1020, 750 cm⁻¹;
HRMS for C₃₃H₃₆N₃O₆ requires 570.2604 found 570.260₄ (MH⁺, 100 %);
[α]_D¹⁹ (c = 0.49, MeOH): -0.4 °.

20

Step 2.

Method as for Example 1, step 5 to give a straw coloured gum (3.46g, 59 %);
 δ_{H} 2.26 (6H, s, 2x CH₃), 2.83 (1H, d, CHHN, *J* 13.6 Hz), 3.23 (1H, d, IndCHH, *J* 14.4 Hz), 3.32 (1H, d, CHHN, *J* 13.6 Hz), 3.64 (1H, dd, IndCHH, *J* 14.4 Hz),
25 4.49 (1H, d, CHHO, *J* 13.2 Hz), 4.59 (1H, d, CHHO, *J* 6.0 Hz), 5.08 (2H, dd,

CH₂O, *J* 12.4, 27.6 Hz), 5.23 (1H, d, =CHH, *J* 10.4 Hz), 5.34 (1H, d, =CHH, *J* 14.4 Hz), 5.41 (2H, s, CH₂O), 5.85 (1H, m, =CH), 6.00 (1H, s, NH), 7.14 (2H, m, arom), 7.25-7.48 (12H, m, arom), 8.15 (1H, bd, arom, *J* 6.4 Hz);
 $\nu_{\max}$ 3418, 1736, 1456, 1248, 1084, 1037, 748 cm⁻¹;
5 m/z 570 (MH⁺, 100 %);
[α]_D¹⁹ (c = 0.27, MeOH): -12.6 °.

Step 3.

10 Method as for Example 1, step 6 to yield a straw coloured foam (690 mg, quant.);
 δ_{H} of little use due to impurities and zwitter-ion;
 $\nu_{\max}$ 3373, 1731, 1633, 1485, 1456, 1401, 1388, 1248 cm⁻¹;
HRMS for C₃₀H₃₂N₃O₆ requires 530.2291 found 530.229 (MH⁺).

15 Step 4.

Method as for Example 1, step 7 to afford white crystals (EtOAc/heptane) (150 mg, 34 %);
mp 102-107 °C;
 δ_{H} 1.38 (3H, d, CHCH₃, *J* 6.8 Hz), 2.14 (6H, s, 2x CH₃), 2.43 (1H, d, CHHN, *J* 14.4 Hz), 3.35 (1H, d, CHHN, *J* 14.4 Hz), 3.38 (1H, d, IndCHH, *J* 15.2 Hz), 3.63 (1H, d, IndCHH, *J* 15.2 Hz), 4.98 (1H, dq, CHCH₃, *J* 7.2, 7.2 Hz), 5.02 (2H, dd, CH₂O, *J* 12.4, 28.8 Hz), 5.40 (2H, s, CH₂O), 6.40 (1H, s, NH), 7.15-7.55 (19H, m, arom, NH), 8.16 (H, s, arom), 8.28 (1H, s, arom);
20 $\nu_{\max}$ 3373, 1732, 1666, 1486, 1250, 1077, 747 cm⁻¹;
25 m/z 633 (MH⁺, 100 %), 486 (37 %); Anal. calc. for C₃₈H₄₀N₄O₅ C 72.13, H 6.36, N 8.86 % found C 71.77, H 6.16, N 8.66 %; [α]_D²⁰ (c = 0.36, MeOH): -34.6 °.

Step 5. Intermediate 3

30 Method as for Example 1, step 8 to give a clear glass (342 mg, quant.);

δ_{H} 1.43 (3H, d, CHCH_3 , J 7.6 Hz), 2.32 (6H, s, $2\times\text{NCH}_3$) 2.46 (1H, d, CHHN , J 12.4 Hz), 2.83 (1H, d, IndCHH , J 14.4 Hz), 3.13 (1H, d, CHHN , J 12.4 Hz), 3.20 (1H, d, IndCHH , J 14.4 Hz), 5.00 (1H, dq, CHCH_3 , J 7.6, 7.6 Hz), 6.74 (1H, s, arom), 7.04-7.26 (7H, m, arom), 7.33 (1H, d, arom, J 7.6 Hz), 7.61 (1H, d, arom, J 7.8 Hz), 7.89 (1H, bs, NHInd), 8.14 (1H, d, NH);
5 $[\alpha]_{\text{D}}^{19}$ ($c = 0.56$, MeOH): 4.5° .

Step 6

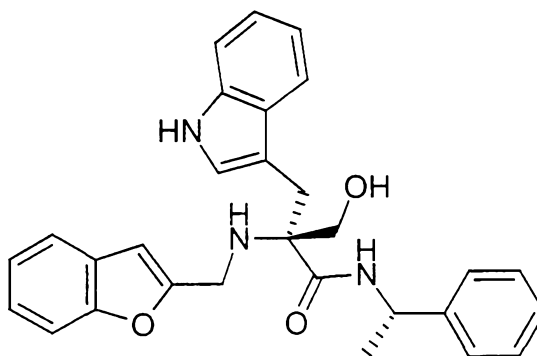
Method as for Example 1, step 9 to yield a yellow glass (30 mg, 19 %);

10 δ_{H} 1.44 (3H, d, CHCH_3 , J 7.0 Hz), 1.59 (1H, bs, NH), 2.34 (6H, s, $\text{N}(\text{CH}_3)_2$), 2.67 (1H, d, CHHN , J 13.4 Hz), 2.96 (1H, d, CHH , J 13.4 Hz), 3.06 (1H, d, IndCHH , J 15.2 Hz), 3.29 (1H, d, IndCHH , J 15.2 Hz), 3.99 (2H, dd, CH_2N , J 14.0, 24.4 Hz), 5.00 (1H, m, CHCH_3), 6.45 (1H, s, arom), 6.90 (1H, d, arom, J 7.4 Hz), 7.02 (2H, m, arom), 7.08-7.26 (7H, m, arom), 7.31 (1H, m, arom), 7.42 (1H, d, arom, J 8.0 Hz), 7.49 (1H, m, arom), 7.64 (1H, d, arom, J 8.0 Hz), 7.80 (1H, bs, NHInd), 7.99 (1H, d, NH, J 8.0 Hz);
15 ν_{max} 3312, 1655, 1454, 741 cm^{-1} ;
 m/z 495.3 (MH^+ , 100 %);

20

EXAMPLE 3.

2-[(Benzofuran-2-ylmethyl)-amino]-2-hydroxymethyl-3-(1*H*-indol-3-yl)-*N*-(1-phenyl-ethyl)-propionamide [S-(*R**,*R**)]



25

Step 1.

LHMDS (7.81 ml, 7.81 mmol, 1M in THF) was added to a solution of Intermediate 1 (2.00 g, 3.91 mmol), DMPU (0.47 ml, 3.91 mmol) in THF (30 ml) at -78 °C under dry N₂. After 2 h at this temperature, iodoethane (1.22 g, 7.81 mmol) was added and the mixture allowed to warm to RT overnight. The solvent was removed *in vacuo* and the product extracted into EtOAc, washed with 10 % HCl, brine and dried (MgSO₄). Purification was achieved by chromatography (15-20 EtOAc in heptane) to leave a clear oil (1.53 g, 61 %);

δ_{H} 0.04 (9H, s, Si(CH₃)₃), 0.85 (2H, t, CH₂Si, *J* 8.0 Hz), 2.52 (1H, d, IndCHH, *J* 13.2 Hz), 2.84 (1H, dd, IndCHH, *J* 7.6, 13.2 Hz), 3.47 (2H, t, OCH₂, *J* 8.0 Hz), 3.58 (1H, d, CHH, *J* 9.6 Hz), 3.78 (1H, dd, OCHH, *J* 5.6?, 13.2 Hz), 3.90 (1H, t, CH, *J* 7.0 Hz), 4.15 (2H, m, OCHH, CHH), 4.96-5.15 (6H, m, 2x CH₂O, CH₂=), 5.38 (1H, m, CH=), 6.44 (1H, d, CH, *J* 6.0 Hz), 7.00 (1H, t, arom, *J* 6.4 Hz), 7.07 (1H, d, arom, *J* 7.6 Hz), 7.19 (1H, t, arom, *J* 7.6 Hz), 7.26-7.34 (10H, m, arom), 7.60 (1H, d, arom, *J* 7.6 Hz);

ν_{max} 2952, 1720, 1483, 1412, 1275, 838, 751 cm⁻¹;

HRMS for C₃₆H₄₃NO₇Si requires 643.2840 found 643.2840;

$[\alpha]_{\text{D}}^{21}$ (c = 0.45, MeOH): + 13.9 °.

Step 2.

TFA (2 ml) was added to a solution of the above compound (1.66 g, 3.07 mmol) in dichloromethane (10 ml) and the resulting solution stirred at RT for 24 h. The solvent was removed and the residue diluted with EtOAc, the organics were washed with saturated NaHCO₃, brine and dried (MgSO₄). The product was purified by chromatography (15 % EtOAc in heptane) to yield a straw coloured oil (910 mg, 71 %);

δ_{H} 3.01 (1H, bs, OH), 3.24 (1H, d, IndCHH, *J* 14.7 Hz), 3.54 (1H, d, IndCHH, *J* 14.7 Hz), 4.01 (1H, m, CHHO), 4.35 (1H, m, CHHO), 4.56 (2H, m, CH₂O), 5.08 (1H, s, CH₂O), 5.22 (2H, m, CH₂=), 5.42 (1H, s, CH₂O), 5.73 (1H, s, NH), 5.79 (1H, m, CH=), 7.16 (1H, t, arom, *J* 7.2 Hz), 8.14 (1H, bs, arom);

ν_{max} 3413, 1732, 1456, 1399, 1251, 1085, 749 cm⁻¹;

HRMS for $C_{31}H_{31}N_2O_7$ requires 543.2130 found 543.2130;

$[\alpha]_D^{19}$ ($c = 0.2$, MeOH): + 2.4 °.

Step 3.

5 Imidazole (351 mg, 5.24 mmol) was added to a solution of triisopropylsilyl chloride (606 mg, 3.14 mmol) in DMF (5 ml), followed by the amino acid (1.42 g, 2.62 mmol). The resulting mixture warmed to 80 °C for 36 h, then the solvent was removed *in vacuo* and the residue diluted with EtOAc, washed with 10 % HCl, brine and dried ($MgSO_4$). The crude material was purified by
10 chromatography (10 % EtOAc in heptane) to yield a clear oil which solidified on standing. (1.36 g, 74%);
mp 72-74 °C (pentane/ Et_2O);
 δ_H 1.02 (18H, s, 6x CH_3), 1.26 (3H, m, 3xCH), 3.17 (1H, d, IndCHH, J 14.4 Hz), 3.67 (1H, s, IndCHH, J 14.4 Hz), 4.09 (1H, d, CHHO, J 9.2 Hz), 4.49 (3H, m, CH_2O , CHHO), 5.05 (2H, s, CH_2O), 5.20 (2H, m, $CH_2=$), 5.41 (2H, s CH_2O),
15 5.83 (2H, m, $CH=$, NH), 7.13 (1H, t, J 7.6 Hz), 7.26 -7.48 (13, m, arom), 8.17 (1H, bs, arom);
 ν_{max} 3422, 2944, 2866, 1741, 1248, 1086 cm^{-1} ;
Anal. calc. for $C_{40}H_{50}N_2O_7Si$ C 68.74, H 7.21, N 4.01 % found C 68.79, H 7.06,
20 N 4.08 %;
 m/z 699.2 (MH^+).

Step 4.

25 Tetrakis(triphenylphosphine)palladium (0) (50 mg, 43 μ mol) was added to a solution of the allyl ester (1.14 g, 2.11 mmol) in THF (10 ml); after 5 min morpholine (1.84 g, 21.1 mmol) was added and the mixture stirred at RT for 30 min. EtOAc was added and the organics washed with 10 % HCl, brine and dried ($MgSO_4$). After removal of the solvent *in vacuo* a clear gum is obtained (845 mg, 94 %);
30 δ_H 1.03 (21H, m, $Si(CHMe_2)_3$), 3.31 (1H, d, IndCHH, J 14.8 Hz), 3.63 (1H, d, IndCHH, J 14.8 Hz), 4.30 (2H, s, CH_2O), 5.05 (2H, s, CH_2O), 5.39 (2H, d,

CH₂O, *J* 2.8 Hz), 5.76 (1H, s, NH), 7.12 (1H, t, arom, *J* 7.6 Hz), 7.26-7.47 (13H, m, arom), 8.17 (1H, bs, arom);

$\nu_{\max}$ 3411, 2944, 2866, 1733, 1456, 1400, 1249, 1086, 746 cm⁻¹;

m/z 659.2 (MH⁺, 100 %);

5 Anal. calc. for C₃₇H₄₆N₃O₇Si C 67.45, H 7.04, N 4.25 % found C, 67.83, H 6.94, N 4.24 %; $[\alpha]_D^{21}$ (c = 0.40, MeOH): -1.0 °.

Step 5.

10 A mixture of the acid (1.01 g, 2.02 mmol), HBTU (766 mg, 2.02 mmol), DIPEA (0.70 ml, 2.02 mmol) in DMF (10 ml) was stirred at RT for 10 min then (*S*)-methylbenzylamine (244 mg, 2.02 mmol) and DIPEA (0.70 ml, 2.02 mmol) added and the resulting solution stirred for 8 h. The solvent was removed and the product extracted into EtOAc, washed with 10 % HCl, 10 % K₂CO₃, brine and dried (MgSO₄). Purification by chromatography gave a clear glass (533 mg, 15 92 %);

δ_H 1.05 (21H, bs, Si(CHMe₂)), 1.35 (3H, d, CHCH₃, *J* 7.2 Hz), 3.40 (1H, d, IndCHH, *J* 13.6 Hz), 3.78 (1H, d, IndCHH, *J* 13.6 Hz), 3.80 (1H, m, CHHO), 4.65 (1H, m, CHHO), 4.93 (1H, m, CHCH₃), 5.03 (2H, s, CH₂O), 5.40 (2H, d, CH₂O, *J* 5.2 Hz), 6.20 (1H, bs, NH), 7.17-7.46 (18H, m, arom), 8.18 (1H, bs, 20 arom);

$\nu_{\max}$ 3372, 2944, 1733, 1674, 1486, 1456, 1398, 1249, 1077 cm⁻¹;

m/z 620 (MH⁺, 100 %);

Anal. calc. for C₄₅H₅₅N₃O₆Si.0.5 H₂O C 70.10, H 7.32, N 5.45 %

found C 70.27, H 7.12, N 5.25 %;

25 $[\alpha]_D^{19}$ (c = 0.62, MeOH): -24.6 °.

Step 6. Intermediate 4.

A mixture of the amide (980 mg, 1.63 mmol), 10 % palladium hydroxide on carbon and methanol (20 ml) were hydrogenated at 50 psi (345 kPa) at 30 °C. 30 After 90 min the mixture was filtered through Kieselguhr and upon removal of the solvent *in vacuo* a white gum (325 mg, quant.) was obtained;

5 δ_{H} 1.10 (21H, m, Si(CHMe₂)₃), 1.40 (3H, s, CHCH₃, *J* 6.8 Hz), 1.61 (2H, bs, NH₂), 3.02 (1H, d, IndCHH, *J* 14.4 Hz), 3.32 (1H, d, IndCHH, *J* 14.4 Hz), 3.76 (1H, d, CHHO, *J* 8.8 Hz), 4.10 (1H, d, CHH, *J* 8.8 Hz), 5.01 (1H, m CHCH₃), 6.68 (1H, s, NH), 7.03 (3H, m, arom), 7.17-7.24 (4H, m, arom), 7.32 (1H, d, arom, *J* 7.6 Hz), 7.58 (1H, d, arom, *J* 8.0 Hz), 7.83 (2H, bs, arom, NH);
 ν_{max} 3304, 2942, 2866, 1651, 1512, 1104, 741 cm⁻¹;
m/z 494 (MH⁺);
Anal. calc. for C₂₉H₄₃N₃O₂Si.0.3 H₂O C 69.78, H 8.80, N 8.42 %
found C 69.84, H 8.49, N 8.11 %;
10 $[\alpha]_{\text{D}}^{19}$ (c = 0.49, MeOH): -37.7 °.

Step 7.

Method as for Example 2 step 6 to yield white fluffy crystals (103 mg, 41 %);
15 mp 110-111 °C;
 δ_{H} 1.17 (21H, m, Si(CHMe₂)₃), 1.36, (3H, d, CHCH₃, *J* 6.8 Hz), 2.23 (1H, bs, NH), 3.17 (2H, dd, IndCH₂, *J* 14.8, 29.2 Hz), 3.92 (1H, d, CHHN, *J* 14.0 Hz), 4.07 (1H, d, CHHN, *J* 14.0 Hz), 4.09 (1H, d, CHHO, *J* 10.0 Hz), 4.23 (1H, d, CHHO, *J* 10.0 Hz), 4.92 (1H, dt, CHCH₃, *J* 7.2, 7.2 Hz), 6.72 (1H, s, arom), 6.73
20 (1H, d, NH, *J* 2.4 Hz), 6.94 (2H, m, arom), 7.05 (1H, m, arom), 7.18 (7H, m, arom), 7.37 (1H, m, arom), 7.49 (1H, m, arom), 7.58 (2H, 2xd, arom, *J* 8.0 Hz), 7.69 (1H, s, NH);
 ν_{max} 3306, 2942, 2866, 1657, 1512, 1455, 1100, 741 cm⁻¹;
m/z 624.1 (MH⁺); Anal. calc. for C₃₈H₃₉N₃O₃Si C 73.15, H 7.92, N 6.73 %
found C 73.48, H 7.81, N 6.73 %;
25 $[\alpha]_{\text{D}}^{19}$ (c = 0.49, MeOH): -22.0 °.

Step 8.

A solution of the TIPS-protected Intermediate (103 mg, 1.65 μ mol) in THF (1 ml) was treated with TBAF (1M in THF, 331 μ mol, 0.33 ml) and the resulting solution left to stir for 1 h at RT. The solution was diluted with EtOAc, washed with brine and dried (MgSO_4). The product was purified by chromatography (20-40 % EtOAc in heptane) to yield a white foam (29 mg, 38 %); mp 53-56 $^{\circ}\text{C}$;

δ_{H} 1.52 (3H, d, CHCH_3 , J 7.2 Hz), 2.00 (1H, bs, NH), 2.98 (1H, d, IndCHH, J 14.6 Hz), 3.45 (1H, d, IndCHH, J 14.6 Hz), 3.75 (1H, d, CHHO, J 10.4 Hz), 3.81 (1H, bs, OH), 3.85 (2H, dd, CH_2N , J 14.2, 24.3 Hz), 4.07 (1H, d, CHHO, J 10.4 Hz), 5.12 (1H, dq, CHCH_3 , J 7.2, 7.2 Hz), 6.45 (1H, s, arom), 7.01 (1H, d, arom, J 2.0 Hz), 7.09-7.40 (9H, m, arom, NH), 7.51 (1H, m, arom), 7.77 (1H, d, arom, J 7.6 Hz), 8.00 (1H, d, arom, J 8.0 Hz), 8.13 (1H, s, NH);

ν_{max} 3312, 1646, 1514, 1455, 740 cm^{-1} ;

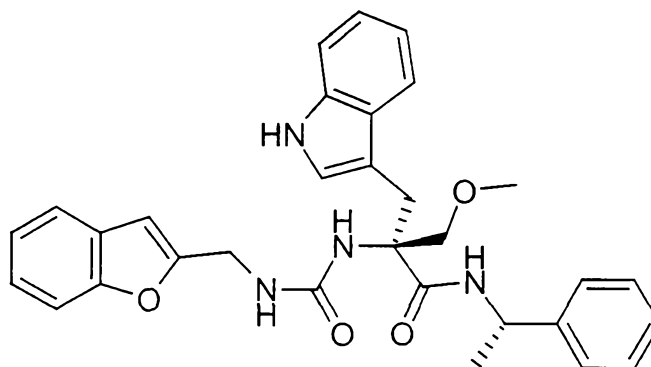
m/z 468.1 (MH^+ , 100 %);

Anal. calc. for $\text{C}_{29}\text{H}_{29}\text{N}_3\text{O}_3 \cdot 0.5 \text{H}_2\text{O}$ C : 73.09, H 6.34, N 8.82 %

found C 73.02, H 6.19, N 8.92 %.

EXAMPLE 4.

2-(3-Benzofuran-2-ylmethyl-ureido)-3-(1*H*-indol-3-yl)-2-methoxymethyl-N-(1-phenyl-ethyl)-propionamide [S-(R^* , R^*)]



A solution of Intermediate 2 (142 mg, 288 μmol) and (2-benzofuranyl)methylisocyanate (50 mg, 288 μmol) were stirred in THF (2 ml) under nitrogen for 2h. The solvent was removed *in vacuo* and the product purified by chromatography (20-25 % EtOAc in heptane) to give a white solid (109 mg, 72 %);

mp 78-82 °C;

δ_{H} (DMSO) 1.38 (3H, d, CH_3CH , J 6.8 Hz), 3.37 (3H, s, CH_3O), 3.42, 3.68 (2H, dd, IndCH_2 , J 14.8 Hz), 3.52, 4.27 (2H, dd, CH_2O , J 13.4 Hz), 4.38 (2H, 2, dd, CH_2N , J 6.0, 16.0 Hz), 4.93 (1H, dq, CHCH_3 , J 7.2 Hz), 5.26 (1H, t, NH, J 5.8 Hz), 5.68 (1H, s, NH), 6.67 (1H, d, NH, J 2.4), 7.06 (1H, dt, arom, J 1.2, 8.0 Hz), 7.15 (1H, dt, arom, J 1.0, 6.8 Hz), 6.52 (1H, s, arom), 7.20-7.32 (8H, m, arom), 7.41 (2H, m, arom), 7.51 (1H, m, arom), 7.60 (1H, d, arom, J 7.6 Hz), 7.65 (1H, d, arom, J 7.6 Hz), 10.80 (1H, bs, NH);

ν_{max} 3327, 1644, 1557, 1455, 1253, 1106, 741 cm^{-1} ;

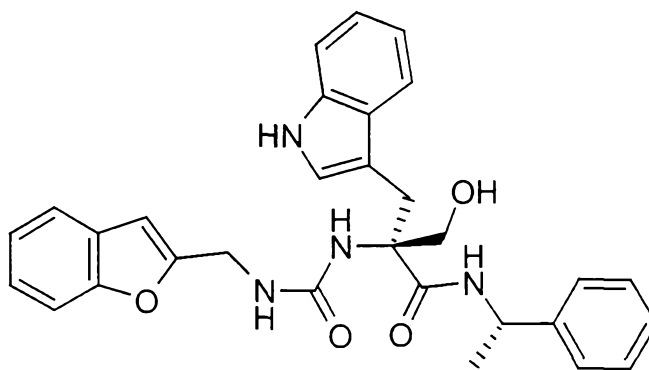
Anal. calc. for $\text{C}_{31}\text{H}_{32}\text{N}_4\text{O}_4 \cdot 0.2 \text{ C}_7\text{H}_{16}$: C 71.45, H 6.51, N 10.29 %

found C 71.34, H 6.38, N 10.02 %;

$[\alpha]_{\text{D}}^{19}$ (c 0.34, MeOH): -19.4 °.

EXAMPLE 5

2-(3-Benzofuran-2-ylmethyl-ureido)-2-hydroxymethyl-3-(1*H*-indol-3-yl)-N-(1-phenyl-ethyl)-propionamide [S-(R*,R*)]



Step 1.

Method as for Example 4 to give a clear glass (110 mg, 57 %);

δ_{H} 1.07 (21H, m, 18xCH₃), 1.21 (3H, d, CH₃CH, *J* 7.2 Hz), 3.42 (1H, d, IndCHH, *J* 14.8 Hz), 3.78 (1H, d, CHHO, *J* 10.0 Hz), 4.03 (1H, d, IndCHH, *J* 14.8 Hz), 4.12 (1H, m, CHHN, 4.30 (1H, dd, CHHN, *J* 6.0, 15.6 Hz), 4.69 (1H, dq, CHCH₃, *J* 7.2 Hz), 4.89 (1H, d, CHHO, *J* 9.6 Hz), 5.73 (1H, t, NH, *J* 5.6 Hz), 6.10 (1H, d, NH, *J* 2.4 Hz), 7.05-7.25 (9H, m, arom), 7.33 (1H, m, arom), 7.43 (1H, m, arom), 7.62 (1H, d, arom, *J* 8.0 Hz), 7.91 (1H, d, arom, *J* 8.0 Hz) IndNH ?;

ν_{max} 3337, 1634, 1548, 1495, 1455, 1060, 741 cm⁻¹;

HRMS for C₃₉H₅₁N₄O₄Si 667.368 found 667.3680 (MH⁺);

$[\alpha]_{\text{D}}^{19}$ (c 0.70, MeOH): -18.9 °.

Step 2.

A solution of the TIPS-protected alcohol (110 mg, 165 μ mol) in THF (1 ml) was treated with TBAF (0.33 ml, 330 μ mol, 1M/THF) and the solution stirred at RT for 10 min. The mixture was diluted with EtOAc, washed with 10 % HCl, brine and dried (MgSO₄). The product was purified by chromatography (20-70% EtOAc in heptane) to yield a clear glass (20 mg, 24 %);

mp 82-82 °C;

δ_{H} (DMSO) 1.27 (3H, d, CH₃CH, *J* 6.8 Hz), 3.27 (2H, dd, IndCH₂, *J* 14.8, 38.0 Hz), 3.79 (1H, dd, CHHO, *J* 5.8, 12.0 Hz), 4.07 (1H, dd, CHHO, *J* 7.0, 11.6 Hz), 4.29 (1H, dd, CHHN, *J* 5.6, 16.0 Hz), 4.33 (1H, dd, CHHN, *J* 5.6, 16.4 Hz), 4.91 (1H, dq, CHCH₃, *J* 6.8, 6.8 Hz), 4.93 (1H, bs, OH), 5.95 (1H, t, NHCH₂, *J* 5.4 Hz), 6.02 (1H, s, NH), 6.43 (1H, s, arom), 6.68 (1H, d, NH, *J* 6.0 Hz), 7.04 (1H, m, arom), 7.09-7.27 (8H, m, arom), 7.35 (1H, d, arom, *J* 8.0 Hz), 7.47 (2H, m, arom), 7.54 (1H, s, arom), 8.01 (1H, d, NH, *J* 7.6 Hz) IndH ?;

ν_{max} 3346, 1644, 1557, 1455, 1253, 742 cm⁻¹;

m/z 448 (M⁺-61, 100 %), 101 (16 %);

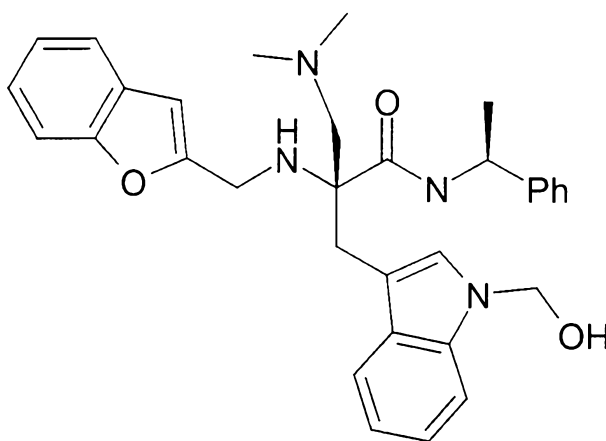
Anal. calc. for C₃₀H₃₀N₄O₄.0.5 EtOAc : C 69.30, H 6.18, N 10.10 %

found C 69.18, H 6.03, N 10.29 %;

$[\alpha]_D^{19}$ (c 0.46, MeOH): -15.6 °.

EXAMPLE 6

(R)-C-[(Benzofuran-2-ylmethyl)-amino]-dimethylamino-C-(1-hydroxymethyl-
1*H*-indol-3-ylmethyl)-*N*-((*S*)-1-phenyl-ethyl)-propionamide

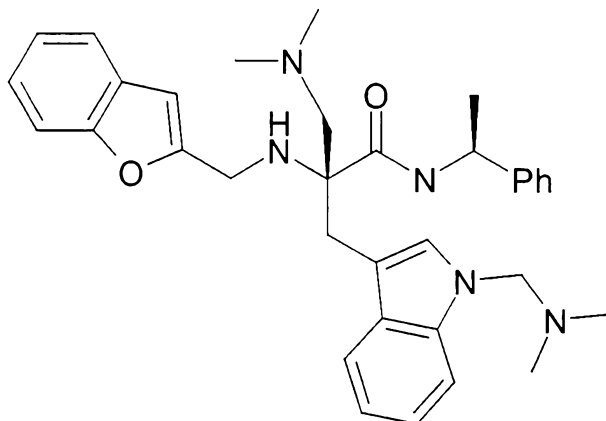


Potassium hexamethyldisilazide (4.4 ml, 2.02 mmol, 0.5 M in toluene) was added to a solution of Example 2 (1.0 g, 2.02 mmol) in THF (15 ml) at -78 °C under N₂. Stirring was continued at this temperature for 10 min then a freshly prepared solution of formaldehyde (approximately 250 mg in 15 ml) was added and stirring continued at -78 °C for 3 h. The mixture was diluted with EtOAc, washed with saturated NaHCO₃, brine and dried (MgSO₄). The product was purified by chromatography (0-1 % MeOH in CH₂Cl₂) to yield a yellow foam (182 mg, 17 %).

MS m/z 525.6 (MH⁺, BP); IR ν 3353, 1646, 1454, 1040, 741 cm⁻¹; ¹H NMR δ 1.42 (3H, d, CHCH₃, J 7.2 Hz), 2.33 (6H, s, N(CH₃)₂), 2.55 (1H, bs, NH), 2.65 (1H, d, CHHN, J 13.6 Hz), 2.97 (2H, 2xd, CHHN, CHHInd, J 15.6 Hz), 3.25 (1H, d, CHHInd, J 15.6 Hz), 3.94 (2H, dd, CH₂N, J 13.6, 19.6 Hz), 4.98 (1H, dq, CHCH₃, J 7.6 Hz), 5.26 (2H, bs, CH₂O), 6.44 (1H, s, ar), 6.84 (1H, s, ar), 7.05 (2H, m, ar), 7.12-7.26 (7H, m, ar), 7.41 (2H, m, ar), 7.51 (1H, d, ar, J 5.6 Hz), 7.60 (1H, d, ar, J 8.0 Hz), 8.00 (1H, d, NH, J 7.2).

EXAMPLE 7

(R)-C-[(Benzofuran-2-ylmethyl)-amino]-dimethylamino-C-(1-dimethylaminomethyl-1*H*-indol-3-ylmethyl)-*N*-((S)-1-phenyl-ethyl)-propionamide



Lithium hexamethyldisilazide (1.1 ml, 1.01 mmol, 1 M in THF) was added to a solution of Example 2 (500 mg, 1.01 mmol) in THF (5 ml) at -78°C under N_2 . Stirring was continued at this temperature for 15 min, then Eschenmoser's salt (37 mg, 2.02 mmol) was added and stirring continued at -78°C for 1 h and the mixture allowed to warm to RT overnight. The mixture was diluted with EtOAc, washed with saturated NaHCO_3 , brine and dried (MgSO_4). The product was purified by chromatography (0-2 % MeOH in CH_2Cl_2) to yield a yellow gum (68 mg, 12 %).

MS m/z 552 (MH^+ , BP); IR ν 3366, 1661, 1494, 1454, 740 cm^{-1} ; ^1H NMR δ 1.42 (3H, d, CHCH_3 , J 7.2 Hz), 2.15 33 (6H, s, $\text{N}(\text{CH}_3)_2$), 2.33 (6H, s, $\text{N}(\text{CH}_3)_2$), 2.66 (1H, d, CHHN , J 13.6 Hz), 2.95 (1H, d, CHHN , J 13.6 Hz), 3.03 (1H, d, CHHInd , J 15.6 Hz), 3.30 (1H, d, CHHInd , J 15.2 Hz), 3.95 (2H, dd, CH_2N , J 14.0, 25.2 Hz), 4.50 (2H, s, NCH_2N), 4.98 (1H, dq, CHCH_3 , J 7.2 Hz), 6.43 (1H, s, ar), 6.94 (1H, s, ar), 7.01 (2H, m, ar), 7.08 (1H, t, ar, J 7.6 Hz), 7.16-7.26 (6H, m, ar), 7.35 (1H, d, ar, J 8.4 Hz), 7.38 (1H, d, ar, J 8.0 Hz), 7.48 (1H, d, ar, 8.0 Hz), 7.61 (1H, d, ar, J 7.6 Hz), 8.00 (1H, d, NH , J 7.6 Hz).

EXAMPLE 8

Alternative synthesis of 2-[(Benzofuran-2-ylmethyl)-amino]-2-dimethylaminomethyl-3-(1*H*-indol-3-yl)-*N*-(1-phenyl-ethyl)-propionamide (S,S)

5 Example 8.A: synthesis of Intermediate 5

1) Preparation of (S)-2-(benzylidene-amino)-3-(1*H*-indol-3-yl)-propionic acid methyl ester (Schiff's base).

10 245 g (S)-Tryptophan methyl ester and 118 g benzaldehyde are dissolved in 1837 ml dichloromethane and mixed with 245 g dry magnesium sulphate. The reaction mixture is stirred for 4 hours at ambient temperature. After filtering off the magnesium sulphate, the solvent is distilled off on a rotary evaporator. The very viscous mass remaining behind (364 g) can be used directly in the next step.

15

2) Preparation of racemic α -dimethylaminomethyltryptophan methyl ester

117.9 g Diisopropylamine are dissolved in 1170 ml anhydrous tetrahydrofuran in a reaction flask gassed with nitrogen with the exclusion of moisture. 728 ml 20 of a 1.6 M butyl lithium/hexane solution are added dropwise at -30°C within the course of about 1 hour. After stirring for about 15 minutes, 340 g of the Schiff's base prepared in Example 1, dissolved in 1020 ml anhydrous tetrahydrofuran, are added dropwise at -30°C over the course of 1 hour. After a further 15 minutes, 205 g 1-dimethylaminomethyl-benzotriazole, dissolved in 1025 ml anhydrous 25 tetrahydrofuran are added dropwise at -30°C over the course of 1 hour.

Subsequently, the reaction mixture is allowed to warm up slowly to ambient temperature. During the following approximately 16 hours stirring at ambient temperature, a thick slurry results.

30 With ice cooling, a solution of 386 ml 37% hydrochloric acid in 1544 ml ice water is allowed to run in in such a manner that the temperature in the reaction vessel does not exceed 25°C. The separating tetrahydrofuran phase is separated

off and the aqueous phase extracted five times with 500 ml amounts of ethyl acetate.

The aqueous phase is covered with 500 ml ethyl acetate and mixed portionwise, while stirring, with 247 g sodium carbonate. The organic phase is separated off
5 and the aqueous phase again extracted twice with, in each case, 500 ml ethyl acetate. The combined organic phases are washed twice with, in each case, 300 ml of a saturated aqueous solution of sodium chloride.

After drying over anhydrous sodium sulphate, the solution was filtered clear and evaporated in a vacuum.

10 There remain 242 g (79.1% of theory) of a brown, viscous residue. According to HPLC analysis, this crude product contains about 62% of the desired product. For further purification, the crude product is recrystallised from diethyl ether to give 94 g (30.7% of theory) racemic α -dimethylaminomethyltryptophan methyl ester; m.p. 105°C; HPLC purity 96.2 rel.%.

15 3) Separation of racemic α -dimethylaminomethyltryptophan methyl ester into the two enantiomeric compounds.

15 g of the racemic α -dimethylaminomethyltryptophan methyl ester obtained in
20 Example 2 are separated on a preparative HPLC apparatus on the chiral phase Chiracel OJ 20 μ m into 6.2 g of the (R)-enantiomer and 6.45 g of the (S)-enantiomer.

Example 8.B: synthesis of 2-[(Benzofuran-2-ylmethyl)-amino]-2-
25 dimethylaminomethyl-3-(1*H*-indol-3-yl)-*N*-(1-phenyl-ethyl)-propionamide (S,S)

Step 1: (S)-2-[(Benzofuran-2-ylmethyl)-amino]-2-dimethylaminomethyl-3-(1*H*-indol-3-yl)-propionic acid methyl ester

30 (S)-2-Amino-2-dimethylaminomethyl-3-(1*H*-indol-3-yl)-propionic acid methyl ester (5.69 g, 20.7 mmol), benzofuran-2-carbaldehyde (4.77 g, 32.7 mmol) and sodium triacetoxyborohydride (9.24 g, 43.6 mmol) were stirred in 1,2-

dichloroethane (100 ml) for 8 h at RT. The mixture was diluted with CH₂Cl₂, washed with NaOH (0.5 M), brine and dried (MgSO₄). After removal of the solvent the material was washed with heptane to leave fawn coloured solid (6.45 g, 77 %).

5 δ_{H} 2.27 (6H, s, N(CH₃)₂), 2.74 (2H, dd, CH₂N, *J* 13.6, 20.4 Hz), 3.27 (2H, s, CH₂Ind), 3.63 (3H, s, OMe), 4.08 (2H, dd, CH₂N, *J* 14.0, 38.8 Hz), 6.57 (1H, s, arom), 7.09-7.34 (6H, m, arom), 7.42 (1H, m, arom), 7.51 (1H, m, arom), 7.63 (1H, d, arom, *J* 8.0 Hz), 8.03 (1H, s, NH).

ν_{max} 1718, 142, 1174, 742 cm⁻¹;

10 *m/z* 406 (MH⁺, 100);

Step 2: (S)-2-[(Benzofuran-2-ylmethyl)-amino]-2-dimethylaminomethyl-3-(1*H*-indol-3-yl)-propionic acid *bis*-hydrochloride

15 (S)-2-[(Benzofuran-2-ylmethyl)-amino]-2-dimethylaminomethyl-3-(1*H*-indol-3-yl)-propionic acid methyl ester (6.35 g, 15.7 mmol) and sodium hydroxide (608 mg, 15.7 mmol) in 1,4-dioxan/water were heated under reflux conditions for 4 days. The solvent was removed and the mixture acidified with 10 % HCl, the solvent was again removed to leave a brown foam (~10 g, > quant.)

20 δ_{H} (DMSO-*d*₆) 2.18 (6H, s, N(CH₃)₂), 2.48 (2H, s, CH₂N), *J* 13.6, 20.4 Hz), 3.01 (2H, s, CH₂Ind), 3.88 (2H, dd, CH₂N), 6.57 (1H, d, arom, *J* 0.4 Hz), 6.89 (1H, m, arom), 6.96 (1H, m, arom), 7.14-7.28 (4H, m, arom), 7.45 (1H, m, arom), 7.52 (1H, m, arom), 7.57 (1H, d, arom, *J* 8.0 Hz), 10.69 (1H, s, NH).

25 Step 3: (S)-2-[(Benzofuran-2-ylmethyl)-amino]-2-dimethylaminomethyl-3-(1*H*-indol-3-yl)-*N*-((S)-1-phenyl-ethyl)-propionamide

30 (S)-2-[(Benzofuran-2-ylmethyl)-amino]-2-dimethylaminomethyl-3-(1*H*-indol-3-yl)-propionic acid *bis*-hydrochloride (6.13 g, 15.7 mmol assumed), HBTU (5.95 g, 15.7 mmol), (S)- α -methylbenzylamine (2.85 g, 23.6 mmol) and DIPEA (10.13 g, 78.5 mmol) were stirred at RT in DMF (75 ml) for 6 h. The solvent was removed and the material taken up in EtOAc, washed with 15 % K₂CO₃, brine and dried (MgSO₄). The crude material was purified by chromatography (20-50 % EtOAc in C₇) to leave a yellow solid which was washed with heptane

to leave a yellow powder. Further material was obtained by re-purifying the impure fractions by RP-HPLC (0-100 % MeOH in H₂O) to leave a yellow-white solid.

Total yield (1.91 g , 25 %).

5 Data as example 2.

EXAMPLE 9

Binding to NK₁ receptors

10

The compounds of the present invention are highly selective and competitive antagonists of the NK₁ receptor. They have been evaluated in an NK₁ receptor binding assay which is described below.

Methods

15

Human lymphoma IM9 cells are grown in RPMI 1640 culture medium supplemented with 10% foetal calf serum and 2mM glutamine and maintained under an atmosphere of 5% CO₂. Cells are passaged every 3-4 days by reseeding to a concentration of 4-8 million/40 ml per 175 cm² flask. Cells are harvested for experiments by centrifugation at 1000 g for 3 min. Pelleted cells are washed once

20

by resuspension into assay buffer (50 mM Tris HCl pH 7.4, 3 mM MnCl₂, 0.02 % BSA, 40 mg/mL bacitracin, 2 mg/mL chymostatin, 2 mM phosphoramidon, 4 mg/mL leupeptin) and repeating the centrifugation step before resuspending at a concentration of 2.5 x 10⁶ cells/mL assay buffer. Cells (200 ml) are incubated with [¹²⁵I]Bolton-Hunter Substance P (0.05-0.1 nM) in the presence and absence of

25

varying concentrations of test compounds for 50 min at 21°C. Non-specific binding (10% of the total binding observed under these conditions) is defined by 1 mM [Sar⁹,Met(0₂)¹¹]substance P. Reactions are terminated by rapid filtration under vacuum onto GF/C filters presoaked in 0.2 % PEI for 1-2 h, using a Brandel cell harvester. Filters are washed with 6 x 1 ml ice-cold Tris HCl (50 mM, pH 7.4) and radioactivity bound determined using a gamma counter. Results are analysed using

30

iterative curve fitting procedures in RS1 or Graphpad Inplot.

Results

Table I: In Vitro Human NK₁ Receptor Binding Assay

Example No.	NK ₁ binding IC ₅₀ (nM)
1	6.56
2	0.89
3	1.41
4	4.93
5	1.07
6	28.8
7	6.96

5 Because the compounds are potent ligands to the NK₁ receptor, they are effective
at displacing substance P at that position, and therefore are useful for treating
biological conditions otherwise mediated by substance P. Accordingly,
compounds capable of antagonising the effects of substance P at NK₁ receptors
will be useful in treating or preventing a variety of CNS disorders including pain
10 (inflammatory, surgical and neuropathic), anxiety, panic, depression, major
depression with anxiety, schizophrenia, neuralgia, stress, sexual dysfunction,
bipolar disorders, movement disorders, cognitive disorders, and addiction
disorders; inflammatory diseases such as arthritis, asthma, bronchitis, COPD and
psoriasis; gastrointestinal disorders including colitis, Crohn's disease, irritable
15 bowel syndrome and satiety; allergic responses such as eczema and rhinitis;
vascular disorders such as angina and migraine; neuropathological disorders
including scleroderma and emesis. The compounds of the invention, NK₁
receptor antagonists, are also useful as anti-angiogenic agents, for the treatment
of conditions associated with aberrant neovascularization such as rheumatoid
20 arthritis, atherosclerosis and tumour 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.

EXAMPLE 10.

Carrageenan-induced hypersensitivity model in the guinea-pig

5 Methods

Male Dunkin Hartley guinea-pigs (200-250 g) are housed in groups of 4 under a 12 hour light/dark cycle (lights on at 7:00) with food and water ad libitum.

Carrageenan-induced hypersensitivity:

10 Guinea-pigs are administered carrageenan (100 μ l of 20 mg/ml) by intraplantar injection into the right hind paw. They are tested for hypersensitivity in the weight-bearing test, using an "Incapacitance tester" (Linton Instruments, U.K.): the animal is placed in the apparatus and the weight load exerted by the hind paws is noted. The measurements are taken three times at one-minute intervals and the average is calculated. The duration of the measurement is adjusted to 4 s
15 for the guinea-pig. The animals are tested before (baseline) and at different intervals after the injection of carrageenan. The compound of Example 2 was administered subcutaneously 1 h before carrageenan in a dosing volume of 1 ml/kg, in PEG 200 vehicle. Hypersensitivity was assessed using the weight bearing test.

20 The difference in weight-bearing between the ipsilateral and contralateral paws is calculated and is then subjected to a one-way-ANOVA followed by Dunnett's t-test, for each time-point studied (*P<0.05, **P<0.01, significantly different from vehicle treated animals).

25 Results are expressed as mean difference in weight load between ipsilateral and contralateral paws $\pm$ SEM (g) (n per group = 6-19).

Results

The intraplantar injection of carrageenan (100 μ l of 20 mg/ml) into the hindpaw induces hypersensitivity in the guinea-pig, as assessed by the weight bearing test.

30 The subcutaneous injection of the compound of Example 2 (0.1 and 1 mg/kg, in PEG 200 vehicle) 1 h before carrageenan dose-dependently prevents the development of hypersensitivity 3 h after carrageenan (Figure. 1).

As noted above, the compounds of Formula I will be best utilized in the form of pharmaceutical formulations. The following examples further illustrate specific formulations that are provided by the invention.

5

EXAMPLE 11
Tablet Formulation

<u>Ingredient</u>	<u>Amount</u>
2-[(Benzofuran-2-ylmethyl)-amino]-2-dimethylaminomethyl-3-(1 <i>H</i> -indol-3-yl)-N-(1-phenyl-ethyl)-propionamide (S,S)	50 mg
potato starch	100 mg
talc	50 mg
magnesium carbonate	20 mg
dextrose	20 mg
	240 mg

10

The above ingredients are blended to uniformity and pressed into a tablet. Such tablets are administered to human subjects from one to four times a day for the treatment of conditions associated with aberrant neovascularization such as rheumatoid arthritis, atherosclerosis and tumour cell growth.

EXAMPLE 12

Parenteral injection

<u>Ingredient</u>	<u>Amount</u>
2-(3-Benzofuran-2-ylmethyl-ureido)-3-(1 <i>H</i> -indol-3-yl)-2-methoxymethyl-N-(1-phenyl-ethyl)-propionamide [S-(R*,R*)]	20 mg
Citric acid monohydrate	0.75 mg
Sodium phosphate	4.5 mg
Sodium chloride	9 mg
Water for injection	to 10 ml

5

The sodium phosphate, citric acid monohydrate and sodium chloride are dissolved in a portion of the water. The active ingredient is dissolved in the solution and made up to volume.

10

EXAMPLE 13

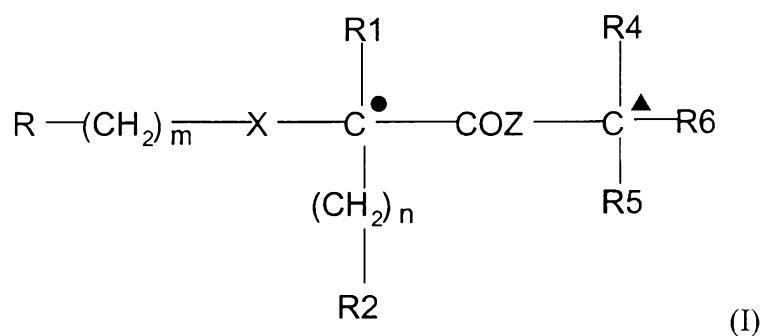
Parenteral injection

<u>Ingredient</u>	<u>Amount</u>
2-[(Benzofuran-2-ylmethyl)-amino]-2-dimethylaminomethyl-3-(1 <i>H</i> -indol-3-yl)-N-(1-phenyl-ethyl)-propionamide (S,S)	20 mg
Citric acid monohydrate	0.75 mg
Sodium phosphate	4.5 mg
Sodium chloride	9 mg
Water for injection	to 10 ml

The sodium phosphate, citric acid monohydrate and sodium chloride are dissolved in a portion of the water. The active ingredient is dissolved in the solution and made up to volume.

We claim:

1. A compound of Formula I



or a pharmaceutically acceptable salt thereof wherein:

● and ▲ indicate all stereoisomers;

R is phenyl,

pyridyl,

thienyl,

furyl,

quinolyl

isoquinolyl

naphthyl,

benzofuryl,

benzo[1,3]dioxole

benzothienyl or,

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

alkyl,

hydroxy,

alkoxy,

halogen,

CF₃ or

OCF₃;

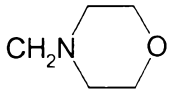
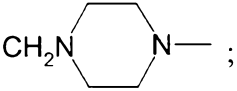
m is an integer from 1 to 3;

X is NR₈ or NHCONH where R₈ is H or alkyl of 1 to 3 carbon atoms;

R₁ is (CH₂)_pY where p is 0 to 3 and Y is OH, OCH₃, F, CF₃, CO₂H, N(CH₃)₂, NHCH₃, NH₂, COCF₃, COCH₃ or NO₂;

5 n is an integer from 1 to 2;

R₂ is naphthyl or indolyl unsubstituted or N-substituted with hydroxy, alkyl,

formyl, CH₂OH, CH₂N(CH₃)₂,  or  ;

Z is NR₃ or O, where R₃ is H or C₁-C₄ alkyl;

10 R₄ and R₅ are each independently hydrogen, or (CH₂)_pR₇ where:

p is an integer of 1 to 3, and

R₇ is H, CH₃, CN, OH, OCH₃, CO₂CH₃, NH₂, NHCH₃, or N(CH₃)₂;

R₆ is phenyl,

pyridyl,

15 thienyl,

furyl,

pyrrolyl,

pyrazolyl,

imidazolyl,

20 quinolyl,

isoquinolyl,

naphthyl,

indolyl,

benzofuryl,

25 benzothiophenyl,

benzimidazolyl, or

benzoxazolyl, wherein each of the foregoing is unsubstituted, mono-, di- or trisubstituted by alkyl,

hydroxy,

30 alkoxy,

halogen,

CF₃,

NO₂,

N(CH₃)₂,

5

OCF₃,

SONH₂,

NH₂,

CONH₂,

CO₂CH₃ or

10

CO₂H,

or R₆ is:

straight alkyl of from 1 to 3 carbons,

branched alkyl of from 3 to 8 carbons,

cycloalkyl of from 5 to 8 carbons or

15

heterocycloalkyl,

each of which can be substituted with up to one or two substituents

selected from

OH,

CO₂H,

20

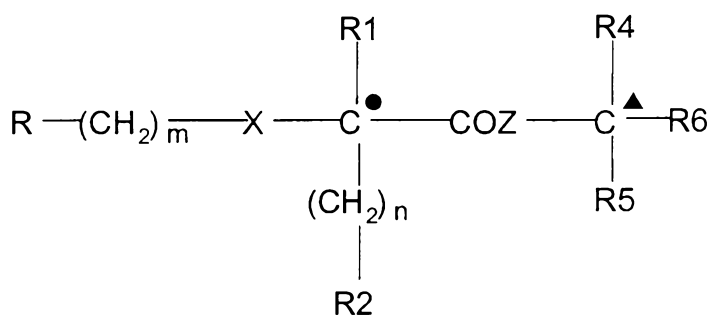
N(CH₃)₂,

NHCH₃ and

CH₃; or

R₅ and R₆, when joined by a bond, form a ring.

2. A compound of Formula I wherein



● is R or S, and ▲ is R or S;

5

-R is phenyl,

pyridyl,

thienyl,

furyl,

quinolyl

10

isoquinolyl

benzofuryl,

benzo[1,3]dioxole

benzothienyl or

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

15

alkyl,

hydroxy,

alkoxy,

halogen,

CF₃ or

20

OCF₃;

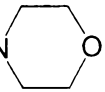
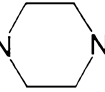
m is an integer from 1 to 3;

X is NR₈ or NHCONH where R₈ is H or alkyl of 1 to 3 carbon atoms;

R₁ is (CH₂)_pY where p is 0 to 3 and Y is OH, F, CF₃, OCH₃, CO₂H, N(CH₃)₂, NHCH₃, NH₂, COCF₃, COCH₃ or NO₂;

n is an integer from 1 to 2;

R₂ is naphthyl or indolyl unsubstituted or N-substituted with hydroxy, alkyl,

formyl, CH₂OH, $\text{CH}_2\text{N}(\text{CH}_3)_2$, CH_2N  or CH_2N  N— ;

5 Z is NR₃ or O, where R₃ is H or CH₃;

R₄ and R₅ are each independently hydrogen, CH₃ or CH₂OH;

R₆ is phenyl,

pyridyl,

thienyl,

10 furyl,

pyrrolyl,

cyclohexyl or

benzimidazolyl,

wherein each of the foregoing is unsubstituted, mono-, di- or

15 trisubstituted by

alkyl,

hydroxy,

alkoxy,

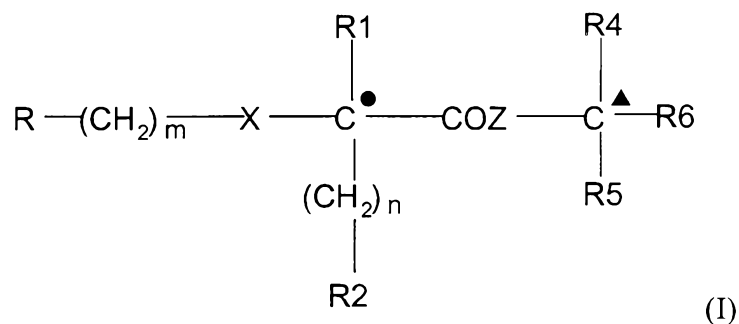
halogen,

20 CF₃,

NO₂, or

N(CH₃)₂.

3. A compound of Formula I wherein



● is R or S, and ▲ is R or S;

R is phenyl,

pyridyl,

thienyl,

furyl,

benzofuryl,

benzo[1,3]dioxole

benzothienyl or

benzimidazolyl,

each unsubstituted, mono-, di- or trisubstituted by

alkyl,

hydroxy,

alkoxy,

halogen,

CF₃ or

OCF₃;

m is an integer from 1 to 3;

X is NR₈ or NHCONH where R₈ is H or alkyl of 1 to 3 carbon atoms;

R₁ is (CH₂)_pY where p is 0 to 3 and Y is OH, OCH₃, F, CF₃, CO₂H, N(CH₃)₂, NHCH₃, NH₂, COCF₃, COCH₃ or NO₂;

n is an integer from 1 to 2;

R₂ is indolyl unsubstituted or N-substituted with alkyl or formyl;

Z is NR₃ or O, where R₃ is H or CH₃;

R₄ and R₅ are each independently hydrogen, CH₃, or CH₂OH;

R₆ is phenyl,

pyridyl,

5 thienyl,

furyl,

pyrrolyl,

cyclohexyl or

benzimidazolyl,

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

alkyl,

hydroxy,

alkoxy,

halogen,

15 CF₃,

NO₂ or

N(CH₃)₂.

4. A compound according to Claim 1 selected from:

20 2-[(Benzofuran-2-ylmethyl)-amino]-3-(1*H*-indol-3-yl)-2-methoxymethyl-N-(1-phenyl-ethyl)-propionamide [S-(R*,R*)],

2-[(Benzofuran-2-ylmethyl)-amino]-2-dimethylaminomethyl-3-(1*H*-indol-3-yl)-N-(1-phenyl-ethyl)-propionamide (S,S),

25 2-[(Benzofuran-2-ylmethyl)-amino]-2-hydroxymethyl-3-(1*H*-indol-3-yl)-N-(1-phenyl-ethyl)-propionamide [S-(R*,R*)],

2-(3-Benzofuran-2-ylmethyl-ureido)-2-hydroxymethyl-3-(1*H*-indol-3-yl)-N-(1-phenyl-ethyl)-propionamide [S-(R*,R*)], and

2-(3-Benzofuran-2-ylmethyl-ureido)-3-(1*H*-indol-3-yl)-2-methoxymethyl-N-(1-phenyl-ethyl)-propionamide [S-(R*,R*)].

30 (R)-C-[(Benzofuran-2-ylmethyl)-amino]-dimethylamino-C-(1-hydroxymethyl-1*H*-indol-3-ylmethyl)-N-((S)-1-phenyl-ethyl)-propionamide

(R)-C-[(Benzofuran-2-ylmethyl)-amino]-dimethylamino-C-(1-dimethylaminomethyl-1*H*-indol-3-ylmethyl)-*N*-((S)-1-phenyl-ethyl)-propionamide

- 5 5. A method for antagonizing NK₁ receptors in a mammal in need of treatment comprising administering to a mammal an effective amount of a compound of Claim 1.
- 10 6. A method for treating or preventing:
- CNS disorders such as pain (inflammatory, surgical and neuropathic), anxiety, panic, depression, major depression with anxiety, schizophrenia, neuralgia, stress, sexual dysfunction, bipolar disorders, movement disorders, cognitive disorders, obesity and addiction disorders;
- 15 - inflammatory diseases such as arthritis, asthma, bronchitis, chronic obstructive pulmonary disease (COPD) and psoriasis;
- gastrointestinal disorders including colitis, Crohn's disease, irritable bowel syndrome and satiety;
- allergic responses such as eczema and rhinitis;
- 20 - vascular disorders such as angina and migraine;
- neuropathological disorders including scleroderma and emesis; and
- conditions associated with aberrant neovascularization such as rheumatoid arthritis, atherosclerosis and tumour cell growth,
- 25 comprising administering to a mammal in need of treatment an effective amount of a compound of Claim 1.
7. A compound according to Claim 1 to be used as a medicament.
- 30 8. A pharmaceutical formulation comprising a compound of Claim 1 admixed with at least one pharmaceutically acceptable diluent, carrier or excipient.

- 5
9. A pharmaceutical formulation comprising a compound of Claim 3 admixed with at least one pharmaceutically acceptable diluent, carrier or excipient.
- 10
10. A method for treating conditions associated with aberrant neovascularization such as rheumatoid arthritis, atherosclerosis and tumour cell growth.
- 15
11. A method for imaging NK₁ receptors in vivo in conditions such as ulcerative colitis and Crohn's disease.
- 20
12. Use of a compound of Claim 1 for the preparation of a medicament intended for preventing or treating CNS disorders such as pain (inflammatory, surgical and neuropathic), anxiety, panic, depression, major depression with anxiety, schizophrenia, neuralgia, stress, sexual dysfunction, bipolar disorders, movement disorders, cognitive disorders, obesity and addiction disorders; inflammatory diseases such as arthritis, asthma, bronchitis, chronic obstructive pulmonary disease (COPD) and psoriasis; gastrointestinal disorders including 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 scleroderma and emesis; conditions associated with aberrant neovascularization such as rheumatoid arthritis, atherosclerosis and tumour cell growth.
- 25
13. Process for the preparation of ((S)-2-benzylideneamino)-3-(1H-indol-3-yl)-propionic acid methyl ester which comprises reacting (S)-tryptophan methyl ester with benzaldehyde and recovering the desired product.
- 30

14. Process for the preparation of α -dimethylaminomethyltryptophan methyl ester, wherein (S)-2-benzylidene-amino-3-(1H-indol-3-yl)-propionic acid methyl ester is reacted with 1-dimethylaminomethylbenzotriazole to yield racemic α -dimethylaminomethyltryptophan methyl ester.
- 5
15. Process according to claim 14 wherein the racemic methyl ester obtained is separated into the (R)- and (S)-enantiomers.
- 10
16. Process for the preparation of 2-[(Benzofuran-2-ylmethyl)-amino]-2-dimethylaminomethyl-3-(1H-indol-3-yl)-N-(1-phenyl-ethyl)-propionamide (S,S) wherein (S)-2-[(Benzofuran-2-ylmethyl)-amino]-2-dimethylaminomethyl-3-(1H-indol-3-yl)-propionic acid *bis*-hydrochloride is reacted with (S)- α -methylbenzylamine.
- 15
17. Process for the preparation of (R)-C-[(Benzofuran-2-ylmethyl)-amino]-dimethylamino-C-(1-hydroxymethyl-1H-indol-3-ylmethyl)-N-((S)-1-phenyl-ethyl)-propionamide wherein 2-[(Benzofuran-2-ylmethyl)-amino]-2-dimethylaminomethyl-3-(1H-indol-3-yl)-N-(1-phenyl-ethyl)-propionamide (S,S) is reacted with potassium hexamethyldisilazide and formaldehyde.
- 20
18. Process for the preparation of (R)-C-[(Benzofuran-2-ylmethyl)-amino]-dimethylamino-C-(1-dimethylaminomethyl-1H-indol-3-ylmethyl)-N-((S)-1-phenyl-ethyl)-propionamide wherein 2-[(Benzofuran-2-ylmethyl)-amino]-2-dimethylaminomethyl-3-(1H-indol-3-yl)-N-(1-phenyl-ethyl)-propionamide (S,S) is reacted with lithium hexamethyldisilazide and Eschenmoser's salt.
- 25

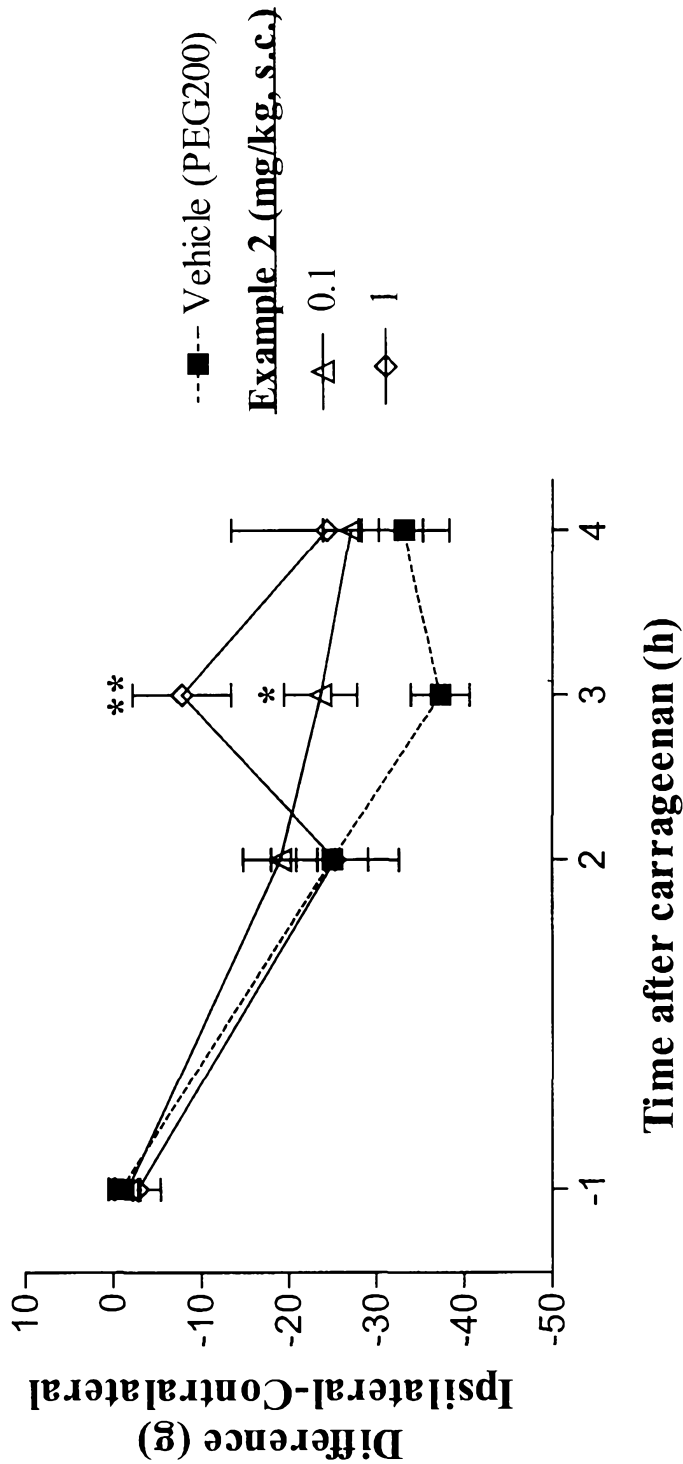


FIGURE 1