EUROPEAN PATENT SPECIFICATION

TRIPEPTIDYL PEPTIDASE INHIBITORS
TRIPEPTIDYLPEPTIDASEINHIBITOREN
INHIBITEUR DE TRIPEPTIDYL PEPTIDASE

Designated Contracting States:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE


Date of publication of application:

Proprietors:
• INSTITUT NATIONAL DE LA SANTE ET DE LA RECHERCHE MEDICALE (INSERM)
75654 Paris Cedex 13 (FR)
• BIOPROJET
75003 Paris (FR)

Inventors:
• SCHWARTZ, Jean-Charles
F-75014 Paris (FR)
• ROSE, Christiane
F-78320 Le Mesnil Saint Denis (FR)
• VARGAS, Froylan,
Nathan SmithKline Instit.
Neuroch
Orangeburg, NY 10962 (US)
• GANELLIN, Charon, Robin
Welwyn, Hertz AL6 0TD (GB)

• ZHAO, Lihua
Glasgow, G41 ZNN (GB)
• SAMAD, Sanjeeda
London, SW12 8RR (GB)
• CHEN, Yongjun
Beijing 100080 (CN)

Representative: Bernasconi, Jean Raymond et al
c/o Cabinet Lavoix,
2, Place d’Estienne d’Orves
75441 Paris Cedex 09 (FR)

References cited:
EP-A- 0 618 221
WO-A-93/20099
EP-A- 0 697 403
WO-A-96/35805


Remarks:
The file contains technical information submitted after the application was filed and not included in this specification

Note: Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).
The present invention relates to inhibitors of a membrane tripeptidyl peptidase responsible for the inactivation of endogenous neuropeptides such as cholecystokinin (CCKs).

Cholecystokinin (CCKs) are a family of hormonal and neuronal peptides which exert pleiotropic biological effects in the gut and brain. For example, CCK-33, the sulphated triatriaconta-peptide is implicated in the control of gall-bladder contraction, gastric emptying and intestinal motility (Dockray, G.J., Gastrointestinal Endocrinology: Receptors and Post-receptors Mechanisms (ed. Thompson, J.) 321-332 (Academic, New York 1990)).


Tripeptidyl peptidase II (TPP II) is a CCK inactivating peptidase. TPP II is found in neurons responding to cholecystokinin as well as in non-neuronal cells. TPP II is considered to be a neuropeptidase responsible for CCK-8 inactivation (Rose, C et al, Nature, 380, 403-409, (1996)). TPP II has the following characteristics:

1) in two steps, it rapidly cleaves the neuropeptide CCK-8 into biologically inactive fragments with a reasonably high degree of specificity;
2) it is expressed by CCK-responsive neurons; and
3) its inhibition allows neuronal CCK-8 to escape inactivation and results in CCK-like effects such as satiation in rodents.

TPP II could be involved in CCK-8 inactivation in the gastrointestinal tract. Exogenous CCK reduces food intake and elicits other behavioural concomitants of satiation. Food intake is increased by systemic administration of CCK A receptor agonists (Smith, G.P. and Gibb, J., Ann. N.Y. Acad. Sci., 713, 236-241, (1994)). Endogenous CCK-controlling food intake seems to be of neuronal rather than hormonal origin and acts upon peripheral CCK A receptors on vagal afferent fibres (Smith, G.P. et al., Am. J. Physiol., 249, R638-R641 (1985)). In addition TPPII, although displaying preference for CCK, is also able to hydrolyse several other peptides with a free N-terminal ammonium group.

Inhibitors of TPP II are useful tools in investigating the functions of CCK neurons and may be useful drugs for the treatment of disorders such as over-eating, problems with gastrointestinal motility and psychotic syndromes.

The present invention relates to compounds which are useful in inhibiting TPP II, processes for producing these compounds, pharmaceutical compositions comprising these compounds and the use of the compounds to inhibit TPP II.

The present invention provides a compound of the following formula I:

wherein: each R¹ may be the same or different, and is chosen from halogen; OH; C1-C6 alkyl, C2-C6 alkenyl or C2-C6 alkylnyl, optionally substituted by at least one halogen, OH or mixtures thereof; X(C1-C6 alkyl), wherein X is S, O or OCO, and the alkyl is optionally substituted by at least one halogen, OH or mixtures thereof; SO2(C1-C6 alkyl), optionally substituted by at least one halogen; or YSO3H, YSO2(C1-C6 alkyl), wherein Y is O or NH and the alkyl is optionally substituted by at least one halogen; a diradical -X¹-(C1-C6 alkyne)-X¹- wherein X¹ is O or S; a benzene ring fused to the indoline ring;
alkyl groups are C₁-₄ straight chain alkyl. Typically a substituted alkyl group has from 1 to 6 substituents and preferably from 1 to 4 carbon atoms. Suitable alkyl groups include methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl or t-butyl. Preferred alkyl groups are C₁-₄ straight chain alkyl. Typically a substituted alkyl group has from 1 to 6 substituents and preferably from 1 to 3 substituents. Halogen is typically F, Cl, Br, or I, preferably Cl or F, most preferably F.

According to another aspect, the invention is directed to compounds (I) wherein n is not 0 and R¹ represents a C₁-C₆ alkyl or C₁-₆ alkynyl group.

The alkenyl or alkynyl groups may be straight-chain or branched. The alkenyl groups have from 1 to 6 carbon atoms, preferably from 1 to 4 carbon atoms. Suitable alkenyl groups include methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl or t-butyl. Preferred alkenyl groups are C₁-₄ straight chain alkyl. Typically a substituted alkenyl group has from 1 to 6 substituents and preferably from 1 to 3 substituents. Halogen is typically F, Cl, Br, or I, preferably Cl or F, most preferably F.

The alkenyl or alkynyl groups may be straight-chain or branched. These groups contain from 1 to 6 carbon atoms, preferably from 1 to 4 carbon atoms.

Typical alkyl groups include ethenyl.

Typical alkynyl groups include ethynyl.

Unsaturated alkyl groups (in R²) contain one or more double or triple bonds.

According to another aspect, the invention is directed to compounds (I) wherein n is not 0 and R¹ represents a C₁-C₆ alkyl or C₁-₆ alkynyl group.

The diradical is preferably attached to the indoline ring at the positions 4 and 5 (4,5-positions) or at the positions 5 and 6 (5,6-positions).

According to another aspect, the invention is directed to compounds (I) wherein n¹ represents a C₁-C₆ alkyl or C₁-₆ alkynyl group.

The benzene ring is preferably attached at the 4-positions, or at the 5,6-positions.

The present invention provides also compounds (I) wherein R³ represents a C₁-C₆ alkyl substituted by at least one halogen; (CH₂)₂Z (CH₂)₃CH₃, wherein Z is O, S or N, p is from 0 to 5 and q is from 0 to 5, provided that p + q is from 0 to 5; C₂-C₆ unsaturated alkyl; or C₃-C₆ cycloalkyl; or R² is C₁-C₆ alkyl, optionally substituted by at least one halogen; R³ is H; or C₁-C₃ alkyl; benzylic; or a pharmaceutically acceptable acid addition salt thereof.

The invention provides in particular a compound of the above formula I wherein: each R¹ may be the same or different, and is chosen from halogen; OH; C₁-C₆ alkyl, optionally substituted by at least one halogen, OH or mixtures thereof; X(C₁-C₆ alkyl), wherein X is S, O or OCO, optionally substituted by at least one halogen, OH or mixtures thereof; SO₂(C₁-C₆ alkyl), optionally substituted by at least one halogen; or YSO₃H, YSO₂(C₁-C₆ alkyl), wherein Y is O or NH optionally substituted by at least one halogen; n is from 0 to 4; R² is CH₂R₄, wherein R⁴ is C₁-C₆ alkyl substituted by at least one halogen, (CH₂)₂Z(CH₂)₃CH₃, wherein Z is O, S or N, p is from 0 to 5 and q is from 0 to 5, provided that p + q is from 0 to 5; C₂-C₆ unsaturated alkyl; or C₃-C₆ cycloalkyl, or R² is C₁-C₆ alkyl optionally substituted by at least one halogen; R³ is H or C₁-C₆ alkyl; or a pharmaceutically acceptable acid addition salt thereof.

Compounds of formula (I) wherein n = 0 or when n is not 0 wherein R¹ is a halogen atom, a O(C₁-C₆ alkyl), OH or a (C₁-C₆ alkyl) group, R² is CH₂R₄ with R₄ being (CH₂)₂SCH₃ or cyclohexyl or R² is a (C₁-C₆) alkyl group, and R³ is an hydrogen atom or a (C₁-C₆) alkyl group, are known from WO 96/35805 and are not included in the present invention.

According to another aspect of the present invention, it is relative to compounds of formula (I) wherein R² is CH₂R₄, R³ being C₁-C₆ alkyl substituted by at least one halogen; (CH₂)₂Z(CH₂)₃CH₃ wherein Z is O (p and q are as defined above); C₂-C₆ unsaturated alkyl.

According to another aspect of the present invention, it is relative to compounds of formula (I) wherein n is not 0 and R¹ represents a C₁-C₆ alkynyl or C₁-₆ alkynyl group.

The alkenyl or alkynyl groups may be straight-chain or branched. The alkenyl or alkynyl groups may be straight-chain or branched. These groups contain from 1 to 6 carbon atoms, preferably from 1 to 4 carbon atoms.

Typical alkyl groups include ethenyl.

Typical alkynyl groups include ethynyl.

Unsaturated alkyl groups (in R²) contain one or more double or triple bonds.

According to another aspect of the present invention, it is relative to compounds of formula (I) wherein n is not 0 wherein R¹ is a halogen atom, a O(C₁-C₆ alkyl), OH or a (C₁-C₆ alkyl) group, R² is CH₂R₄ with R₄ being (CH₂)₂SCH₃ or cyclohexyl or R² is a (C₁-C₆) alkyl group, and R³ is an hydrogen atom or a (C₁-C₆) alkyl group, are known from WO 96/35805 and are not included in the present invention.

According to another aspect, the invention is directed to compounds (I) wherein n is not 0 and R¹ represents a C₁-C₆ alkynyl or C₁-₆ alkynyl group.

According to another aspect, the present invention is directed to compounds (I) wherein n is not 0 and R¹ represents a C₁-C₆ alkynyl or C₁-₆ alkynyl group.
The number of substituents $R^1$ is 0, 1, 2, 3 or 4, and preferably, $n$ is 0, 1 or 2. When $n$ is 1, $R^1$ is preferably at the 4-, 5- or 6-position, most preferably at the 4- or 5-position. When $n$ is 2, the two $R^1$ groups are preferably at the 4- and 5-positions, 4- and 6-positions or 5- and 6-positions, and are most preferably at the 4- and 5-positions. When $n$ is 3, the three $R^1$ groups are preferably at the 4-, 5- and 6-positions.

The compounds of the invention generally have at least two chiral centres. These are the carbon atoms at the 2-position on the indoline ring and the carbon atom to which $R^3$ is attached. The stereochemistry at each of the chiral centres may independently be (S) or (R). Preferably the stereochemistry of at least one chiral centre is (S). Most preferably the stereochemistry at both chiral centres is (S). The (S),(S) stereochemistry corresponds to the stereochemistry of naturally occurring amino acids. However, it is not essential that the stereoisomers are separated. For example 1-(2(S)-aminobutyryl)-4-chloroindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethy)amide trifluoroacetate and 1-(2(S)-aminobutyryl)-4-fluoroindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl)amide trifluoroacetate have been shown to have useful activity.

The invention also provides a method for inhibiting the activity of TPP II which comprises administering an effective amount of a compound of formula I or a pharmaceutically acceptable acid addition salt thereof to a mammalian subject.

In this respect, the invention provides a medicament acting as an inhibitor of the CCK-inactivating peptidase tripeptidyl peptidase (TPPII) and/or for the treatment of eating disorders, especially obesity and/or for the treatment of psychotic syndromes and associated psychiatric disorders, which comprises a therapeutically effective amount of a compound of formula I.

The invention also provides a compound of formula I or pharmaceutical compositions comprising a compound of formula I for use in the treatment of the human or animal body, particularly for the treatment of eating disorders, especially obesity.

The invention further provides the use of a compound of formula I for the manufacture of a medicament for inhibiting the activity of TPP II and/or for treating eating disorders, especially obesity.

The compounds of the invention may be administered alone or together with any other known compound for the treatment for obesity. Suitable treatments include those known in the art, for example treatment with an adrenergic $\beta_3$-receptor agonist, a histamine $H_3$-receptor antagonist, a neuropeptide Y receptor (NPY-5) antagonist, a compound acting on the amylín receptor or a compound that increases the levels of noradrenaline, dopamine or serotonin in the brain e.g. dexfenfluramine, sibutramine or fluoxetine. The compound of formula I and the other obesity treatment compound may be provided in a form for simultaneous, separate or sequential administration.

The invention also provides a compounds of formula I or a pharmaceutical composition comprising a compound of formula I for the treatment of psychotic syndromes and associated psychiatric disorders.

In this respect, the invention provides a cosmetic composition comprising a compound of formula I together with a physiologically acceptable carrier or diluent

It is provided also a method of improving the bodily appearance of a human or animal comprising administering an effective amount of a compound of formula I optionally with a physiologically acceptable carrier or diluent to aid slimming.

The compounds of formula I may be prepared by the following general procedure:
R¹, R², R³ are as defined above and R¹⁰ is H or a protecting group (e.g. benzylxycarbonyl or t-butyloxycarbonyl).

a. Indole (or appropriately substituted indole)-2-carboxylic acid alkyl ester is reduced to the indoline ester (II) by magnesium turnings in methanol, and this is coupled with a suitably protected amino acid (III) in the presence of a coupling reagent, such as bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOPCI) or a carbodiimide such as disopropylcarbodiimide (DIC), dicyclohexylcarbodiimide (DCC) or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide methiodide to form IV, where R¹ is OMe.

b. The acid of formula IV, where R¹ is OH, may then be prepared by hydrolyzing the corresponding ester of formula IV wherein R¹ is OMe with sodium hydroxide or lithium hydroxide in methanol-water solution at room temperature.

c. The diamides of formula IV, wherein R¹ is NHR², are formed by coupling the acid of formula IV, where R¹ is OH, with an amine, R²NH₂, or a salt thereof in the presence of a coupling reagent, such as BOPCI, DIC, DCC etc.; or by reacting the ester of formula IV wherein R¹ is OMe with excess amine, e.g. MeOCH₂CH₂NH₂, MeSCH₂CH₂NH₂, MeCH(OH)CH₂NH₂ etc., at a temperature between 15 and 60°C.

d. Removal of the protecting group R¹⁰ from the compound of formula IV where R¹ is NHR² to give compound I can be effected by hydrogenation when R¹⁰ is benzylxycarbonyl over a catalyst such as palladium on activated carbon; or by trifluoroacetic acid when R¹⁰ is tert-butyloxycarbonyl in dichloromethane.

e. An alternative route to obtain the diamides of formula IV wherein R¹ is NHR², is to prepare an indoline 2-substituted carboxamide of formula V, then couple it with the amino acid of formula III to obtain a compound of formula IV wherein R¹ is NHR². Removal of the protecting group R¹⁰ can be effected as described above. The compound of formula V can be prepared by reacting the indoline ester II with excess amine with or without methanol (when the amine is reactive), at a temperature between 15 and 60°C, or by hydrolyzing the protected indoline ester to its acid, then treating the acid with an amine in the presence of a coupling reagent (such as BOPCI, DIC or DCC), followed by the removal of the protecting group, R¹⁰ as described above.
In addition to the above, compounds of formula I which, in vitro, have a Ki value of less than 1.0nM are especially and pharmaceutically acceptable salts thereof.

Particular compounds of formula I include:

1-(2-(S)-aminobutyryl)-5-chloroindoline-2(S)-carboxylic acid (2,2,2-trifluoroethyl)amide;
1-(2-(S)-aminobutyryl)-5-chloroindoline-2(S)-carboxylic acid 2-chloroethylamide;
1-(2-(S)-aminobutyryl)-indole-2(S)-carboxylic acid (2-methylthioethyl)amide;
1-(2-(S)-aminobutyryl)-indole-2(S)-carboxylic acid N-(cyclopropylmethyl)amide;
1-(2-(S)-aminobutyryl)-indole-2(S)-carboxylic acid (2,2,2-trifluoroethyl)amide;
1-(2-(S)-aminobutyryl)-5-hydroxyindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl)amide;
1-(2-(S)-aminobutyryl)-4-chloroindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl)amide;
1-(2-(S)-aminobutyryl)-4-fluoroindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl)amide;
1-(2-(S)-aminobutyryl)-5-methoxyindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl)amide;
1-(2-(S)-aminobutyryl)-5-trifluoromethoxyindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl)amide;

and pharmaceutically acceptable salts thereof.

Particular compounds of formula I include also:

1-(2-(S)-aminobutyryl)-4,5-dichloroindoline-2(S)-carboxylic acid 2,2,2-trifluoroethylamide;
1-(2-(S)-aminobutyryl)-5,6-dichloroindoline-2(S)-carboxylic acid 2,2,2-trifluoroethylamide;
1-(2-(S)-aminobutyryl)-[benz[e]-indole-2(S)-carboxylic acid 2,2,2-trifluoroethylamide;
1-(2-(S)-aminobutyryl)-5-O-sulfato-indole-2(R/S)-carboxylic acid butyl amide;
1-(2-(S)-aminobutyryl)-benz[e]-indole-2(S)-carboxylic acid butyl amide;
1-(2-(S)-aminobutyryl)-5-dichloro-indoline-2(R/S)-carboxylic acid 2,2,2-trifluoroethylamide;
1-(2-(S)-aminobutyryl)-5-O-sulfato-indole-2(R/S)-carboxylic acid trifluoroethylamide;
1-(2-(S)-aminobutyryl)-benz[f]-indole-2-(S/R)-carboxylic acid 2,2,2-trifluoroethylamide;
1-(2-(S)-phenylalaninyl)-5-Chloro-indoline-2(R/S)-carboxylic acid 2,2,2-trifluoroethylamide;
1-(2-(S)-aminobutyryl)-4-methoxyindoline-2(S)-carboxylic acid (2,2,2-trifluoroethyl)amide;
1-glycyl]-5-chloroindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl)amide;
1-(2-(S)-alanyl)-5-chloroindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl)amide;
1-(2-(S)-norvalyl]-5-chloroindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl)amide;
1-(2-(S)-methionyl]-5-chloroindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl)amide;
1-(2-(S)-aminobutyryl]-4-methylindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl)amide;
1-(2-(S)-aminobutyryl]-4-5-dimethoxyindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl)amide;
1-(2-(S)-aminobutyryl]-4,5-methylenedioxyindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl)amide;
1-(2-(S)-aminobutyryl]-5-ethynylindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl)amide;

and pharmaceutically acceptable salts thereof.

In addition to the above, compounds of formula I which, in vitro, have a Ki value of less than 1.0nM are especially preferred.

The compounds of formula I may be used in vitro or in vivo as TPP II inhibitors. For in vivo use, the compounds may be useful in the development and standardisation of assays for TPP II and inhibitors thereof.

For in vivo use the compounds may be useful in the control of stomach emptying and control of appetite for food.

The compounds of formula I may be administered to mammals including humans, by any route appropriate to the condition to be treated.

Suitable routes include oral, rectal, nasal, topical (including buccal and sublingual), vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural). It will be appreciated that the preferred route may vary with, for example, the condition of the recipient.

For each of the above-identified utilities and indications, the amount required of the individual active ingredients will depend upon a number of factors including the severity of the condition to be treated and the identity of the recipient, and will also be at the discretion of the attendant physician. In general, however, for each of these utilities and indications, a suitable, effective dose will be in the range of from 0.001 to 10mg per kilogram body weight per day and most preferably in the range of from 0.01 to 1 mg per kilogram body weight per day. Unless otherwise indicated, all weights of active ingredient are calculated as the parent compound, and for salts thereof the figures would be increased proportionately.

The desired dose may suitably be presented as two, three, four or more sub-doses administered at appropriate
Doses of compounds of the invention may be administered at sub-daily or daily intervals, or less frequently, for example on alternate days, weekly or fortnightly. In general the doses will be the same as the above daily dose, although higher doses, particularly when formulated to be released over a prolonged period of time, may be used.

While it is possible for the compounds to be administered alone it is preferable to present them as pharmaceutical formulations. The formulations of the present invention comprise at least one active ingredient, as above defined, together with one or more acceptable carriers thereof and optionally other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipients thereof.

The formulations include those suitable for oral, rectal, nasal, topical (including buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural) administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

Formulations suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder (e.g. povidone, gelatin, hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (e.g. sodium starch glycolate, cross-linked povidone, cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent.

A capsule may be made by filling a loose or compressed powder on an appropriately fitting machine, optionally with one or more additives. Examples of suitable additives include binders such as povidone; gelatin, lubricants, inert diluents and disintegrants as for tablets.

Compositions suitable for transdermal administration may be presented as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. Such patches suitably contain the active compound 1) in an optionally buffered, aqueous solution or 2) dissolved in an adhesive or 3) dispersed in a polymer. A suitable concentration of the active compound is about 1% to 35%, preferably about 3% to 15%.

Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain antioxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents, and liposomes or other microparticulate systems which are designed to target the compound to blood components or one or more organs. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use.

The following Examples illustrate the invention.

1. The following abbreviations are used hereafter:

Abu: aminobutyryl; Ar:aromatic; Bn: benzyl; Boc: t-butoxycarbonyl; Ph: phenyl; t-Bu: t-butyl; s: singlet; d: doublet; t: triplet; m: multiplet; dd: double doublet; w: weak; vs: very small; str: strong.

**EXAMPLE 1**

**Synthesis of 1-(2(S)-aminobutyryl)-5-chloroindoline-2(S)-carboxylic acid (2,2,2-trifluoroethyl)amide trifluoroacetate**

**5-Chloroindoline-2(R/S)-carboxylic acid methyl ester**

5-Chloroindole-2-carboxylic acid ethyl ester (3g, 13.4 mmol) and magnesium turnings (0.652g, 26.8 mmol) were suspended in dried methanol (300 ml). This mixture was stirred at 5 to 10°C under nitrogen for 3 hours, then poured into dichloromethane (400 ml), and washed with saturated ammonium chloride solution, the organic layer was separated, and the aqueous layer was extracted with dichloromethane (3 x 100 ml). The combined organic layers were dried over sodium sulphate and evaporated. The resulting solid was chromatographed on silica gel using dichloromethane as
eluent, to furnish the indoline ester as a yellow solid.
MS (El) m/z 211 (M+, 100), 152 (M, 81).
1H NMR (CDCl₃, 400 MHz)  δ (ppm) 6.60-7.05 (m, 2H, ArH), 6.63 (d, 1H, ArH), 4.25-4.45 (m, 2H, NH and NCHCO of indoline), 3.77 (s, 3H, OCH₃), 3.29-3.42 (m, 2H, CH₂ of indoline).

1-(N-Butoxycarbonyl-2(S)-aminobutyryl)-5-chloroindoline-2(S)-carboxylic acid methyl ester

[0063] To a solution of 5-chloroindoline-2(R,S)-carboxylic acid methyl ester (1.2g, 5.69 mmol) and N-t-butoxycarbonyl-2(S)-aminobutyric acid (1.27g, 6.25 mmol) dissolved in dried dichloromethane (10 ml) under nitrogen at 0°C, was added diisopropylcarbodiimide (0.98 ml, 6.30 mmol). The mixture was stirred at room temperature for 24 hours, then filtered. The filtrate was evaporated under vacuum to afford a brown solid which was purified by column chromatography on silica gel using 7:3 petroleum spirit:diethyl ether as eluent. A white foam was obtained which was pure enough for the next reaction.

MS (Fab) m/z 464

IR (KBr) cm⁻¹ 3430(broad, w), 1614(w), 1604(s), 1580(w), 1538(s), 1479(s), 1250(w), 1126(s), 1105(m), 1075(w), 1050(m), 903(s), 580(m).

Elemental Analysis: calculated for C₁₅H₁₅ClF₂N₂O₂, C: 43.75, H: 3.92, N: 7.31%, found C: 43.72, H: 3.90, N: 7.32%.

1-(N-Butoxycarbonyl-2(S)-aminobutyryl)-5-chloroindoline-2(S)-carboxylic acid

[0064] To the solution of 1-(N-t-butoxycarbonyl-2(S)-aminobutyryl)-5-chloroindoline-2(S)-carboxylic acid methyl ester (1.2g, 3 mmol) in methanol (20 ml), was added sodium hydroxide (0.24 g, 6 mmol) in water (10 ml). The solution was stirred at 5-10°C for 4 hours. The mixture was poured into dichloromethane (50 ml), and washed with cold potassium hydrogen sulphate (3 x 20 ml), then water (30 ml). The organic layer was dried over sodium sulphate, and evaporated to provide a white foam which was pure enough for the next reaction.

MS (Fab) m/z 383(MH⁺, 8), 327(14), 197(12), 145(63), 58(100).

IR (KBr) cm⁻¹ 3410(s, w), 3273(m), 1648(s), 1602(s), 1580(s), 1534(m), 1478(s), 1436(m), 1280(s), 1232(w), 1150(m), 1126(s), 1105(should), 938(w), 670(w).

Elemental Analysis: calculated for C₁₄H₁₄FN₂O₂, C: 43.75, H: 3.92, N: 7.31%, found C: 43.72, H: 3.90, N: 7.32%.

1-(N-Butoxycarbonyl-2(S)-aminobutyryl)-5-chloroindoline-2(S)-carboxylic acid (2,2,2-trifluoroethyl)amide

[0065] 1-(N-Butoxycarbonyl-2(S)-aminobutyryl)-5-chloroindoline-2(S)-carboxylic acid (0.192g, 0.5 mmol) and 2,2,2-trifluoroethylamine hydrochloride (0.205g, 1.5 mmol) were dissolved in dried dichloromethane (5 ml) under nitrogen at 0°C, and triethylamine (0.63 ml, 4.5 mmol) was added followed by bis(2-oxo-3-oxazolidinyl)phosphinic chloride (0.382g, 1.5 mmol). The temperature was allowed to rise to room temperature and the mixture was stirred at room temperature for 24 hours, then filtered. The filtrate was concentrated under vacuum to give a brown solid which was columned on silica gel using 7:3 petroleum spirit:ethyl acetate as eluent to provide a white solid.

MS (Fab) m/z 446(MH⁺, 4), 408(8), 278(14), 152(24), 58(100).

IR (KBr) cm⁻¹ 3410(s, w), 3273(m), 1648(s), 1602(s), 1580(s), 1534(m), 1478(s), 1436(m), 1280(s), 1232(w), 1150(m), 1126(s), 1105(should), 938(w), 670(w).

Elemental Analysis: calculated for C₁₄H₁₄FN₂O₂, C: 43.75, H: 3.92, N: 7.31%, found C: 43.72, H: 3.90, N: 7.32%.

1-(2(S)-Aminobutyryl)-5-chloroindoline-2(S)-carboxylic acid (2,2,2-trifluoroethyl)amide trifluoroacetate

[0066] 1-(N-Butoxycarbonyl-2(S)-aminobutyryl)-5-chloroindoline-2(S)-carboxylic acid (2,2,2-trifluoroethyl)amide (120 mg, 0.26 mmol) was dissolved in dichloromethane (1 ml) in an ice-water bath, and trifluoroacetic acid (1 ml) was added under nitrogen. The solution was stirred at 0 to 5°C until gas evolution ceased. The solution was evaporated to dryness in vacuo and the residue was treated with dried diethyl ether. A white foam was obtained after drying.

m.p. 34-35°C.
MS (Fab) m/z 364(MH⁺, 29), 58(100).

IR (KBr) cm⁻¹ 3430(broad, w), 3280(w), 3125(w), 2920(s), 2850(s), 2360(w), 1730(s), 1610(w), 1550(w), 1470(s), 1230(s), 1121(s), 1070(s), 580(s).

Elemental Analysis: calculated for C₁₅H₁₄FN₂O₂, C: 43.75, H: 3.92, N: 7.31%, found C: 43.72, H: 3.90, N: 7.32%.
EXAMPLE 2

Synthesis of 1-(2(S)-aminobutyl)-5-chloroindoline-2(S)-carboxylic acid 2-chloroethylamide trifluoroacetate

1-(N-t-Butoxycarbonyl-2(S)-aminobutyl)-5-chloroindoline-2(S)-carboxylic acid 2-chloroethylamide

Triethylamine (0.42 mL, 3 mmol) was added to the solution of 1-(N-t-butoxycarbonyl-2(S)-aminobutyl)-5-chloroindoline-2(S)-carboxylic acid (0.152 g, 0.4 mmol) and 2-chloroethylamine hydrochloride (0.116 g, 1 mmol) in dried dichloromethane (10 ml) under nitrogen at 0°C, followed by bis(2-oxo-3-oxazolidinyl)phosphonic chloride (0.255 g, 1.0 mmol). The temperature was allowed to rise to room temperature and the mixture was stirred at room temperature for four hours, then filtered. The filtrate was concentrated under vacuum to give a brown solid which was purified by column chromatography (silica gel, diethyl ether) to provide a white solid.

MS (FAB) m/z 445(MH+, 12), 444(33), 330(52), 258(46), 152(63), 57(100). ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 8.0-8.1 (m, 1H, ArH), 7.18-7.25 (m, 2H, ArH), 5.02-5.10 (m, 1H, H₂ of indoline), 4.80-4.90 (m, 1H, CH₂ of indoline), 3.40-3.75 (m, 6H, H₃ of indoline, CH₂ of indoline), 1.63-1.89 (m, 2H, CH₂ of Abu), 1.46 (s, 9H, t-Bu), 0.95-1.23 (m, 3H, CH₃ of Abu).

EXAMPLE 3

Synthesis of 1-(2(S)-aminobutyl)-5-chloroindoline-2(S)-carboxylic acid 2-chloroethylamide trifluoroacetate

1-(2(S)-Aminobutyl)-5-chloroindoline-2(S)-carboxylic acid-(2-methylthioethyl)amide trifluoroacetate

Trifluoroacetic acid (1 mL) was added dropwise to the solution of 1-(N-t-butoxycarbonyl-2(S)-aminobutyl)-5-chloroindoline-2(S)-carboxylic acid (100 mg, 0.225 mmol) in dichloromethane (1 mL) in an ice-water bath under nitrogen. This solution was stirred at 0-5°C until gas evolution ceased, then evaporated to dryness under vacuum below 45°C, and the residue was treated with dried diethyl ether. A pink foam was obtained after drying.

m.p. 80-88°C.

MS (FAB) m/z 348(M+=4, 8), 347(M+=3, 8), 346(M+=2, 37), 345(MH+, 13), 344(M, 60), 145(33), 57(100).

¹H NMR (DMSO-d₆, 400 MHz) δ (ppm) 8.70-8.92 (m, 1H, CONH), 8.20-8.50 (m, 3H, acidic H), 8.10 (d, 1H, J=8.5 Hz, ArH), 7.25-7.42 (m, 2H, ArH), 5.10 (dd, 1H, H₂ of indoline), 3.10-3.76 (m, 7H, CONCH₂), CH of Abu, H3 of indoline), 1.75-2.00 (m, 2H, CH₂ of Abu), 0.9-1.18 (m, 3H, CH₃ of Abu).

Elemental Analysis: calculated for C₁₉H₁₉Cl₂N₂O₂: 1.2CF₃COOH: C, 43.44; H, 4.23; N, 8.73%. Found: C, 43.17; H, 4.52; N, 8.40%.

EXAMPLE 3

Synthesis of 1-(2(S)-aminobutyl)-indoline-2(S)-carboxylic acid (2-methylthioethyl)amide trifluoroacetate

1-(N-t-Butoxycarbonyl-2(S)-aminobutyl)-indoline-2(S)-carboxylic acid-(2-methylthioethyl)amide

To a solution of 1-(N-t-butoxycarbonyl-2(S)-aminobutyl)-indoline-2(S)-carboxylic acid methyl ester (0.5g, 1.4 mmol) in methanol (2 ml), was added 2-methylthioethanol (3 ml) under nitrogen, and the resulting solution was stirred at 60°C for 48 hours. The solution was poured into dichloromethane (20 ml), and washed with 1 M potassium hydrogen sulphate, the aqueous layer was extracted with dichloromethane (3 x 15 ml). The combined organic layers were dried over Na₂SO₄, and then the solvent was evaporated. A white solid was obtained after column chromatography on silica gel using diethyl ether as eluent.

MS (Fab) m/z 422 (M+H, 69), 322 (52), 237 (61), 118 (100), 57 (30).

¹H NMR (CDCl₃, 400 MHz) δ (ppm) 8.0-8.123 (m, 1H, ArH), 7.50-7.56 (m, 1H, CONH), 7.22 - 7.26 (m, 2H, ArH), 7.08-7.11 (m, 1H, ArH), 5.05-5.09 (m, 2H, NCHCO of indoline and NH of Abu), 4.31 - 4.21 (m, 1H, CH of Abu), 3.58 - 3.65 (m, 4H, CONHC₂H₂, CH₂ of indoline), 2.59-2.60 (m, 2H, CH₂S), 2.01 (s, 3H, SCH₃), 1.67-1.91 (m, 2H, CH₂ of Abu), 1.45 (s, 9H, t-Bu), 1.06-1.192 (t, 3H, CH₃ of Abu).

1-(2(S)-Aminobutyl)-indoline-2(S)-carboxylic acid(2-methylthioethyl) amide trifluoroacetate

1-(N-t-Butoxycarbonyl-2(S)-aminobutyl)-indoline-2(S)-carboxylic acid (2-methylthioethyl)amide (0.19g, 0.45 mmol) was dissolved in dichloromethane (1.5 ml) in an ice-water bath, and trifluoroacetic acid (1.5 ml) was added under nitrogen. The solution was stirred at 0 to 5°C until gas evolution ceased. The solution was evaporated to dryness in
vacuo and the residue was treated with dried diethyl ether. A pink foam was obtained after flash column chromatography on silica gel using 20:1 dichloromethane : methanol as eluent. m.p. 59.5 - 60.5°C
MS (Fab) m/z 322 (MH⁺, 10), 155(35), 137(100).

1HNMR (DMSO-d₆, 400 MHz): δ (ppm) 8.60 (m, 1H, CONH), 8.25-8.36 (m, 2H, acidic hydrogen), 8.14 (d, 1H, ArH), 7.22 -7.29, 7.08-7.12 (m, 3H, ArH), 5.03-5.06 (m, 1H, NCHCO of indoline), 3.15-3.73 (m, 13H, CH₃ of indoline, CONHC₃H₂, overlap of H₂O) 2.53-2.73 (m, 2H, CH₂S), 2.06(s, 3H, SCHR₂), 1.79-2.00 (m, 2H, CH₂ of Abu), 0.99 (t, 3H, CH₃ of Abu).

[0071] IR (KBr) cm⁻¹ 3449(m), 3073(m), 1596(w) (N-H), 1563 (s) (C=O); 1485 (w) (C=O); 1203(s), 1179(s), 1132(s) (O-C, N-C, C-F).

[0072] Elemental Analysis: calculated for C₉H₁₆N₂O₂S, 1.2CF₃COOH, 0.5H₂O, C 47.30, H 5.44, N 8.99%, found C 47.32, H 5.35, N 8.97%.

EXAMPLE 4

Synthesis of 1-(2(S)-aminobutyryl)-indoline-2(S)-carboxylic acid N-(cyclopropylmethyl)amide trifluoroacetate

1-(N-t-Butoxycarbonyl-2(S)-aminobutyryl)-indoline-2(S)-carboxylic acid N-(cyclopropylmethyl)amide

[0073] In a like manner to example 1, 1-(N-t-butoxycarbonyl-2(S)-aminobutyryl)-indoline-2(S)-carboxylic acid (0.30 g, 0.8 mmol) and cyclopentamethylamine hydrochloride (0.26 g, 2.5 mmol) were dissolved in dried dichloromethane (10 mL) under nitrogen at 0°C, and triethylamine (1.03 mL, 7.4 mmol) was added followed by bis(2-oxo-3-oxazolidinyl) phosphonic chloride (0.63 g, 2.5 mmol). The temperature was allowed to rise to room temperature and the mixture was stirred at room temperature for 5 hours. The mixture was poured into dichloromethane (100 mL), and washed with cold potassium hydrogen sulphate (3 x 50 mL), water (50 mL). The organic layer was dried over sodium sulphate, and evaporated to provide a white foam which was pure enough for the next step.

MS (FAB) m/z 410 (MH⁺, 10)

1HNMR (DMSO-δ₆, 400 MHz): δ (ppm) 8.18-8.07 (m, 1H, NH of CONH), 7.34-7.01 (m, 4H, ArH), 5.47-4.78 (m, 1H, NCHCO of indoline), 4.10-4.21 (m, 1H, NCH of indoline), 3.62-3.41, 3.34-2.98 (m, 3H, CH₃ of Abu, CH₁ of CONH), 2.08-1.66 (m, >2H, CH₂ of Abu + H₂O), 1.52-1.34 (s, 9H, t-Bu of Boc), 1.19-0.99 (m, 3H, CH₃ of Abu), 0.52-0.33, 0.221-0.09 (m, 5H, cyclopropane).

1-(2(S)-Aminobutyryl)-indoline-2(S)-carboxylic acid (N-cyclopropylmethyl)amide trifluoroacetate

[0074] 1-(N-t-Butoxycarbonyl-2(S)-aminobutyryl)-indoline-2(S)-carboxylic acid N-(cyclopropylmethyl)amide (20 mg, 0.04 mmol) was dissolved in dichloromethane (3 mL) in an ice-water bath, and trifluoroacetic acid (0.2 mL) was added under nitrogen. The solution was evaporated to dryness under vacuum and the residue was treated with dried diethyl ether. A very hygroscopic pale yellow foam was obtained after drying.

m.p. 57-74°C
MS (FAB) m/z 302 (MH⁺)

1HNMR (DMSO-400 MHz): δ (ppm) 8.09-8.17, 7.03-7.37 (m, 4H, ArH), 4.96-5.11 (m, 1H, NCHCO of indoline), 3.55-3.78 (m, >10H, CH of Abu & CH of CONHC₃H₂ + D₂O), 2.87-3.17 (m, 3H, CH₂ of indoline & NH of CONH & CH of CONHC₃H₂), 1.75-2.02 (m, 2H, CH₂ of Abu), 0.88-1.15 (m, 3H, CH₃ of Abu), 0.36-0.49, 0.14-0.23 (m, 5H, cyclopropane).

IR 3420(br, N-H, str overlapped by H₂O peak); 1675(s, C=O str); 1464(m, aromatic C=O); 1204(s, C-N str); 1135(s, C-O str)

Elemental Analysis: calculated for C₁₇H₂₃N₂O₅S, 1.4(CF₃CO₂H): C, 51.59; H, 5.33; N, 9.11 %. Found: C, 51.66; H, 5.61; N, 8.90 %.

EXAMPLE 5

Synthesis of 1-(2(S)-Aminobutyryl)-indoline-2(S)-carboxylic acid (2,2,2-trifluoroethyl)amide oxalate

1-(N-Benzoxycarbonyl-2(S)-aminobutyryl)-indoline-2(S)-carboxylic acid

[0075] To the solution of 1-(N-benzoxycarbonyl-2(S)-aminobutyryl)-indoline-2(S)-carboxylic acid methyl ester (2.0g, 5 mmol) in methanol (100 ml), was added lithium hydroxide(0.233g, 5.5 mmol) in water (5 ml). The solution was stirred at 5-10°C for 5 hours. The mixture was poured into dichloromethane (100 ml), and washed with cold potassium hydrogen sulphate (3 x 50 ml), water (50 ml). The organic layer was dried over sodium sulphate, and evaporated to provide a white foam which was pure enough for the next step.
1-(N-Benzoylcarbonyl-(S)-aminobutyryl)-indoline-2(S)-carboxylic acid (2,2,2-trifluoroethyl)amide

**[0076]** 1-(N-Benzoylcarbonyl-(S)-aminobutyryl)-indoline-2(S)-carboxylic acid (0.382g, 1 mmol) and 2,2,2-trifluoroethylamine hydrochloride (0.207g, 1.5 mmol) were dissolved in dried dichloromethane (10 ml), and triethylamine (5.5 ml) was added, followed by bis(2-oxo-3-oxazolidinyl)phosphinic chloride (0.508g, 2.0 mmol) under nitrogen at 0°C. The temperature was allowed to rise to room temperature and the mixture was stirred at room temperature for 24 hours, then filtered. The filtrate was concentrated under reduced pressure to give a brown solid which was purified by column chromatography on silica gel using 7:1 methanol (40:60) as eluent to afford a white solid.

10 m.p. 189.5-190.5°C.

**[0077]** 10% Palladium on activated carbon (20 mg) was added to the solution of 1-(N-benzoylcarbonyl-(S)-aminobutyryl)-indoline-2(S)-carboxylic acid (90 mg, 0.19 mmol) in methanol (10 ml), and the mixture was hydrogenated at 40 psi for 2.5 hours. After the catalyst was removed by filtration through celite, oxalic acid (18 mg) was added to the filtrate, and the solution was evaporated to dryness under reduced pressure at a bath temperature less than 50°C. The pure white crystalline product was obtained by recrystallization from dried diethyl ether-methanol (40:1).

m.p. 148.5-149.0°C.

MS (Fab) m/z 383(MH+), 34, 254 (19), 163 (16), 118 (28), 91 (100).

1H NMR (CDCl3, 400 MHz) δ (ppm) 8.09-8.18, 7.60-7.68 (m, 1H, CONH), 7.10-7.36 (m, 9H, ArH), 4.88-5.60 (m, 4H, CH of Abu, CH2 of indoline, CONHCH2), 1.60-2.07 (m, 2H, CH2 of Abu), 1.05-1.13 (m, 3H, 3H, CH3 of Abu).

**EXAMPLE 6**

**Synthesis of 1-(2(S)-Aminobutyryl)-indoline-2(S)-carboxylic acid (2,2,2-trifluoroethyl)amide oxalate**

**[0078]** 10% Palladium on activated carbon (20 mg) was added to the solution of 1-(N-benzoylcarbonyl-(S)-aminobutyryl)-indoline-2(S)-carboxylic acid (90 mg, 0.19 mmol) in methanol (10 ml), and the mixture was hydrogenated at 40 psi for 2.5 hours. After the catalyst was removed by filtration through celite, oxalic acid (18 mg) was added to the filtrate, and the solution was evaporated to dryness under reduced pressure at a bath temperature less than 50°C. The pure white crystalline product was obtained by recrystallization from dried diethyl ether-methanol (40:1).

m.p. 148.5-149.0°C.

MS (Fab) m/z 330(MH+), 100, 463 (17), 335(55), 244(29).

1H NMR (CDCl3, 400 MHz) δ (ppm) 8.09-8.18, 7.60-7.68 (m, 1H, CONH), 7.10-7.36 (m, 9H, ArH), 4.88-5.60 (m, 4H, CH of Abu, CH2 of indoline, CONHCH2), 1.60-2.07 (m, 2H, CH2 of Abu), 1.05-1.13 (m, 3H, CH3 of Abu).

**Synthesis of 1-(2(S)-Aminobutyryl)-5-hydroxyindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl)amide trifluoroacetate**

**[0079]** 1-(3,3-Dimethylaminopropyl)-3-ethylcarbodiimide methiodide (2.98 g, 11 mmol) was added to a cold solution (0°C) of 5-benzoylindole-2(R/S)-carboxylic acid methylester (2.83 g, 10 mmol) and N-(t-butoxycarbonyl)-(S)-aminobutyric acid (0.203 g, 11 mmol) in dichloromethane (20 ml) under nitrogen. The mixture was stirred at room temperature...
1-(N-t-Butoxycarbonyl-2(S)-aminobutyryl)-5-benzylxoyindoline-2(R/S)-carboxylic acid

[0080] To a solution of 1-(N-t-butoxycarbonyl-2(S)-aminobutyryl)-5-benzylxoyindoline-2(R/S)-carboxylic acid methylester (2.75 g, 5.76 mmol) in methanol (20 mL), was added the water solution of sodium hydroxide (0.46 g, 11.52 mmol) under nitrogen at 10-15°C. The solution was stirred at room temperature for fourteen hours, then poured into dichloromethane and washed with potassium hydrogen sulphate solution, water. The organic layer was separated and dried over magnesium sulphate, solvent removal gave a yellow foam which was pure enough for the next step. MS (FAB) m/z 477(MNa+), 455 (MH+, 28), 399(40), 269(94), 178(31), 57(100)

1-(N-t-Butoxycarbonyl-2(S)-aminobutyryl)-5-benzylxoyindoline-2(R/S)-carboxylic acid (2,2,2-trifluoro)ethylamide

[0081] Triethylamine (4.9 mL, 33 mmol) was added to the solution of 1-(N-t-butoxycarbonyl-2(S)-aminobutyryl)-5-benzylxoyindoline-2(R/S)-carboxylic acid (2.6 g, 5.72 mmol) and 2,2,2-trifluoroethylamine hydrochloride (1.55g, 11.4 mmol) in dried dichloromethane (50 mL) at 0°C under nitrogen, followed by bis[2-oxo-3-oxazolidinyl]phosphinic chloride (2.902 g, 11.4 mmol). The temperature was allowed to rise to room temperature and the mixture was stirred at room temperature for twenty-four hours, then filtered. The filtrate was concentrated under vacuum to give a brown solid which was purified by column chromatography (silica gel, 8:2 petroleum spirit: diethyl ether) to provide a white solid as the desired product. MS (FAB) m/z 536(MH+, 26), 535(34), 350(64), 259(67), 91(89), 57(85)

1-(N-t-Butoxycarbonyl-2(S)-aminobutyryl)-5-hydroxyindoline-2(R/S)-carboxylic acid 2,2,2-trifluoroethylamide

[0082] A mixture of 1-(N-t-butoxycarbonyl-2(S)-aminobutyryl)-5-hydroxyindoline-2(R/S)-carboxylic acid 2,2,2-trifluoroethylamide (0.9 g, 1.68 mmol) and palladium on activated carbon (0.1 g, 10% wet) in ethyl acetate (20 mL) was hydrogenated under 30 psi hydrogen at room temperature overnight. Then the catalyst was removed by filtration over celite, and the filtrate was evaporated to provide a white solid.

MS (FAB) m/z 468(MNa+, 23), 445 (MH+, 13), 346 (31), 260 (88), 134 (100) 1HNMR (CDCl3, 300 MHz) δ (ppm) 8.30-8.35 (m, 1H, CONH). 7.50-7.90 (m, 1H, ArH), 6.40-6.73 (m, 2H, ArH), 5.20-5.52 (m, 2H, OH, H2 of indoline), 4.80-5.05 (m, 1H, NH of Abu), 3.70-4.20 (m, 3H, CH2CF3, CH of Abu), 3.00-3.55 (m, 2H, H3 of indoline), 0.80-2.00 (m, 14H, CH2 of Abu, t-Bu, CH3 of Abu).

1-(2(S)-Aminobutyryl)-5-hydroxyindoline-2(R/S)-carboxylic acid (2, 2, 2-trifluoro)ethylamide trifluoroacetate

[0083] Trifluoroacetic acid (0.8 mL) was added dropwise to the solution of 1-(N-t-butoxycarbonyl-2(S)-aminobutyryl)-5-hydroxyindoline-2(R/S)-carboxylic acid (200 mg, 0.44 mmol) in dichloromethane (1 mL) in an ice-water bath under nitrogen. This solution was stirred at 0-5°C until gas evolution ceased, then evaporated to dryness under vacuum below 45°C, and the residue was treated with dried diethyl ether to give a brown foam.

m.p. 76-88°C

MS (FAB) m/z 691 (2MH+, 7), 346 (MH+, 100), 261 (31), 154(27), 58(64)

1HNMR (DMSO-d6, 400 MHz) δ (ppm) 9.00-9.20, 8.7-8.85 (m, 1H, CONH). 8.18-8.40 (m, 2H, acidic H), 7.92, 7.84 (d, 1H, J= 9 Hz, ArH), 6.5-6.75 (m, 2H, ArH), 5.2-5.3, 5.0-5.1 (m, 1H, H2 of indoline), 3.35-4.10 (m, 5H, CH2CF3, OH, CH of Abu, one H3 of indoline), 2.75-3.05 (m, 1 H, one H3 of indoline), 1.55-2.05(m, 2H, CH2 of Abu), 1.01, 0.95, 0.87 (3t, 3H, J=7.3 Hz, CH3 of Abu).

IR (KBr disc) cm-1 3291, 3090, 2970(broad, m) (N-H, O-H); 1674(vs), 1675(vs) (C=O); 1620(w), 1490(m) (C=C); 1275 (vs), 1160(s) (C-O, C-N, C-F).

Elemental Analysis: calculated for C18H18F3N3O3.1.8CF3COOH: C, 40.58; H, 3.62; N, 7.63%. Found: C, 40.29; H, 3.70; N, 7.63 %.
EXAMPLE 7

Synthesis of 1-(2(S)-aminobutyryl)-4-chloroindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl)amide trifluoroacetate

Methyl azidoacetate

[0084] A solution of methyl bromoacetate (150 g, 0.901 mol) in dry acetonitrile (800 ml) was treated with sodium azide (58.57 g, 0.901 mol) under nitrogen and the mixture was heated for 20 hours at reflux. After cooling, water (150 ml) was added and the mixture was stirred for half an hour. The top layer was separated and the bottom layer was treated with salt and extracted with diethyl ether. The organic phases were combined and solvent removed in vacuum at a bath temperature not exceeding 50°C to give a yellow oil which was used for the next step without further purification.

\[ ^1\text{H NMR (CDCl}_3\text{, }200 \text{ MHz)} \delta (\text{ppm}) \text{ 9.06-9.16 (m, 1H, ArCH=), 7.24-7.43 (m, 4H, ArH), 3.93 (s, 3H, OCH}_2\text{)} \]

MS (FAB) m/z 210 (MH+ 100).

Methyl 2-azido-3-(2-chlorophenyl)propenoate

[0085] Sodium pieces (3.678 g, 160 mmol) were added in portions to methanol (200 ml) over a 30 minute period. The resulting solution was cooled in a dry ice/acetone bath to -18°C and then over one hour a mixture of 2-chlorobenzaldehyde (4.832 g, 40 mmol) and methyl azidoacetate (160 mmol) was added at a rate that maintained the temperature below -15°C. After three hours, the solution was stored at 5°C for two days to give crystalline material which was collected by filtration and washed with cold hexane to give pure product as a yellow crystals.

\[ ^1\text{H NMR (CDCl}_3\text{, }200 \text{ MHz)} \delta (\text{ppm}) \text{ 8.15-8.20 (m, 1H, ArCH=), 7.24-7.43 (m, 4H, ArH), 3.93 (s, 3H, OCH}_2\text{)} \]

MS (FAB) m/z 212 (MH+ 100).

4-Chloroindole-2-carboxylic acid methyl ester

[0086] Methyl 2-azido-3-(2-chlorophenyl)-propenoate (3.566 g, 144 mmol) was suspended in toluene (800 ml) and the mixture was heated at reflux for three hours, then cooled and allowed to stir at room temperature overnight. A yellow crystalline material was obtained by filtration and recrystallised from hexane. After column chromatography on silica gel using dichloromethane as eluent. A yellow oil was obtained.

\[ ^1\text{H NMR (CDCl}_3\text{, }200 \text{ MHz)} \delta (\text{ppm}) \text{ 9.06-9.16(m, 1H, H-N), 7.18-7.40 (m, 4H, H-Ar), 3.98(s, 3H, OCH}_2\text{)} \]

4-Chloroindole-2(R/S)-carboxylic acid methyl ester

[0087] 4-Chloroindole-2-carboxylic acid methyl ester (0.8 g, 3.8 mmol) and magnesium turnings (0.37 g, 15.2 mmol) were suspended in dried methanol (50 ml). This mixture was stirred at 5 to 10°C under nitrogen for 3 hours, then poured into dichloromethane (200 ml), and washed with saturated ammonium chloride solution. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (3 x 100 ml). The combined organic layers were dried over sodium sulphate and evaporated. A brown solid was obtained. After column chromatography on silica gel using dichloromethane as eluent. A yellow oil was obtained.

\[ ^1\text{H NMR (CDCl}_3\text{, }400 \text{ MHz)} \delta (\text{ppm}) \text{ 8.99-9.05(m, 2H, ArH), 6.58 (m, 1 H, ArH), 4.53-4.62(m, 1 H, NH of indoline), 4.42-4.46 (m, 1H, NCHCO of indoline), 3.76 (s, 3H, OCH}_2\text{}, 3.31-3.42 (m, 2H, CH}_2\text{ of indoline).} \]

1-(N-t-Butoxycarbonyl-2(S)-aminobutyryl)-4-chloroindoline-2(R/S)-carboxylic acid methyl ester

[0088] To a solution of 4-chloroindole-2(R/S)-carboxylic acid methyl ester (0.41 g, 1.94 mmol) and N-t-butoxycarbonyl-2(S)-aminobutyric acid (0.47 g, 2.33 mmol) dissolved in dried dichloromethane (10 ml) under nitrogen at 10°C, was added diisopropylcarbodiimide (0.36 ml, 2.33 mmol). The mixture was stirred at room temperature for 24 hours, then filtered. The filtrate was evaporated under vacuum to afford a brown solid which was purified by column chromatography on silica gel using 20:1 dichloromethane: diethyl ether as eluent. A white foam was obtained which was the mixture of two diastereomers .

\[ ^1\text{H NMR (CDCl}_3\text{, }400 \text{ MHz)} \delta (\text{ppm}) \text{ 8.06-8.17(dd, 1H, ArH), 7.04-7.27 (m, 2H, ArH), 4.94-5.41 (m, 2H, NCHCO of indoline, NH of Abu), 4.27-4.59 (m, 1H, CH of Abu), 3.79, 3.16 (2S, 3H, OCH}_3\text{), 0.87-2.0 (m, CH}_2\text{ of Abu, t-Bu, CH}_3\text{ of Abu).} \]
ter (0.38g, 0.96 mmol) in methanol (10 ml), was added sodium hydroxide (0.046g, 1.15 mmol) in water (4 ml). The solution was stirred at 5 to 10°C for 4 hours. The mixture was poured into dichloromethane (20 ml), and washed with cold potassium hydrogen sulphate (3 x 20 ml), and water (20 ml). The organic layer was dried over sodium sulphate, and evaporated to provide a white foam which was pure enough for the next step.

\[ \text{MS (Fab) m/z 486 (MNa}^+ \text{, 36), 330(35), 189(30), 145(100) 89(60)} \]

1HNMR (CDCl\textsubscript{3}, 400 MHz) \( \delta \) (ppm) 8.16 (2d, 1 H, ArH), 7.06-7.27 (m, 2H, ArH), 4.80-6.20 (m, COOH overlap), 5.68-5.70 (m, 1H, NCHCO of indoline), 5.06-5.09 (m, 1H, NH of Abu), 4.66-4.86 (m, 1H, CH of Abu), 4.20-4.30, 3.56-3.75 (m, 2H, CH\textsubscript{2} of indoline), 0.84-2.05 (m, 14H, CH\textsubscript{2} of Abu, t-Bu, CH\textsubscript{3} of Abu).

1-(N-t-Butoxycarbonyl-2(S)-aminobutyryl)-4-chloroindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl)amide

[0090] 1-(N-t-Butoxycarbonyl-2(S)-aminobutyryl)-4-chloroindoline-2(R/S)-carboxylic acid (0.2g, 0.52 mmol) and 2,2,2-trifluoroethylamine hydrochloride (0.142g, 1.0 mmol) were dissolved in dried dichloromethane (10 ml) under nitrogen at 0°C, and triethylamine (0.44 ml, 3 mmol) was added followed by bis(2-oxo-3-oxazolidinyl)phosphinic chloride (0.265g, 1.0 mmol). The temperature was allowed to rise to room temperature and the mixture was stirred at room temperature for 24 hours, then filtered. The filtrate was concentrated under vacuum to give a brown solid which was columned on silica gel using 95:5 dichloromethane:diethyl ether as eluent to provide a white solid as the desired product.

\[ \text{MS (Fab) m/z 486(MNa}^+ \text{, 25), 408(20), 364(30), 280(35), 152(100)} \]

1HNMR (CDCl\textsubscript{3}, 400 MHz) \( \delta \) (ppm) 7.92-8.30 (m, 1H, CONH), 6.85-7.55 (m, 3H, ArH), 4.85-5.50 (m, 2H, NCHCO of indoline and NH of Abu), 3.18-4.15 (m, 5H, CH of Abu, CH\textsubscript{2} of indoline, CH\textsubscript{2}CF\textsubscript{3}), 1.44-2.00 (m, 2H, CH\textsubscript{2} of Abu), 1.44 (s, 9H, t-Bu), 0.87-1.39 (m, 3H, CH\textsubscript{3} of Abu).

1-(2(S)-Aminobutyryl)-4-chloroindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl)amide trifluoroacetate

[0091] 1-(N-t-Butoxycarbonyl-2(S)-aminobutyryl)-4-chloroindoline-2(R/S)-carboxylic acid (70 mg, 0.15 mmol) was dissolved in dichloromethane (1 ml) in an ice-water bath, and trifluoroacetic acid (1 ml) was added under nitrogen. The solution was stirred at 0 to 5°C until gas evolution ceased. The solution was evaporated to dryness in vacuo and the residue was treated with dried diethyl ether. A white foam was obtained after column chromatography on flash silica gel by using 20:1 dichloromethane: methanol as eluent.

m.p. 104-106°C.

\[ \text{MS (Fab) m/z 386(MNa}^+ \text{, 40), 364(MH}^+ \text{, 100), 152(60).} \]

1HNMR (DMSO-d\textsubscript{6}, 400 MHz) \( \delta \) (ppm) 9.10-9.26 (m, 1H, CONH), 8.02-8.10 (m, 1H, ArH), 7.08-7.40 (m, 2H, ArH), 5.25-5.40 (m, 1H, NCHCO of indoline), 2.96-4.10 (m, 5H, CH\textsubscript{2}CF\textsubscript{3}, CH of Abu, CH\textsubscript{2} of indoline, H\textsubscript{2}O), 1.60-1.90 (m, 2H, CH\textsubscript{2} of Abu), 0.95, 0.84(2t, 3H, CH\textsubscript{3} of Abu).

IR (KBr) cm\textsuperscript{-1} 3370 (broad, w) (N-H, O-H); 1730 (vs), 1670 (vs), 1650(m) (C=O); 1590(s) 1470(m), (C=C); 1205(s), 1162 (vs), 1130(s) (C-C, C-N, C-F).

Elemental Analysis: calculated for C\textsubscript{17}H\textsubscript{17}ClF\textsubscript{3}N\textsubscript{3}O\textsubscript{2}, 1.2CF\textsubscript{3}COOH, 0.5H\textsubscript{2}O C 41.01, H 3.80, N 8.25%, found C 40.92, H 3.81, N 8.10 %.

EXAMPLE 8

Synthesis of 1-(2(S)-aminobutyryl)-4-fluoroindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl)amide trifluoroacetate

4-Fluoroindole-2-carboxylic acid

[0092] To a mixture of potassium ethoxide (5.317g, 63mmol) in diethyl ether (250 ml), ethyl oxalate (8.65 ml, 63 mmol) was added. After the solid ethoxide disappeared, 2-fluoro-6-nitrotoluene (10g, 63.18 mmol) in diethyl ether (20 ml) was added, and the mixture was stirred at 35 to 38°C for eighteen hours. Water (200 ml) was added, and the aqueous layer separated from the ether layer. The deep red aqueous solution was washed with ether (2 x 30 ml) to remove the unchanged starting materials and acidified with a slight excess of hydrochloric acid, then the aqueous layer was extracted with ethyl acetate (3 x 100 ml). The combined ethyl acetate layers were evaporated and a brown solid was obtained which gave a yellow solid after recrystallization from acetic acid. This yellow solid was dissolved in ammonia (70 ml, d=0.88 diluted to 100 ml with water), then a hot solution of ferrous sulphate (90 g of hydrated crystals in 100 ml of water) added, and the mixture was stirred on a water bath for an hour. After cooling, the black sludge of ferric hydroxide was filtered off and washed well with warm water containing a little ammonia until a test portion gave only a faint milkiness on acidification. The filtration and washings were concentrated, the solution acidified and extracted with ethyl acetate. The organic layer was concentrated to give a brown solid as the desired product.
4-Fluoroindole-2-carboxylic acid methyl ester

[0093] 4-Fluoroindole-2-carboxylic acid (0.65g, 3.40 mmol) was dissolved in methanol (50 ml), and 4-toluenesulfonyl acid (1.4g, 7.36 mmol) was added under nitrogen. The solution was stirred at reflux for 24 hours. Most of the methanol was removed by evaporation, and the residue was dissolved in dichloromethane (100 ml), washed with saturated sodium carbonate, and the organic layer was separated. The aqueous layer was extracted with dichloromethane (3 x 50 ml). The combined organic layers were washed with water, dried over sodium sulphate, and evaporated to yield a yellow crystalline material.

MS (EI) m/z 193(M+, 65), 161(100), 133(50), 107(35)

1HNMR (CDCl₃, 200 MHz) δ (ppm) 7.90-8.12 (m, 1H, NH of indole), 7.20-7.30 (m, 2H, ArH), 6.76-6.85 (m, 1H, ArH), 3.95 (s, 1H, OCH₃)

4-Fluoroindoline-2(R/S)-carboxylic acid methyl ester

[0094] 4-Fluoroindoline-2-acetic acid methyl ester (0.52g, 2.7 mmol) and magnesium turnings (0.136g, 5.6 mmol) were suspended in dried methanol (30 ml). This mixture was stirred at 5 to 10°C under nitrogen for 3 hours, then poured into dichloromethane (100 ml), and washed with saturated ammonium chloride solution. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (3 x 40 ml). The combined organic layers were dried over sodium sulphate and evaporated. A brown solid was obtained. After column chromatography on silica gel using dichloromethane as eluent, a reddish oil was obtained.

MS (EI) m/z 195(M+, 17), 172(20), 136(100), 109(40)

1HNMR (CDCl₃, 200 MHz) δ (ppm) 7.01-7.03 (m, 1H, H-Ar), 6.42-6.50 (m, 2H, ArH), 4.42-4.58 (m, 2H, NH and NCHCO of indoline), 3.78 (s, 3H, OCH₃), 3.39-3.41 (m, 2H, CH₂ of indoline).

1-(N-t-Butoxycarbonyl-2(S)-aminobutyryl)-4-fluoroindoline-2(R/S)-carboxylic acid methyl ester

[0095] To a solution of 4-fluoroindoline-2(R/S)-carboxylic acid methyl ester (0.43g, 2.205 mmol) and N-t-butoxycarbonyl-2-(S)-aminobutyric acid (0.47g, 2.33 mmol) dissolved in dried dichloromethane (10 ml) under nitrogen at 10°C, was added diisopropylcarbodiimide (0.36 ml, 2.33 mmol). The mixture was stirred at room temperature for 24 hours, then filtered. The filtrate was evaporated under vacuum to afford a brown solid which was pure enough for the next reaction.

MS (EI) m/z 381 (M+), 307(10), 195(80), 136(100), 57(96)

1HNMR (CDCl₃, 200 MHz) δ (ppm) 7.90-8.12 (2d, 1H, ArH), 7.10-7.20 (m, 1H, ArH), 6.70-7.00 (m, 1H, ArH), 4.90-5.50 (m, 2H, NCHCO of indoline and NH of Abu), 4.10-4.45 (m, 1H, CH of Abu), 3.80, 3.72 (2s, 3H, OCH₃), 3.37-3.65, 3.10-3.25 (m, 2H, CH₂ of indoline), 1.50-1.95 (m, 2H, CH₂ of Abu), 1.45 (s, 9H, t-Bu), 0.90-1.30 (m, 3H, CH₃ of Abu).

1-(N-t-Butoxycarbonyl-2(S)-aminobutyryl)-4-fluoroindoline-2(R/S)-carboxylic acid

[0096] To the solution of 1-(N-t-butoxycarbonyl-2(S)-aminobutyryl)-4-fluoroindoline-2(R/S)-carboxylic acid methyl ester (0.27g, 0.71 mmol) in methanol (10 ml), was added sodium hydroxide (0.028g, 0.71 mmol) in water (4 ml). The solution was stirred at 5 to 10°C for 4 hours. The mixture was poured into dichloromethane (20 ml), and washed with cold potassium hydrogen sulphate (3 x 20 ml), and water (20 ml). The organic layer was dried over sodium sulphate, and evaporated to provide a white foam which was pure enough for the next reaction.

MS (Fab) m/z 389(MNa+, 100), 311 (60), 182(55), 136(52), 136(52), 57(75)

1HNMR (CDCl₃, 400 MHz) δ (ppm) 7.92-8.05 (m, 1H, ArH), 6.30-7.28 (m, 3H, ArH, COOH), 5.60-5.75 (dd, 1H, NCHCO of indoline), 5.03-5.20 (m, 1H, NH of Abu), 4.62-4.74 (m, 1H, CH of Abu), 3.25-3.65 (m, 2H, CH₂ of indoline), 0.85-2.05 (m, 14H, CH₂ of Abu, t-Bu, CH₃ of Abu).

1-(N-t-Butoxycarbonyl-2(S)-aminobutyryl)-4-fluoroindolene-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl)amide

[0097] 1-(N-t-Butoxycarbonyl-2(S)-aminobutyryl)-4-fluoroindolene-2(S)-carboxylic acid (0.12g, 0.32 mmol) and 2,2,2-trifluoroethylamine hydrochloride (0.136g, 1.0 mmol) were dissolved in dried dichloromethane (10 ml) under nitrogen at 0°C, and triethylamine (0.44 ml, 3 mmol) was added followed by bis(2-oxo-3-oxazolidinyl)phosphinic chloride (0.265g, 1.0 mmol). The temperature was allowed to rise to room temperature and the mixture was stirred at room temperature for 24 hours, then filtered. The filtrate was concentrated under vacuum to give a brown solid. A white solid was obtained by column chromatography on silica gel using 7:3 petroleum spirit: ethyl acetate as eluent followed by recrystallization from diethyl ether.
10
25
30
40
50
1-(2-S)-Aminobutyryl)-4-fluoroindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl)amide trifluoroacetate

[0098] 1-(N-t-Butoxycarbonyl-2(S)-aminobutyryl)-4-fluoroindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl)amide (80 mg, 0.179 mmol) was dissolved in dichloromethane (1 ml) in an ice-water bath, and trifluoroacetic acid (0.8 ml) was added under nitrogen. The solution was stirred at 0 to 5°C until gas evolution ceased. The solution was evaporated to provide a white foam which was pure enough for the next step.

[0100] To a solution of 5-methoxyindoline-2(R/S)-carboxylic acid methyl ester (1.5g, 7.23 mmol) and N-t-butoxycarbonyl-2(S)-aminobutyric acid (1.62g, 7.96 mmol) dissolved in dichloromethane (15 ml) under nitrogen at 10°C, was added diisopropylcarbodiimide (1.00 ml, 7.96 mmol). The mixture was stirred at room temperature for 24 hours, then filtered. The filtrate was evaporated under vacuum to afford a brown solid which was purified by column chromatography on silica gel using dichloromethane:methanol as eluent. A white foam was obtained after column chromatography on flash silica gel by using 20:1 dichloromethane:methanol as eluent.

EXAMPLE 9

5-Methoxyindoline-2(R/S)-carboxylic acid methyl ester

[0099] 5-Methoxyindole-2-carboxylic acid ethyl ester (2g, 9.13 mmol) and magnesium turnings (0.432g, 18 mmol) were suspended in dried methanol (30 ml). This mixture was stirred at 5 to 10°C under nitrogen for 3 hours, then poured into dichloromethane (200 ml), and washed with saturated ammonium chloride solution. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (3 x 100 ml). The combined organic layers were dried over sodium sulphate and evaporated. A brown solid was obtained. After column chromatography on silica gel using dichloromethane as eluent, a brown solid was obtained.

[0101] To the solution of 1-(N-t-butoxycarbonyl-2(S)-aminobutyryl)-5-methoxyindoline-2(R/S)-carboxylic acid methyl ester (1.3g, 3.3 mmol) in methanol (20 ml), was added sodium hydroxide (0.265g, 6.6 mmol) in water (10 ml). The solution was stirred at 5 to 10°C for 4 hours. The mixture was poured into dichloromethane (40 ml), and washed with cold potassium hydrogen sulphate (3 x 20 ml), and water (20 ml). The organic layer was dried over sodium sulphate, and evaporated to provide a white foam which was pure enough for the next step.
1-(N-Butoxycarbonyl-2(S)-aminobutyryl)-5-methoxyindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl) amide

**[0102]** 1-(N-Butoxycarbonyl-2(S)-aminobutyryl)-5-methoxyindoline-2(S)-carboxylic acid (0.38g, 1 mmol) and 2,2,2-trifluoroethylamine hydrochloride (0.271 g, 2.0 mmol) were dissolved in dried dichloromethane (20 ml) under nitrogen at 0°C, and triethylamine (0.7 ml, 5 mmol) was added followed by bis(trifluoroethyl)amine hydrochloride (0.271 g, 2.0 mmol). The temperature was allowed to rise to room temperature and the mixture was stirred at room temperature for 24 hours, then filtered. The filtrate was concentrated under vacuum to give a brown solid which was columned on silica gel using 7:2 dichloromethane as eluent, a brown solid was obtained. After column chromatography on silica gel using 7:2 dichloromethane as eluent, a brown solid was obtained. After column chromatography on silica gel using 7:2 dichloromethane as eluent, a brown solid was obtained. After column chromatography on silica gel using 7:2 dichloromethane as eluent, a brown solid was obtained. After column chromatography on silica gel using 7:2 dichloromethane as eluent, a brown solid was obtained.

**[0103]** 1-(N-Butoxycarbonyl-2(S)-aminobutyryl)-5-methoxyindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl)amide trifluoroacetate

**[0104]** 5-Trifluoromethoxyindole-2-carboxylic acid ethyl ester (2.25g, 8.24 mmol) and magnesium turnings (0.50g, 21.7 mmol) were suspended in dried methanol (60 ml). This mixture was stirred at 5 to 10°C under nitrogen for 3 hours, then poured into dichloromethane (200 ml), and washed with saturated ammonium chloride solution. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (3 x 100 ml). The combined organic layers were dried over sodium sulphate and evaporated. A brown solid was obtained. After column chromatography on silica gel using dichloromethane as eluent, a brown solid was obtained.

**[0105]** To a solution of 5-trifluoromethoxyindole-2(R/S)-carboxylic acid methyl ester (1.95g, 7.47 mmol) and N-butoxycarbonyl-2(S)-aminobutyric acid (1.52g, 7.47 mmol) dissolved in dried dichloromethane (15 ml) under nitrogen...
at 10°C, was added diisopropylcarbodiimide (1.00 ml, 7.96 mmol). The mixture was stirred at room temperature for 24 hours, then filtered. The filtrate was evaporated under vacuum to afford a brown oil which was purified by column chromatography on silica gel first by using 95:5 dichloromethane: diethyl ether as eluent, then another column on silica gel by using 7:3 petroleum spirit: diethyl ether. A yellow foam was obtained which was the mixture of two diastereomers. MS (Fab) m/z 447 (MH+•, 31), 391 (80), 347 (56), 261 (100), 202 (99)  

1H NMR (CDCl3, 300 MHz) δ (ppm) 8.15-8.32 (2d, 1H, ArH), 7.05-7.15 (m, 2H, ArH), 5.25-5.45 (m, 1H, NCHCO of indoline), 4.90-5.10 (m, 1H, NH of Abu), 4.15-4.45 (m, 1H, CH of Abu), 3.74, 3.80, 3.82 (3s, 3H, COOCH3), 3.30-3.70 (m, 2H, CH2 of indoline), 1.65-2.05 (m, 2H, CH2 of Abu), 1.46, 1.42 (2s, 9H, t-Bu), 0.80-1.20 (m, 3H, CH3 of Abu).

1-(N-t-Butoxycarbonyl-2-(S)-aminobutyryl)-5-trifluoromethoxyindoline-2(R/S)-carboxylic acid

[0106] To the solution of 1-(N-t-butoxycarbonyl-2-(S)-aminobutyryl)-5-trifluoromethoxyindoline-2(R/S)-carboxylic acid methyl ester (1.0g, 2.24 mmol) in methanol (15 ml), was added sodium hydroxide (0.134g, 3.36 mmol) in water (10 ml). The solution was stirred at 5 to 10°C for 4 hours. The mixture was poured into dichloromethane (40 ml), and washed with cold potassium hydrogen sulphate (3 x 20 ml), and water (20 ml). The organic layer was dried over sodium sulphate, and evaporated to provide a white foam which was pure enough for the next step. MS (Fab) m/z 455(MNa+•, 100), 377(35), 248(30), 202(40), 57(61)  

1H NMR (CDCl3, 400 MHz) δ (ppm) 8.15-8.30 (2d, 1H, ArH), 7.00-7.70 (m, 3H, COOH, ArH), 5.70-5.76, 5.18-5.23 (m, 1H, NCHCO of indoline), 5.40-5.50, 5.00-5.10 (m, 1H, NH of Abu), 4.65-4.75, 4.20-4.30 (m, 1H, CH of Abu), 3.20-3.70 (m, 2H, CH2 of indoline), 1.60-2.00 (m, 2H, CH2 of Abu), 1.45, 1.42, 1.37 (3s, 9H, t-Bu), 0.90-1.15 (m, 3H, CH3 of Abu).

1-(N-t-Butoxycarbonyl-2-(S)-aminobutyryl)-5-trifluoromethoxyindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl)amide

[0107] 1-(N-t-Butoxycarbonyl-2-(S)-aminobutyryl)-5-trifluoromethoxy-indoline-2(S)-carboxylic acid (0.432g, 1 mmol) and 2,2,2-trifluoroethylamine hydrochloride (0.271g, 2 mmol) were dissolved in dried dichloromethane (20 ml) under nitrogen at 0°C, and triethylamine (0.7ml, 5 mmol) was added followed by bis(2-oxo-3-oxazolidinyl)phosphinic chloride (0.509g, 2 mmol). The temperature was allowed to rise to room temperature and the mixture was stirred at room temperature for 24 hours, then filtered. The filtrate was concentrated under vacuum to give a brown solid which was columned on silica gel using 8: 1 (petroleum ether: ether) as eluent to provide an off-white foam which was pure enough for the next step. MS (Fab) m/z 514(MH+•, 25), 458(35), 414(35), 328(65), 202(100), 57(85)  

1H NMR (CDCl3, 300 MHz) δ (ppm) 8.35-8.45 (m, 1H, CONH), 8.04-8.20, 7.50-7.60 (m, 1H, ArH), 6.90-7.20 (m, 2H, ArH), 4.80-5.55 (m, 2H, NCHCO of indoline, NH of Abu), 3.20-4.20 (m, 5H, CH2CF3, CH of Abu, CH2 of indoline), 1.55-2.00 (m, 2H, CH2 of Abu), 1.45 (s, 9H, t-Bu), 0.85-1.25 (m, 3H, CH3 of Abu).  

Elemental analysis : calculated for C21H25F3N2O5 C 49.13, H 4.91, N 8.18%, found C 49.20, H 4.83, N 8.11%

1-(2-(S)-Aminobutyryl)-6-trifluoromethoxyindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl)amide trifluoroacetate

[0108] 1-(N-t-Butoxycarbonyl-2-(S)-aminobutyryl)-5-trifluoromethoxyindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl)amide (260mg, 0.5 mmol) was dissolved in dichloromethane (2 ml) in an ice-water bath, and trifluoroacetic acid (0.8 ml) was added under nitrogen. The solution was stirred at 0 to 5°C until gas evolution ceased. The solution was evaporated to dryness in vacuo and the residue was treated with dried diethyl ether. A brown foam was obtained. MS (Fab) m/z 827(2MH+•, 5), 414 (MH+•, 100), 328(10), 202(15), 58(50)  

1H NMR (DMSO-d6, 400 MHz) δ (ppm) 9.20-9.35 (2t, 1H, CONH), 8.04-8.50 (m, 3H, acidic H), 8.19, 8.08 (d, 1H, ArH), 7.20-7.50 (m, 2H, ArH), 5.39-5.42, 5.19-5.93 (m, 1H, NCHCO of indoline), 3.50-4.10 (m, 4H, CH2CF3, CH of Abu, one CH2 of indoline), 2.90-3.20 (m, 1H, CH2 of Abu), 1.70-2.05 (m, 2H, CH2 of Abu), 1.04, 0.98, 0.90 (3t, 3H, CH3 of Abu).  

IR (KBr) cm⁻¹ 3463(broad, w) (N-H, O-H); 1688(vs), 1671 (vs) (C=O); 1620(w), 1486(m) (C=C); 1268(vs), 1209(vs), 1171(s) (C-O, C-N, C-F).  

Elemental Analysis: calculated for C16H17F4N3O3, 1.9CF3COOH, C 37.75, H 3.02, N 6.67% , found C 37.97, H 3.09, N 6.42 %.

1-[N-t-Butoxycarbonyl-2-(S)-aminobutyryl]-4.5-dichloroindoline-2-(S)-carboxylic acid methyl ester

[0109] This compound was prepared by the procedure described in Example 11. The (S)-isomer was separated by flash column chromatography on silica gel using petroleum ether: ether (7:3) as eluent.
1-[N-t-Butoxycarbonyl-2-(S)-aminobutyryl]-4,5-dichloroindoline-2-(S)-carboxylic acid

[0110] This compound was prepared from 1-(N-t-Butoxycarbonyl-2-(S)-aminobutyryl)-4,5-dichloroindoline-2-(S)-carboxylic acid methyl ester as described in Example 1.

1-[N-t-Butoxycarbonyl-2-(S)-aminobutyryl]-4,5-dichloroindoline-2-(S)-carboxylic acid 2,2,2-trifluoroethylamide

[0111] This compound was prepared from 1-(N-t-butoxycarbonyl-2-(S)-aminobutyryl)-4,5-dichloroindoline-2-(S)-carboxylic acid as described in Example 1.

1-[2-(S)-Aminobutyryl]-4,5-dichloroindoline-2-(S)-carboxylic acid-2,2,2-trifluoroethylamide trifluoroacetate

[0112] This compound was prepared from the above compound as described in Example 1.

MP: 92-108°C;
Element analysis: C 15.63 %, H 1.52 %, Cl 3.78 %, F 3.12 %, N 7.08 %;
Calculated: C 15.58 %, H 1.59 %, Cl 3.82 %, F 3.09 %, N 7.06 %

EXAMPLE 13

Synthesis of 1-[2-(S)-aminobutyryl]-5,6-dichloroindole-2-(S)-carboxylic acid 2,2,2-trifluoroethylamide trifluoroacetate

Ethyl 5,6-dichloroindole-2-carboxylate

[0113] This compound was prepared from 3,4-dichlorobenzylhydrazine hydrochloride and ethyl -pyruvate using the procedure described in Example 11.

5,6-Dichloro indole 2-carboxylic acid methyl ester

[0114] This compound was prepared from ethyl 5,6-dichloroindole-2-carboxylate as described in Example 11.

1-[N-t-Butoxycarbonyl-2-(S)-aminobutyryl]-5,6-dichloroindoline-2-(S)-carboxylic acid methyl ester

[0115] This compound was prepared from 5,6-dichloroindoline 2-carboxylic acid methyl ester as described in Example 11.

1-[N-t-Butoxycarbonyl-2-(S)-aminobutyryl]-5,6-dichloroindoline-2-(S)-carboxylic acid

[0116] This compound was prepared from 1-(N-t-butoxycarbonyl-2-(S)-aminobutyryl)-5,6-dichloroindoline-2-(S)-carboxylic acid methyl ester as described in Example 1.

1-[N-t-Butoxycarbonyl-2-(S)-aminobutyryl]-5,6-dichloroindoline-2-(S)-carboxylic acid 2,2,2-trifluoroethylamide

[0117] This compound was prepared from 1-(N-t-butoxycarbonyl-2-(S)-aminobutyryl)-5,6-dichloroindoline-2-(S)-carboxylic acid as described in Example 1.

1-[2-(S)-Aminobutyryl]-5,6-dichloroindoline-2-(S)-carboxylic-acid-2,2,2-trifluoroethylamide trifluoroacetate

[0118] This compound was prepared from the above compound as described in Example 1.

MP: 145-158°C;
Element analysis: C 15.56 %, H 1.48 %, Cl 3.76 %, F 3.08 %, N 7.04 %;
Found: C 39.09 %, H 3.29 %, N 7.53 %;
Calculated: C 39.06 %, H 3.24 %, N 7.85 %
EXAMPLE 14

Synthesis of 1-[2-(S)-aminobutyryl]-benz[e]indoline-2-(S)-carboxylic acid 2,2,2-trifluoroethylamide trifluoroacetate

Methyl 2-azido-3-(1-naphthyl) propionate

[0119] 1-Naphthaldehyde (7 g, 44.87 mmol) and methyl azidoacetate (20.64 g, 179.5 mmol) were dissolved in 210 ml of methanol and cooled to -20°C. Then sodium methoxide (9.66 g, 25 % wt.) was added dropwise such that the temperature was kept below -10°C. After stirring at -15°C for 3 hours, the reaction mixture was kept in refrigerator (4°C) for 2 days to give the yellow crystalline product which was collected by filtration and washed with cooled hexane to afford pure product as a yellow crystalline solid (8 g, 70 %).

Methyl benz[e]indole-2-carboxylate

[0120] This compound was prepared from methyl 2-azido-3-(1-naphthyl)propionate as described in Example 7.

Methyl benz[e]indoline-2-carboxylate

[0121] This compound was prepared from methyl benz[e] indole-2-carboxylate as described in Example 11.

1-[N-t-Butoxycarbonyl-2-(S)-aminobutyryl]-benz[e]indoline-2-(S)-carboxylic acid methyl ester

[0122] This compound was prepared from methyl benz[e] indoline-2-carboxylate as described in Example 1. The (S)-isomer was obtained by recrystallization from a solvent mixture of dichloromethane, ether, hexane as well as methanol.

1-[N-t-Butoxycarbonyl-2-(S)-aminobutyryl]-benz[e]indoline-2-(S)-carboxylic acid

[0123] This compound was prepared from 1-(N-t-butoxycarbonyl)-2-(S)-aminobutyryl)-benz[e]-indoline-2-(S)-carboxylic acid methyl ester as described in Example 1.

1-[N-t-Butoxycarbonyl-2-(S)-aminobutyryl]-benz[e]indoline-2-(S)-carboxylic acid 2,2,2-trifluoroethylamide

[0124] This compound was prepared from 1-(N-t-butoxycarbonyl)-2-(S)-aminobutyryl)-benz[e]-indoline-2-(S)-carboxylic acid as described in Example 1. Element analysis: C_{24}H_{28}F_{3}N_{3}O_{4}. Found: C 60.24 %, H 5.79 %, N 8.64 %; Calculated: C 60.12 %, H 5.88 %, N 8.76 %; HPLC purity: 99.6 %

1-[2-(S)-Aminobutyryl]-benz[e]-indoline-2-(S)-carboxylic acid 2,2,2-trifluoroethylamide trifluoroacetate

[0125] This compound was prepared from the above compound as described in Example 1. MP: 64-78°C. Element analysis: C_{19}H_{20}F_{3}N_{3}O_{2}(CF_{3}COOH)1.7(CH_{3}COCH_{3})0.5. Found: C 47.73 %, H 4.04 %, N 6.81 %; Calculated: C 47.66 %, H 4.13 %. N 6.98 %

EXAMPLE 15

Synthesis of 1-[2-(S)-aminobutyryl]-5-O-sulfato-indoline-2-(R/S)-carboxylic acid butyl amide trifluoroacetate

1-[N-t-Butoxycarbonyl-2(S)-aminobutyryl]-5-benzyloxyindoline-2-(R/S)-carboxylic acid butyl amide

[0126] This compound was prepared from 1-(N-t-butoxycarbonyl)-2(S)-aminobutyryl)-5-benzyloxyindoline-2-(R/S)-carboxylic acid and butyl amine as described in Example 6.
1-[N-t-Butoxycarbonyl-2(S)-aminobutyryl]-5-hydroxyindoline-2-(R/S)-carboxylic acid butyl amide

[0127] This compound was prepared from 1-(N-t-butoxycarbonyl-2(S)-aminobutyryl)-5-benzoxindole-2-(R/S)-carboxylic acid butyl amide as described in Example 6.

1-[N-t-Butoxycarbonyl-2(S)-aminobutyryl]-5-O-triethylammonium-sulfate indole-2-(R/S)-carboxylic acid butyl amide

[0128] 1-(N-t-Butoxycarbonyl-2(S)-aminobutyryl)-5-hydroxyindoline-2-(R/S)-carboxylic acid butyl amide (70 mg, 0.17 mmol) was dissolved in the minimum volume of anhydrous pyridine (1.5 ml) required to effect complete solution. To this solution was added solid triethylamine-sulfur trioxide (152 mg, 0.84 mmol). After stirring at 0°C for 3 hours and room temperature for 2 days, the pyridine was removed by vacuum and the remaining solid was purified by preparative TLC using dichloromethane/methanol as eluent to afford 65 mg of the title product as a white crystalline solid.

MS[ESP](negative)=498 [M-NHEt3] (100 %)

1-[2(S)-Aminobutyryl]-4,5-dichloro-indole-2-(R/S)-carboxylic acid 2,2,2-trifluoroethylamide trifluoroacetate

[0129] This compound was prepared from the above compound as described in Example 1, using less excess trifluoroacetic acid and low reaction temperature (-10 to -5°C).

MP: 85-135°C;
Element analysis: C17H25N3O6S(CF3COOH)1.5(CH3COCH3)0.5,
Found: C 47.25 %, H 6.31 %, N 9.10 %;
Calculated: C 46.94 %, H 6.07 %, N 8.97 %;
HPLC purity: 99.3 % (55.53 %+43.8 %) (R+S isomer);
MS(FAB): 400[M+1](40 %), 422[M+Na](16 %)

EXAMPLE 16

Synthesis of 1-[2-(S)-aminobutyryl]-benz[e]-indoline-2-(S)-carboxylic acid butyl amide trifluoroacetate

1-[N-t-Butoxycarbonyl]-2-(S)-aminobutyryl]-benz[e]-indoline-2-(S)-carboxylic acid butyl amide

[0130] was prepared from 1-(N-t-butoxycarbonyl)-2-(S)-aminobutyryl]-benz[e]-indoline-2-(S)-carboxylic acid and butylamine as described in Example 14 and deprotected to give the title product as described in Example 1.

MP: 76-88°C;
Element analysis: C21H27N3O2[S(CF3COOH)1.5(CH3COCH3)0.5,
Found: C 55.32 %, H 5.46 %, N 7.56 %;
Calculated: C 55.33 %, H 5.74 %, N 7.59 %.
HPLC purity: 98.97 %

EXAMPLE 17

Synthesis of 1-[2-(S)-aminobutyryl]-4,5-dichloro-indole-2-(R/S)-carboxylic acid 2,2,2-trifluoroethylamide trifluoroacetate

1-[N-t-Butoxycarbonyl]-2-(S)-aminobutyryl]-4,5-dichloroindoline-2-(R/S)-carboxylic acid 2,2,2-trifluoroethylamide

[0131] This compound was prepared from 1-(N-t-butoxycarbonyl)-2-(S)-aminobutyryl]-4,5-dichloroindoline-2-(S/R)-carboxylic acid and butylamine as described in Example 1.

1-[2(S)-Aminobutyryl]-4,5-dichloroindoline-2-(R/S)-carboxylic acid-2,2,2-trifluoroethylamide trifluoroacetate

[0132] This compound was prepared from the above compound as described in Example 1.

MP: 68-78°C
Element analysis: C15H16Cl2F3N3O2(CF3COOH)1.5(CH3COCH3)0.3
Found: C 38.6 %, H 3.62 %, N 7.22 %;
Calculated: C 38.7 %, H 3.32 %, N 7.16 %.
MS(FAB): 398(M+), 32.5 %.
HPLC: 98.33 %.

EXAMPLE 18

Synthesis of 1-[2-(S)-aminobutyryl]-5-O-sulfato-indoline-2(R/S)-carboxylic acid trifluoroethylamide trifluoroacetate

1-[N-t-Butoxycarbonyl-2(S)-aminobutyryl]-5-benzyloxyindoline-2-(R/S)-carboxylic acid trifluoroethylamide

This compound was prepared from 1-(N-t-butoxycarbonyl-2(S)-aminobutyryl)-5-benzyloxyindoline-2-(R/S)-carboxylic acid and trifluoroethylamine as described in Example 15.

1-[N-t-Butoxycarbonyl-2(S)-aminobutyryl]-5-hydroxyindoline-2-(R/S)-carboxylic acid trifluoroethylamide

This compound was prepared from 1-(N-t-butoxycarbonyl-2(S)-aminobutyryl)-5-hydroxyindoline-2-(R/S)-carboxylic acid trifluoroethylamide as described in Example 15.

1-[N-t-Butoxycarbonyl-2(S)-aminobutyryl]-5-O-triethylammonium-sulfate indoline-2-(R/S)-carboxylic acid trifluoroethylamide

This compound was prepared from 1-(N-t-butoxycarbonyl-2(S)-aminobutyryl)-5-hydroxyindoline-2-(R/S)-carboxylic acid trifluoroethylamide as described in Example 15.

MS(EPS-negative): 524(M-NEt 3 H), 100 %

1-[2(S)-Aminobutyryl]-5-O-sulfato-indoline-2-(R/S)-carboxylic acid trifluoroethylamide trifluoroacetate

This compound was prepared from the above compound as described in Example 15.

MP: 145-160°C;
Element analysis: C 15 H 18 F 3 N 3 O 6 S(CF 3 COOH) 0.5(H 2 O) 0.5(CH 3 OH) 1.0,
Found: C 38.96 %, H 4.63 %, N 8.14 %;
Calculated: C 39.01 %, H 4.53 %, N 8.03 %;
HPLC purity: 99.4 % (68.35 %+31.2 %)(R+S isomer);
MS(FAB): 426[M+1](100 %).

EXAMPLE 19

Synthesis of 1-[2-(S)-aminobutyryl]-benz[f]-indoline-2-(S/R)-carboxylic acid 2,2,2-trifluoroethylamide trifluoroacetate hemi hydrate

2-(Trichloroacetyl)pyrrole

This compound was prepared from pyrrole as described in literature (J. Org. Chem. 1993 58, 26, 7246).

Ethyl pyrrole -2-carboxylate

This compound was prepared from 2-(trichloroacetyl) pyrrole as described in literature (J. Org. Chem. 1993, 58, 25, 7246).

2-[(5-Ethoxycarbonylpyrrole-3-yl)carbonyl] benzoic acid.

This compound was prepared from ethyl pyrrole-2-carboxylate as described in literature (J. Chem. Soc. Perkin Trans I 1988; 3005).

2-[(5-Ethoxycarbonylpyrrol-3-yl)methyl] benzoic Acid

This compound was prepared from 2-[(5-ethoxycarbonylpyrrole-3-yl)carbonyl] benzoic acid as described in

**Ethyl 4-[[2-hydroxymethyl]phenyl][methyl]-1H-pyrrole-2-carboxylate**

[0141] This compound was prepared from 2-[(5-ethoxycarbonyl)pyrrole-3-yl) methyl] benzoic acid as described in literature (J. Heterocyclic Chem. 1993, 30, 217).

**Ethyl 4-[[2-formyl][phenyl][methyl]-1H-pyrrole-2-carboxylate**

[0142] This compound was prepared from Ethyl 4-[[2-Hydroxymethyl][phenyl][methyl]-1H-pyrrole-2-carboxylate as described in literature (J. Heterocyclic Chem. 1993, 30, 217).

**Ethyl benz[f]indole 2-carboxylate**

[0143] This compound was prepared from ethyl 4-[[2-formyl][phenyl][methyl]-1H-pyrrole-2-carboxylate as described in literature (J. Heterocyclic Chem. 1993, 30, 217).

**Methyl benz[f]indoline 2-carboxylate**

[0144] This compound was prepared from ethyl benz[f]indole 2-carboxylate as described in Example 1.

1-[N-t-Butoxycarbonyl-2-(S)-aminobutyryl]-benz[f]indoline 2-(S)-carboxylic acid methyl ester

[0145] This compound was prepared from methyl benz[f] indoline 2-carboxylate as described in Example 1. The (S)-isomer was separated by column chromatography on silica gel.

1-[N-t-Butoxycarbonyl-2-(S)-aminobutyryl]-benz[f]indoline 2-(S)-carboxylic acid

[0146] This compound was prepared from the above compound as described in Example 1.

1-[N-t-Butoxycarbonyl-2-(S)-aminobutyryl]-benz[f]indoline 2-(S)-carboxylic acid 2,2,2-trifluoroethylamide

[0147] This compound was prepared from the above compound as described in Example 1.

1-[2-(S)-Aminobutyryl]-benz[f]indoline 2-(S)-carboxylic acid 2,2,2-trifluoroethylamide trifluoroacetate hemihydrate

[0148] This compound was prepared from the above compound as described in Example 1. MP: 102-114°C. Element analysis: C_{19}H_{20}F_{3}N_{3}O_{2}(CF_{3}CO_{2}H)1.2(H_{2}O)0.5(Et_{2}O)0.1, Found: C 49.34 %, H 4.19 %, N 7.54 %. Calculated: C 49.16 %, H 4.39 %, N 7.89 %. HPLC purity: 98.9 %. MS(FAB): 380(M+1), 64.4 %.

**EXAMPLE 20**

Synthesis of 1-[2-(S)-phenylalanyl]-5-Cl-indoline 2(F/S)-carboxylic acid 2,2,2-trifluoroethylamide trifluoroacetate

5-Chloro-indoline 2(R/S)-carboxylic acid methyl ester

[0149] This compound was prepared from ethyl 5-chloro indole carboxylate as described in Example 1.

1-[N-t-Butoxycarbonyl-2(S) phenylalanyl]-5-Cl indoline 2(R/S) carboxylic acid methyl ester

[0150] This compound was prepared from 5-chloro-indoline 2(R/S)-carboxylic acid methyl ester and N-t--Boc-phenyl alanine as described in Example 1.
1-[N-tButoxycarbonyl-2(S) phenylalanyl]-5-Cl indoline 2(R/S) carboxylic acid

[0151] This compound was prepared from 1-(N-t-butoxycarbonyl-2(S) phenylalanyl)-5-Cl indoline 2-(R/S) carboxylic acid methyl ester as described in Example 1.

1-[N-tButoxycarbonyl-2(S) phenylalanyl]-5-Cl indoline 2(R/S) carboxylic acid 2,2,2 trifluoroamide.

[0152] This compound was prepared from 1-(N-t-butoxycarbonyl-2(S) phenylalanyl)-5-Cl indoline 2(R/S) carboxylic acid as described in Example 1.

1-[2-(S)-phenylalanyl]-5-Cl indoline 2(R/S)-carboxylic acid 2,2,2 trifluoroethylamide trifluoroacetate

[0153] This compound was prepared from the above compound as described in Example 1.

MP: 71-80°C.

Element Analysis: C_{20}H_{19}ClF_{3}N_{3}O_{2}; 1.7

Found: C 45.39 %, H 3.39 %, N 6.66 %,

Calculated: C 45.36 %, H 3.37 %, N 6.78 %.

HPLC purity: 99.4 %.

EXAMPLE 21

Synthesis of 1-[2(S)-aminobutyryl]-4-methoxyindoline-2(S)-carboxylic acid (2,2,2-trifluoroethyl)amide trifluoroacetate

4-Methoxyindoline-2(S)-carboxylic acid methyl ester

[0154] This compound was prepared from methyl 4-methoxyindole-2-carboxylate as described in example 1.

1-[N-t-Butoxycarbonyl-2(S)-aminobutyryl]-4-methoxyindoline-2(S)-carboxylic acid methyl ester

[0155] This compound was prepared from 4-methoxyindoline-2(S)-carboxylic acid methyl ester as described for in example 1. However this time the filtrate was washed with water and the aqueous layer extracted with diethyl ether (3 × 15 ml). The combined organic layers were dried over anhydrous sodium sulphate and concentrated under reduced pressure to afford a colourless oil which was purified by column chromatography on silica gel using 20:1 dichloromethane: diethyl ether as eluent. A white foam was obtained after drying.

1-[N-t-Butoxycarbonyl-2(S)-aminobutyryl]-4-methoxyindoline-2(S)-carboxylic acid

[0156] This compound was prepared from 1-[N-t-butoxycarbonyl-2(S)-aminobutyryl]-4-methoxyindoline-2(S)-carboxylic acid methyl ester as described in example 1.

1-[N-t-Butoxycarbonyl-2(S)-aminobutyryl]-4-methoxyindoline-2(S)-carboxylic acid (2,2,2-trifluoroethyl)amide

[0157] This compound was prepared from 1-[N-t-butoxycarbonyl-2(S)-aminobutyryl]-4-methoxyindoline-2(S)-carboxylic acid as described in example 1.

1-[2(S)-Aminobutyryl]-4-methoxyindoline-2(S)-carboxylic acid (2,2,2-trifluoroethyl)amide trifluoroacetate

[0158] This compound was prepared from 1-[N-t-butoxycarbonyl-2(S)-aminobutyryl]-4-methoxyindoline-2(S)-carboxylic acid (2,2,2-trifluoroethyl)amide as described in example 1.

mp 125-149°C

Elemental analysis: C_{16}H_{20}F_{3}N_{3}O_{3}; 1.4(CF_{3}CO_{2}H)

Found: C 43.51 %, H 4.33 %, N 8.07 %

Calculated: C 43.51 %, H 4.16 %, N 8.10 %

HPLC purity: 97.5 % (S isomer)
EXAMPLE 22

Synthesis of 1-[2-glycyl]-5-chloroindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl)amide trifluoroacetate

5-Chloroindoline-2(R/S)-carboxylic acid methyl ester

[0159] This compound was prepared from ethyl 5-chloroindole-2-carboxylate as described in example 1. However this time 5-6 equivalence of magnesium turnings were used instead of 2-3 eq. of magnesium turnings.

1-[N-t-Butoxycarbonyl-2-glycyl]-5-chloroindoline-2(R/S)-carboxylic acid methyl ester

[0160] This compound was prepared from 5-chloroindoline-2(R/S)-carboxylic acid methyl ester and N-t-butoxycarbonylaminoacetic acid as described for in example 21. The product was purified by column chromatography on silica gel using 7:3 petroleum spirit:diethyl ether as eluent.

1-[N-t-Butoxycarbonyl-2-glycyl]-5-chloroindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl)amide

[0161] This compound was prepared from 1-[N-t-butoxycarbonyl-2-glycyl]-5-chloroindoline-2(R/S)-carboxylic acid methyl ester as described in example 1.

HPLC purity: 98.2 %

EXAMPLE 23

Synthesis of 1-[2-(S)-alanyl]-5-chloroindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl)amide hemitrifluoroacetate

5-Chloroindoline-2(R/S)-carboxylic acid methyl ester

[0164] This compound was prepared from ethyl 5-chloroindole-2-carboxylate as described in example 22.

1-[N-t-Butoxycarbonyl-2-(S)-alanyl]-5-chloroindoline-2(R/S)-carboxylic acid methyl ester

[0165] This compound was prepared from 5-chloroindoline-2(R/S)-carboxylic acid methyl ester and N-t-butoxycarbonyl-L-alanine as described in example 21.

1-[N-t-Butoxycarbonyl-2-(S)-alanyl]-5-chloroindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl)amide

[0166] This compound was prepared from 1-[N-t-butoxycarbonyl-2-(S)-alanyl]-5-chloroindoline-2(R/S)-carboxylic acid methyl ester as described in example 1.

[0167] This compound was prepared from 1-[N-t-butoxycarbonyl-2-(S)-alanyl]-5-chloroindoline-2(R/S)-carboxylic acid as described in example 21.
**EP 1 042 288 B1**

1-[2(S)-Alanyl]-5-chloroindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl)amide hemitrifluoroacetate

[0168] This compound was prepared from 1-[N-t-butoxycarbonyl-2(S)-alanyl]-5-chloroindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl)amide as described in example 1.

mp 158-164°C

Elemental analysis: C_{14}H_{15}ClF_{3}N_{2}O_{2}; 0.5(CF_{3}CO_{2}H)

Found: C 44.40 %, H 3.91 %, N 10.23 %

Calculated: C 44.29 %, H 3.84 %, N 10.33 %

HPLC purity: 99.7 % (30.4 %+69.3 %) (R,S isomer)

**EXAMPLE 24**

Synthesis of 1-[2(S)-norvalyl]-5-chloroindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl)amide trifluoroacetate

1-[N-t-Butoxycarbonyl-2(S)-norvalyl]-5-chloroindoline-2(R/S)-carboxylic acid methyl ester

[0169] This compound was prepared from 5-chloroindoline-2(R/S)-carboxylic acid methyl ester and N-t-butoxycarbonylaminopropionic acid as described in example 21. The product was purified by column chromatography on silica gel using 8:2 petroleum spirit:dichethyl ether as eluent.

1-[N-t-Butoxycarbonyl-2(S)-norvalyl]-5-chloroindoline-2(R/S)-carboxylic acid

[0170] This compound was prepared from 1-[N-t-butoxycarbonyl-2(S)-norvalyl]-5-chloroindoline-2(R/S)-carboxylic acid methyl ester as described in example 1.

1-[N-t-Butoxycarbonyl-2(S)-norvalyl]-5-chloroindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl)amide

[0171] This compound was prepared from 1-[N-t-butoxycarbonyl-2(S)-norvalyl]-5-chloroindoline-2(R/S)-carboxylic acid as described in example 21.

1-[2(S)-Norvalyl]-5-chloroindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl)amide trifluoroacetate

[0172] This compound was prepared from 1-[N-t-butoxycarbonyl-2(S)-norvalyl]-5-chloroindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl)amide as described in example 1.

mp 130-138°C

Elemental analysis: C_{15}H_{15}ClF_{3}N_{2}O_{2}; 1.4(CF_{3}CO_{2}H)

Found: C 42.07 %, H 3.63 %, N 8.02 %

Calculated: C 42.02 %, H 3.83 %, N 7.82 %

HPLC purity: 98.3 % (R,S isomer)

**EXAMPLE 25**

Synthesis of 1-[2(S)-methionyl]-5-chloroindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl)amide trifluoroacetate

1-[N-t-Butoxycarbonyl-2(S)-methionyl]-5-chloroindoline-2(R/S)-carboxylic acid methyl ester

[0173] This compound was prepared from 5-chloroindoline-2(R/S)-carboxylic acid methyl ester and N-t-butoxycarbonyl-L-methionine as described in example 21. The product was purified by column chromatography on silica gel using 3:1 petroleum spirit:ethyl acetate as eluent.

1-[N-t-Butoxycarbonyl-2(S)-methionyl]-5-chloroindoline-2(R/S)-carboxylic acid

[0174] This compound was prepared from 1-[N-t-butoxycarbonyl-2(S)-methionyl]-5-chloroindoline-2(R/S)-carboxylic acid methyl ester as described in example 1. The product was purified by column chromatography on silica gel using 5:1 dichloromethane: methanol as eluent.
1-[N-t-Butoxycarbonyl-2(S)-methionyl]-5-chloroindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl)amide

[0175] This compound was prepared from 1-[N-t-butoxycarbonyl-2(S)-methionyl]-5-chloroindoline-2(R/S)-carboxylic acid as described for in example 21.

1-[2(S)-Methionyl]-5-chloroindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl)amide trifluoroacetate

[0176] This compound was prepared from 1-[N-t-butoxycarbonyl-2(S)-methionyl]-5-chloroindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl)amide as described in example 1. The product was purified by column chromatography on silica gel using 5:1 dichloromethane : methanol as eluent.

mp 139-145°C
Elemental analysis: C_{16}H_{19}ClF_3N_3O_2S; 0.1(CF_3CO_2H)
Found: C 46.41 %, H 4.62 %, N 10.04 %
Calculated: C 46.19 %, H 4.57 %, N 9.97 %
HPLC purity: 98.6 % (R+S isomer)

EXAMPLE 26

Synthesis of 1-[2(S)-aminobutyryl]-4-methylindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl)amide trifluoroacetate

Ethyl azidoacetate

[0177] This compound was prepared from ethyl bromoacetate as described in example 7.

Ethyl 2-azido-3-(2-methylphenyl)butanoate

[0178] Sodium pieces (5.15 g, 240 mmol) were added in portions to ethanol (157 ml). The resulting solution was cooled in an ice/acetone bath to -15°C and then over one hour a mixture of 2-methylbenzaldehyde (7.209 g, 60 mmol) and ethyl azidoacetate (30.980 g, 240 mmol) was added at a rate that maintained the temperature below 10°C. After 3 hours, the solution was stored at 5°C for two days to give pure product as yellow crystals.

4-Methylindole-2-carboxylic acid ethyl ester

[0179] This compound was prepared from ethyl 2-azido-3-(2-methylphenyl)butanoate as described in example 7.

4-Methylindoline-2(R/S)-carboxylic acid ethyl ester

[0180] This compound was prepared from 4-methylindole-2-carboxylic acid ethyl ester as described in example 7. The product was purified by column chromatography on silica gel using 20:1 dichloromethane : diethyl ether as eluent.

1-[N-t-Butoxycarbonyl-2(S)-aminobutyryl]-4-methylindoline-2(R/S)-carboxylic acid methyl ester

[0181] This compound was prepared from 4-methylindoline-2(R/S)-carboxylic acid methyl ester as described in example 7.

1-[N-t-Butoxycarbonyl-2(S)-aminobutyryl]-4-methylindoline-2(R/S) carboxylic acid

[0182] This compound was prepared from 1-[N-t-butoxycarbonyl-2(S)-aminobutyryl]-4-methylindoline-2(R/S)-carboxylic acid methyl ester as described in example 7.

1-[N-t-Butoxycarbonyl-2(S)-aminobutyryl]-4-methylindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl)amide

[0183] This compound was prepared from 1-[N-t-butoxycarbonyl-2(S)-aminobutyryl]-4-methylindoline-2(R/S)-carboxylic acid as described in example 7.
1-[2(S)-Aminobutyryl]-4-methylindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl)amide trifluoroacetate

This compound was prepared from 1-[N-t-butoxycarbonyl-2(S)-aminobutyryl]-4-methylindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl)amide as described in example 7.

**EXAMPLE 27**

Synthesis of 1-[2(S)-aminobutyryl]-4,5-dimethoxyindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl)amide trifluoroacetate

**Methyl 2-azido-3-(2,3-dimethoxyphenyl)propenoate**

This compound was prepared from 2,3-dimethoxybenzaldehyde as described in example 7.

**4,5-Dimethoxyindole-2-carboxylic acid methyl ester**

This compound was prepared from methyl 2-azido-3-(2,3-dimethoxyphenyl)propenoate as described in example 26. The product was purified by column chromatography on silica gel using 4:1 petroleum spirit:ethyl acetate as eluent.

**4,5-Dimethoxyindole-2(R/S)-carboxylic acid methyl ester**

This compound was prepared from 4,5-dimethoxyindole-2-carboxylic acid methyl ester as described in example 22. The product was purified by column chromatography on silica gel using 7:3 petroleum spirit:ethyl acetate as eluent.

**1-[N-t-Butoxycarbonyl-2(S)-aminobutyryl]-4,5-dimethoxyindoline-2(R/S)-carboxylic acid methyl ester**

This compound was prepared from 1-[N-t-butoxycarbonyl-2(S)-aminobutyryl]-4,5-dimethoxyindoline-2(R/S)-carboxylic acid methyl ester as described in example 7.

**1-[N-t-Butoxycarbonyl-2(S)-aminobutyryl]-4,5-dimethoxyindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl)amide**

This compound was prepared from 1-[N-t-butoxycarbonyl-2(S)-aminobutyryl]-4,5-dimethoxyindoline-2(R/S)-carboxylic acid as described in example 7.

**1-[2(S)-Aminobutyryl]-4,5-dimethoxyindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl)amide trifluoroacetate**

This compound was prepared from 1-[N-t-butoxycarbonyl-2(S)-aminobutyryl]-4,5-dimethoxyindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl)amide as described in example 7.

Elemental analysis: C_{17}H_{22}F_{3}N_{3}O_{4}; 1.7(CF_{3}CO_{2}H)

Found: C 42.43 %, H 4.27 %, N 6.91 %

Calculated: C 42.01 %, H 4.10 %, N 7.20 %

HPLC purity: 100 % (R+S isomer)
EXAMPLE 28

Synthesis of 1-[2(S)-aminobutyryl]-4,5-methylenedioxyindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl) amide trifluoroacetate

2,3-Methylenedioxy benzaldehyde

To a mechanically stirred degassed mixture of 2,3-dihydroxy benzaldehyde (7.80 g, 56 mmol) and cesium carbonate (16.20 g, 84 mmol) in acetonitrile (110 ml) was added bromochloromethane (5.46 g, 84 mmol) and the resulting suspension was heated to reflux. After 5 hours the reaction was cooled to room temperature and filtered through celite with ethyl acetate washings. The filtrate was concentrated and directly chromatographed on silica gel using 9:1 hexane:ethyl acetate as eluent.

Methyl 2-azido-3-(2,3-methylenedioxyphenyl)propenoate

A solution of 2,3-methylenedioxy benzaldehyde (15.76 g, 104 mmol) and methylazidoacetate (48.38 g, 419 mmol) in methanol was cooled to -15°C using an ice/acetone bath. The resulting solution was then treated over one hour with sodium methoxide (96 ml) at a rate that maintained the temperature below -10°C. After 3 hours, the solution was stored at 5°C for two days to give crystalline material which was filtered off and washed with hexane.

4,5-Methylenedioxyindole-2-carboxylic acid methyl ester

This compound was prepared from methyl 2-azido-3-(2,3-methylenedioxyphenyl)propenoate as described in example 26. The product was purified by column chromatography on silica gel using 8:1 petroleum spirit:ethyl acetate as eluent.

4,5-Methylenedioxyindoline-2(R/S)-carboxylic acid

This compound was prepared from 4,5-methylenedioxyindole-2-carboxylic acid methyl ester as described in example 1. However this time 10 equivalence of magnesium turnings were used instead of 2-3 eq. of magnesium turnings. The product was purified by column chromatography on silica gel using 7:3 petroleum spirit:ethyl acetate as eluent.

1-[N-t-Butoxycarbonyl-2(S)-aminobutyryl]-4,5-methylenedioxyindoline-2(R/S)-carboxylic acid methyl ester

This compound was prepared from 4,5-methylenedioxyindoline-2(R/S)-carboxylic acid methyl ester as described in example 1. The product was purified by column chromatography on silica gel using 10:1 petroleum spirit:ethyl acetate as eluent.

1-[N-t-Butoxycarbonyl-2(S)-aminobutyryl]-4,5-methylenedioxyindoline-2(R/S)-carboxylic acid

This compound was prepared from 1-[N-t-butoxycarbonyl-2(S)-aminobutyryl]-4,5-methylenedioxy indoline-2(R/S)-carboxylic acid methyl ester as described in example 1. The product was purified by column chromatography on silica gel using 5:1 dichloromethane:methanol as eluent.

1-[N-t-Butoxycarbonyl-2(S)-aminobutyryl]-4,5-methylenedioxyindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl)amide

This compound was prepared from 1-[N-t-butoxycarbonyl-2(S)-aminobutyryl]-4,5-methylenedioxy indoline-2(R/S)-carboxylic acid as described in example 7. The product was purified by column chromatography on silica gel using 3:1 petroleum spirit:ethyl acetate as eluent.

1-[2(S)-Aminobutyryl]-4,5-methylenedioxyindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl)amide trifluoroacetate

This compound was prepared from 1-[N-t-butoxycarbonyl-2(S)-aminobutyryl]-4,5-methylenedioxy indoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl)amide as described in example 7.

mp 89-98°C
Elemental analysis: C_{16}H_{18}F_3N_3O_4; 1.5(CF_3CO_2H)
EXAMPLE 29

Synthesis of 1-[2-(S)-aminobutyryl]-5-ethylnindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl)amide trifluoroacetate hydrate

1-[N-t-Butoxycarbonyl-(S)-aminobutyryl]-5-benzyloxindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl) amide

[0200] This compound was prepared from 1-[N-t-butoxycarbonyl-(S)-aminobutyryl]-5-benzyloxindoline-2(R/S)-carboxylic acid (from example 6) as described in example 1. The product was purified by column chromatography on silica gel using 3:1 petroleum spirit:ethyl acetate as eluent.

1-[N-t-Butoxycarbonyl-(S)-aminobutyryl]-5-hydroxyindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl) amide

[0201] 1-[N-t-butoxycarbonyl-(S)-aminobutyryl]-5-benzyloxindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl) amide (1.27 g, 5.39 mmol) in ethyl acetate (28 ml) was hydrogenated under an atmosphere of hydrogen in the presence of palladium on activated carbon at room temperature for 24 hours. The catalyst was filtered through celite with ethyl acetate washing. The filtrate was concentrated and directly chromatographed on silica gel using 2:3 petroleum spirit:ethyl acetate as eluent.

1-[N-t-Butoxycarbonyl-(S)-aminobutyryl]-5-trifluoromethyl sulfonato indoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl)amide

[0202] 1-[N-t-butoxycarbonyl-(S)-aminobutyryl]-5-hydroxyindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl) amide (0.87 g, 1.95 mmol) in pyridine (6 ml) was cooled to 0°C using an ice bath under an atmosphere of nitrogen. Triflic anhydride (0.66 g, 2.34 mmol) was added. After one hour the solution was stored at 5°C for a day. The reaction mixture was then cooled to room temperature, diluted with brine and extracted with ethyl acetate. The organic layers were dried over anhydrous magnesium sulphate and evaporated in vacuo. The crude residue was purified by column chromatography on silica gel using 3:1 petroleum spirit:ethyl acetate as eluent.

1-[N-t-Butoxycarbonyl-(S)-aminobutyryl]-5-(trimethylsilyl)ethylnyl indoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl)amide

[0203] A mixture of 1-[N-t-butoxycarbonyl-(S)-aminobutyryl]-5-trifluoromethyl sulfonatoindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl) amide (0.83 g, 1.43 mmol), trimethylsilyl acetylene (0.24 ml, 2.15 mmol), triethylamine (2.26 ml) and dichlorobis(triphenylphosphine)palladium (70 mg, 0.10 mmol) in dimethylformamide (11 ml) was stirred at 90°C for 4 hours under an atmosphere of nitrogen. The reaction mixture was then cooled to room temperature, diluted with brine and extracted with ethyl acetate. The organic layers were dried over anhydrous magnesium sulphate and evaporated in vacuo. The crude residue was purified by column chromatography on silica gel using 4:1 petroleum spirit:ethyl acetate as eluent.

1-[N-t-Butoxycarbonyl-(S)-aminobutyryl]-5-ethylnindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl)amide

[0204] To the solution of 1-[N-t-butoxycarbonyl-(S)-aminobutyryl]-5-(trimethylsilyl)ethylnylindoline-2(RIS)-carboxylic acid (2,2,2-trifluoroethyl) amide (0.43 g, 0.81 mmol) in anhydrous methanol (7 ml), potassium carbonate (0.02 g) was added under an atmosphere of nitrogen and stirred at room temperature for several hours. The solvent was evaporated in vacuo.

1-[2-(S)-Aminobutyryl]-5-ethynylindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl)amide trifluoroacetate hydrate

[0205] This compound was prepared from 1-[N-t-butoxycarbonyl-(S)-aminobutyryl]-5-ethynylindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl)amide as described in example 7. mp 140-149°C
Elemental analysis: C_{17}H_{18}F_{3}N_{3}O_{3}; 2.3(CF_{3}CO_{2}H):1.0(H_{2}O)
Found: C 40.87 %, H 3.75 %, N 6.46 %
Calculated: C 40.93 %, H 3.55 %, N 6.63 %
HPLC purity: 100 % (45.3 %, 54.6 %) (R+S isomer)

Measurement of the Inhibition of Tripeptidyl Peptidase II (TPP II)

[0206] The inhibition of TPP II was measured using the procedure described in WO 96/35805.
[0207] The potency of the compounds of the invention was evaluated by measuring the activity of membrane TPP II.
The degree of inhibition by the compounds of the invention is expressed as the dissociation constant (Ki), calculated
from the concentration needed to provide 50% inhibition, and from the K_m of the substrate (23 μM).
[0208] Membranes of rat cerebral cortex were obtained by centrifugation (200,000 x g min) of a homogenate in 10
volumes of a 50mM potassium phosphate buffer, pH 7.4.
[0209] The centrifugation pellet was carefully washed and taken up in a buffer containing 10% glycerol and 0.1% Brij
35 to obtain a concentration of 25mg protein/ml.
[0210] After 25 minutes of preincubation, incubation is carried out in 0.1 ml of a buffer containing 0.1% Brij 35, 100mM
bestatin, 25 μg of membrane protein and 50 μM of substrate Ala-Ala-Phe-Amc (AAF-Amc). Liberation of 7-amino-4-
methylcoumarin (Amc) is evaluated by fluorimetry.
[0211] Table 1 shows the inhibition data obtained for the compounds of Examples 1 to 10.

Table 1: Inhibition of AAF-Amc Hydrolysis by Cerebral Membranes.

<table>
<thead>
<tr>
<th>Compound of Example</th>
<th>Ki (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.40</td>
</tr>
<tr>
<td>2</td>
<td>1.7</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>1.2</td>
</tr>
<tr>
<td>6</td>
<td>2.8</td>
</tr>
<tr>
<td>7</td>
<td>0.56</td>
</tr>
<tr>
<td>8</td>
<td>0.36</td>
</tr>
<tr>
<td>9</td>
<td>0.7</td>
</tr>
<tr>
<td>10</td>
<td>1.1</td>
</tr>
</tbody>
</table>

[0212] Table 2 shows comparative data between the following comparative compounds known in the art for their
inhibiting activity on TPP II and some compounds of the invention:

C.C.1 : 1-(2(S)-aminobutyryl)-5-chloroindoline-2(S)-carboxylic acid n-butylamide
C.C.2 : 1-(2(S)-aminobutyryl)-indoline-2(S)-carboxylic acid n-butylamide (named Butabindide);
C.C.3 : 1-(2(S)-aminobutyryl)-indoline-2(S)carboxylic acid ethylamide
C.C.4 : 1-(2(S)-aminobutyryl)-5-hydroxyindoline-2(R/S)-carboxylic acid n-butylamide
C.C.5 : 1-(2(S)-aminobutyryl)-5-methoxyindoline-2(R/S)-carboxylic acid n-butylamide

Table 2: Inhibition of AAF-Amc Hydrolysis by Cerebral Membranes

<table>
<thead>
<tr>
<th>Comparative compound</th>
<th>Ki (nM)</th>
<th>Compound of the invention</th>
<th>Ki (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C.C.1</td>
<td>2.5</td>
<td>ex. 1</td>
<td>0.4</td>
</tr>
<tr>
<td>C.C.2</td>
<td>7</td>
<td>ex. 4</td>
<td>3</td>
</tr>
<tr>
<td>C.C.3</td>
<td>12</td>
<td>ex. 5</td>
<td>1.2</td>
</tr>
<tr>
<td>C.C.4</td>
<td>6.6</td>
<td>ex. 6</td>
<td>2.8</td>
</tr>
</tbody>
</table>
Claims

1. A compound of the following formula I:

![Chemical Structure](image)

wherein: each R¹ may be the same or different, and is chosen from: halogen; OH; C₁⁻C₆ alkyl, C₂⁻C₆ alkenyl or C₂⁻C₆ alkynyl, optionally substituted by at least one halogen, OH or mixtures thereof; X(C₁⁻C₆ alkyl), wherein X is S, O or OCO, and the alkyl is optionally substituted by at least one halogen, OH or mixtures thereof; SO₂(C₁⁻C₆ alkyl), optionally substituted by at least one halogen; or YSO₃H, YSO₂(C₁⁻C₆ alkyl), wherein Y is O or NH and the alkyl is optionally substituted by at least one halogen; a diradical -X₁-(C₁⁻C₂ alkylene)-X₁- wherein X₁ is O or S; a benzene ring fused to the indoline ring; n is from 0 to 4; R² is CH₂R⁴, wherein R⁴ is C₁⁻C₆ alkyl substituted by at least one halogen, (CH₂)pZ(CH₂)qCH₃, wherein Z is O or S, p is from 0 to 5 and q is from 0 to 5, provided that p + q is from 0 to 5; C₂⁻C₆ unsaturated alkyl, or C₃⁻C₆ cycloalkyl; or R² is C₁⁻C₆ alkyl optionally substituted by at least one halogen; R³ is H; C₁⁻C₆ alkyl optionally substituted by at least one halogen; (CH₂)pZR⁵ wherein p is from 1 to 3, Z is O or S and R⁵ is H or C₁⁻C₃ alkyl; benzyl; or a pharmaceutically acceptable acid addition salt thereof; provided that:

when n = 0 or when n is not 0, R¹ representing a halogen atom or a O-(C₁⁻C₄ alkyl), OH or C₁⁻C₄ alkyl group, then R² cannot be a (C₁⁻C₆) alkyl group or CH₂R⁴ with R⁴ being -(CH₂)₂SCH₃, -(CH₂)₂OH or cyclohexyl, R³ representing a hydrogen atom or a (C₁⁻C₄)alkyl group.

2. A compound according to claim 1, wherein:

each R¹ may be the same or different, and is chosen from: halogen; OH; C₁⁻C₆ alkyl, optionally substituted by at least one halogen, OH or mixtures thereof; X(C₁⁻C₆ alkyl), wherein X is S, O or OCO, optionally substituted by at least one halogen, OH or mixtures thereof; SO₂(C₁⁻C₆ alkyl), optionally substituted by at least one halogen; or YSO₃H, YSO₂(C₁⁻C₆ alkyl), wherein Y is O or NH, optionally substituted by at least one halogen; n is from 0 to 4; R² is CH₂R⁴, wherein R⁴ is C₁⁻C₆ alkyl substituted by at least one halogen, (CH₂)pZ(CH₂)qCH₃, wherein Z is O or S, p is from 0 to 5 and q is from 0 to 5, provided that p + q is from 0 to 5; C₂⁻C₆ unsaturated alkyl; or C₃⁻C₆ cycloalkyl; or R² is C₁⁻C₆ alkyl optionally substituted by at least one halogen; R³ is H; C₁⁻C₆ alkyl.

3. A compound according to claim 1 or 2 wherein R³ is hydrogen, methyl or ethyl, preferably ethyl.
4. A compound according to claim 1 or 2, wherein R⁢₃ is a C₁⁻C₆ alkyl optionally substituted by at least one halogen; (CH₂)ₚZR⁵ where p, Z and R⁵ are as defined in claim 1; or benzyl.

5. A compound according to claim 4, wherein R⁢₃ is - (CH₂)₂SCH₃.

6. A compound according to anyone of to claim 1 to 5, wherein R⁡₂ is CH₂R⁴, R⁴ being C₁⁻C₆ alkyl substituted by at least one halogen; (CH₂)ₚZ(CH₂)ₜCH₃ wherein Z is O (p and q are as defined in claim 1); C₂⁻C₆ unsaturated alkyl;

7. A compound according to any one of claims 1 to 6, wherein R⁡₂ is CH₂R⁴, R⁴ being CH₂OCH₃, CH₂SCH₃, SCH₃, CH₃CH₂, C≡CH or cyclopropyl, preferably CH₂OCH₃, CH₂SCH₃, or R² is HCH₃.

8. A compound according to any one of claims 1 to 7, wherein R² contains at least one halogen atom, preferably selected between fluorine and chlorine.

9. A compound according to any one of claims 1 to 8, wherein R² is CH₂R⁴ with R⁴ representing CHF₂, CF₃, CF₂CF₃, CH₂F, CH₂Cl, preferably CF₃ or CF₂CF₃ and most preferably CF₃.

10. A compound according to anyone of claims 1 to 9, wherein n is 0.

11. A compound according to anyone of claims 1 to 9, wherein n is not 0 and R¹ is C₁⁻C₆ alkyl substituted by at least one halogen, OH or mixtures thereof; X (C₁⁻C₆ alkyl) wherein X is S or OCO, optionally substituted by at least one halogen, OH or mixtures thereof; O(C₁⁻C₆ alkyl) substituted by at least one halogen, OH or mixtures thereof; SO₂ (C₁⁻C₆ alkyl), optionally substituted by at least one halogen; or YSO₃H, YSO₂(C₁⁻C₆ alkyl) wherein Y is O or NH optionally substituted by at least one halogen.

12. A compound according to any one of claims 1 to 9 and 11, wherein R¹ is CH₃, OCH₃, Cl, F, OH, OCF₃, OSO₂H, OSO₂CH₃, OOCCH₃, OSO₂CF₃, SO₂CH₃, S(CH₃), NSO₂CH₃ or CF₃, preferably OCH₃, OH, Cl or F.

13. A compound according to anyone of claims 1 to 9, wherein n is not 0 and R¹ is C₂⁻C₆ alkenyl or C₂⁻C₆ alkynyl.

14. A compound according to claim 13, wherein R¹ is -C≡CH-.

15. A compound according to anyone of claims 1 to 9, wherein n is 1 and R¹ is a diradical -X¹-(C₁⁻C₂ alkylene)-X¹- where X¹ is as defined in claim 1, preferably attached to the indoline ring at the 4,5-positions or 5,6-positions.

16. A compound according to claim 15, wherein R¹ is -OCH₂O-.

17. A compound according to anyone of claims 1 to 9, wherein n is 1 and R¹ is a benzene ring fused to the indoline ring preferably at the 4,5-positions or 5,6-positions.

18. A compound according to anyone of claims 1 to 9 and 11 to 14, wherein n is 1 or 2, preferably 2.

19. A compound according to anyone of claims 1 to 18, which is:

1-(2(S)-aminobutyryl)-5-chloroindoline-2(S)-carboxylic acid (2,2,2-trifluoroethyl)amide;
1-(2(S)-aminobutyryl)-5-chloroindoline-2(S)-carboxylic acid 2-chloroethylamide;
1-(2(S)-aminobutyryl)-indoline-2(S)-carboxylic acid (2-methylthioethyl)amide;
1-(2(S)-aminobutyryl)-indoline-2(S)-carboxylic acid N-(cyclopropylmethyl)amide;
1-(2(S)-aminobutyryl)-indoline-2(S)-carboxylic acid (2,2,2-trifluoroethyl)amide;
1-(2(S)-aminobutyryl)-5-hydroxyindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl)amide;
1-(2(S)-aminobutyryl)-4-chloroindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl)amide;
1-(2(S)-aminobutyryl)-4-fluoroindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl)amide;
1-(2(S)-aminobutyryl)-5-methoxyindoline-2(R/S)-carboxylic acid (2,2,2-trifluoroethyl)amide;
1-(2(S)-aminobutyryl)-5-trifluoromethoxyindoline-2 (R/S)-carboxylic acid (2,2,2-trifluoroethyl)amide

or pharmaceutically acceptable salts thereof.

20. A compound according to anyone of claims 1 to 18, which is:
21. A process for preparing a compound of formula I, which process comprises:

a) reacting a compound of the following formula II:

```
R_1n
NH

COOCH_3
```

with an optionally protected amino acid R^{3}CH(NHR^{10})COOH (III), where n, R^{1} and R^{3} are as defined above and R^{10} is H or a protecting group, to obtain a compound of the following formula IV:

```
R_1n
N
```

```
COR'
```

```
O
```

```
NHR_10
```

wherein R' is methoxy,

b) optionally hydrolysing the ester (IV) to the corresponding acid,

c) reacting the acid or ester (IV) with an amine of formula R^{2}NH_{2}, and

d) optionally removing the protecting group R^{10}, and optionally converting the product thus obtained into a salt.
22. A process for preparing the compound of formula I, which process comprises

e) reacting a compound of formula V:

\[
\begin{array}{c}
\text{R}_1^1 \text{CONHR}_2^2 \\
\text{NH}
\end{array}
\]

(V)

with an optionally protected amino acid of the formula (III) R^3 \text{CH(NHR}^{10}\text{)}\text{COOH}, where n, R^1, R^2, R^3 and R^{10} are as defined above, to obtain a compound of the following formula (IV):

\[
\begin{array}{c}
\text{R}_1^1 \\
\text{NHR}^{10} \\
\text{COR'}
\end{array}
\]

(IV)

wherein R' is NHR^2, optionally removing the protecting group R^{10}, and optionally converting the product thus obtained into a salt.

23. A medicament acting as an inhibitor of the CCK-inactivating peptidase tripeptidyl peptidase (TPP II), which comprises a therapeutically effective amount of a compound according to any one of claims 1 to 20.

24. A medicament for the treatment of an eating disorder, which comprises a therapeutically effective amount of a compound according to any one of claims 1 to 20.

25. A medicament according to claim 24 for the treatment of obesity.

26. A medicament according to any one of claims 24 and 25, further comprising a compound effective in the treatment of obesity, for example selected from an adrenergic \(\beta_3\)-receptor agonist, a histamine H3-receptor antagonist, a neuropeptide Y receptor (NPY-5) antagonist, a compound acting on the amylin receptor or a compound that increases the levels of noradrenaline, dopamine or serotonin in the brain e.g. dextfenfluramine, sibutramine or fluoxetine.

27. A medicament for the treatment of psychotic syndromes and associated psychiatric disorders, which comprises a therapeutically effective amount of a compound according to any one of claims 1 to 20.

28. A medicament according to any one of claims 23 to 25 and 27, comprising an effective dosage of a compound suitable for an administration of 0.001 to 10 mg, preferably 0.01 to 1 mg per kg body weight per day.

29. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any one of claims 1 to 20, together with pharmaceutically acceptable carrier or diluent.
30. Use of a compound according to any one of claims 1 to 21 in the manufacture of a medicament for inhibiting the CCK-inactivating peptidase tripeptidyl peptidase (TPP II).

31. Use according to claim 30 for the manufacture of a medicament for the treatment of an eating disorder.

32. Use according to claim 30 or 31 for the manufacture of a medicament for the treatment of obesity.

33. Use according to any one of claims 30 to 32, in combination with a compound effective in the treatment of obesity, for example selected from adrenergic β3-receptor agonist, a histamine H3-receptor antagonist, a neuropeptide Y receptor (NPY-5) antagonist, a compound acting on the amylipin receptor or a compound that increases the levels of noradrenaline, dopamine or serotonin in the brain e.g. dexfenfluramine, sibutramine or fluoxetine.

34. Use according to claim 30 for the manufacture of a medicament for the treatment of psychotic syndromes and associated psychiatric disorders.

35. A cosmetic composition comprising a compound according to any one of claims 1 to 19 together with a physiologically acceptable carrier or diluent.

36. A cosmetic composition according to claim 35, to aid slimming.

37. A method of improving the bodily appearance of a human or animal comprising administering an effective amount of a compound according to any one of claims 1 to 20, optionally with a physiologically acceptable carrier or diluent, to aid slimming.

**Patentansprüche**

1. Verbindung der folgenden Formel I:

   ![Chemical Structure](image_url)

   worin R1 jeweils identisch oder unterschiedlich sein kann und ausgewählt ist aus Halogen; OH; C1-C6-Alkyl, C2-C6-Alkenyl oder C2-C6-Alkiny1, wahlweise substituiert durch mindestens ein Halogen, OH oder Mischungen davon; X (C1-C6-Alkyl), worin X S, O oder OCO darstellt und das Alkyl wahlweise substituiert ist durch mindestens ein Halogen, OH oder Mischungen davon; SO2(C1-C6-Alkyl), wahlweise substituiert durch mindestens ein Halogen; oder YSO3H, YSO3(C1-C6-Alkyl), worin Y O oder NH darstellt und das Alkyl wahlweise substituiert ist durch mindestens ein Halogen; einem Direst -X1-(C1-C2-Alkenyl)-X1-, worin X1 O oder S ist; einem an den Indolring anellierten Benzolring; n von 0 bis 4 reicht; R2 CH2R3 ist, worin R4 C1-C6-Alkyl, substituiert durch mindestens ein Halogen, (CH2)pZ(CH2)qCH3, worin Z O oder S ist, p von 0 bis 5 reicht und q von 0 bis 5 reicht, mit der Maßgabe, dass p+q von 0 bis 5 reicht; ungesättigtes C2-C6-Alkyl; oder C3-C6-Cycloalkyl ist; oder R2 C1-C6-Alkyl, wahlweise substituiert durch mindestens ein Halogen, ist; R3 H; C1-C6-Alkyl, wahlweise substituiert durch mindestens ein Halogen; (CH2)pZR5, worin p von 1 bis 3 reicht, Z O oder S ist und R5 H oder C1-C3-Alkyl darstellt; Benzyl ist;
Verbindung nach Anspruch 1, worin:

- ein jedes R⁴ identisch oder unterschiedlich sein kann und aus Halogenen; OH; C₁₋₆-Alkyl, wahlweise substituiert durch mindestens ein Halogen, OH oder Mischungen davon; X(C₁₋₆-Alkyl), worin X S, O oder OCO ist, wahlweise substituiert durch mindestens ein Halogen, OH oder Mischungen davon; SO₂(C₁₋₆-Alkyl), wahlweise substituiert durch mindestens ein Halogen; oder YSO₂, YSO₃(C₁₋₆-Alkyl), worin Y O oder NH, wahlweise substituiert durch mindestens ein Wasserstoff, ist; 
- n von 0 bis 4 reicht; 
- R² CH₃R⁴ darstellt, worin R¹ C₁₋₆-Alkyl, substituiert durch mindestens ein Halogen, (CH₂)ₚZ(CH₂)ₚ₋₁CH₃, worin Z O, S ist, p von 0 bis 5 reicht und q von 0 bis 5 reicht, mit der Maßgabe, dass p+q von 0 bis 5 reicht; ungesättigtes C₂₋₆-Cycloalkyl ist; 
- oder R² C₁₋₆-Alkyl, wahlweise substituiert durch mindestens ein Halogen, ist; R⁵ H; C₁₋₆-Alkyl ist.

3. Verbindung nach Anspruch 1 oder Anspruch 2, worin R³ Wasserstoff, Methyl oder Ethyl, vorzugsweise Ethyl, ist.

4. Verbindung nach Anspruch 1 oder Anspruch 2, worin R⁵ ein C₁₋₆-Alkyl, wahlweise substituiert durch mindestens ein Halogen; (CH₂)ₚZR⁵, worin p, Z und R⁵ wie in Anspruch 1 definiert sind; oder Benzyl ist.

5. Verbindung nach Anspruch 4, worin R¹ -(CH₂)ₚSCH₃ ist.

6. Verbindung nach einem der Ansprüche 1 bis 5, worin R² CH₃R⁴, wobei R¹ C₁₋₆-Alkyl, substituiert durch mindestens ein Halogen, darstellt; (CH₂)ₚZ(CH₂)ₚ₋₁CH₃, worin Z O ist (p und q wie in Anspruch 1 definiert sind); ungesättigtes C₂₋₆-Cycloalkyl ist.

7. Verbindung nach einem der Ansprüche 1 bis 6, worin R² CH₃R⁴, wobei R¹ CH₂OCH₃, CH₂SCH₃, SCH₃, CH=CH₂, C=CH oder Cyclopropyl, vorzugsweise CH₂OCH₃, CH₂SCH₃ ist, oder R² HCH₃ ist.

8. Verbindung nach einem der Ansprüche 1 bis 7, worin R² mindestens ein Halogenatom, vorzugsweise aus Flur und Chlor, enthält.

9. Verbindung nach Anspruch 8, worin R² CH₃R⁴ darstellt, wobei R¹ CH=CH₂, CF₃, CF₂CF₃, CH₂F, CH₂Cl, vorzugsweise CF₃ oder CF₂CF₃ und am meisten bevorzugt CF₃ darstellt.

10. Verbindung nach einem der Ansprüche 1 bis 9, worin n 0 ist.

11. Verbindung nach einem der Ansprüche 1 bis 9, worin nicht 0 ist und R¹ C₁₋₆-Alkyl, substituiert durch mindestens ein Halogen, OH oder Mischungen davon; X (C₁₋₆-Alkyl), worin X S oder OCO ist, wahlweise substituiert durch mindestens ein Halogen, OH oder Mischungen davon; O(C₁₋₆-Alkyl) substituiert durch mindestens ein Halogen, OH oder Mischungen davon; SO₂(C₁₋₆-Alkyl), wahlweise substituiert durch mindestens ein Halogen; oder YSO₃H, YSO₃(C₁₋₆-Alkyl), worin Y O oder NH, wahlweise substituiert durch mindestens ein Halogen, ist.

12. Verbindung nach einem der Ansprüche 1 bis 9 und 11, worin R¹ CH₃, OCH₃, Cl, F, OH, OCF₃, OSO₂H, OSO₂CH₃, OCOCH₃, OSO₂CF₃, SO₂CH₃, SCH₃, NHSO₂CH₂ oder CF₃, vorzugsweise OCH₃, OH Cl oder F ist.

13. Verbindung nach einem der Ansprüche 1 bis 9, worin n nicht 0 ist und R¹ C₂₋₆-Alkenyl oder C₂₋₆-Alkinyl ist.


15. Verbindung nach einem der Ansprüche 1 bis 9, worin n 1 ist und R¹ einen Dirext -X¹-(C₁₋₂-Alkenyl)-X¹- darstellt, worin X¹ wie in Anspruch 1 definiert ist, vorzugsweise gebunden an den Indolinring an den 4,5-Positionen oder 5,6-Positionen.
16. Verbindung nach Anspruch 15, worin R\(^1\) -OCH\(_2\)O- ist.

17. Verbindung nach einem der Ansprüche 1 bis 9, worin n 1 ist und R\(^1\) ein Benzolring, anelliert an den Indolinring, vorzugsweise an den 4,5-Positionen oder 5, 6-Positionen, ist.

18. Verbindung nach einem der Ansprüche 1 bis 11 und 11 bis 14, worin n 1 oder 2, vorzugsweise 2 ist.

19. Verbindung nach einem der Ansprüche 1 bis 18, welche darstellt:

- 1-(2(S)-Aminobutyryl)-5-chloroindolin-2(S)-carbonsäure-(2,2,2-trifluorethyl)amid;
- 1-(2(S)-Aminobutyryl)-5-chloroindolin-2(S)-carbonsäure 2-chlorethylamid;
- 1-(2(S)-Aminobutyryl)-indolin-2(S)-carbonsäure-(2-methylthioethyl)amid;
- 1-(2(S)-Aminobutyryl)-indolin-2(S)-carbonsäure-N-(cyclopropylmethyl)amid;
- 1-(2(S)-Aminobutyryl)-5-hydroxyindolin-2(R/S)-carbonsäure-(2,2,2-trifluorethyl)amid;
- 1-(2(S)-Aminobutyryl)-4-chloroindolin-2(R/S)-carbonsäure-(2,2,2-trifluorethyl)amid;
- 1-(2(S)-Aminobutyryl)-4-fluorindolin-2(R/S)-carbonsäure-(2,2,2-trifluorethyl)amid;
- 1-(2(S)-Aminobutyryl)-5-methoxyindolin-2(R/S)-carbonsäure-(2,2,2-trifluorethyl)amid;
- 1-(2(S)-Aminobutyryl)-5-trifluormethoxyindolin-2(R/S)-carbonsäure-(2,2,2-trifluorethyl)amid

oder pharmazeutisch annehmbare Salze davon.

20. Verbindung nach einem der Ansprüche 1 bis 18, welche darstellt:

- 1-[2(S)-Aminobutyryl]-4,5-dichlor-indolin-2-(S)-carbonsäure-2,2,2-trifluorethylamid-trifluoracetat
- 1-[2(S)-Aminobutyryl]-5,6-dichlor-indolin-2-(S)-carbonsäure-2,2,2-trifluorethylamid-trifluoracetat
- 1-[2(S)-Aminobutyryl]-benz-[e]-indolin-2-(S)-carbonsäure-2,2,2-trifluorethylamid-trifluoracetat
- 1-[2(S)-Aminobutyryl]-5-O-sulfato-indolin-2(R/S)-carbonsäure-butylamid-trifluoracetat
- 1-[2(S)-Aminobutyryl]-benz-[e]-indolin-2-(S)-carbonsäure-butylamid-trifluoracetat
- 1-[2(S)-Aminobutyryl]-4,5-dichlor-indolin-2-(R/S)-carbonsäure-2,2,2-trifluorethylamid-trifluoracetat
- 1-[2(S)-Aminobutyryl]-5-O-sulfato-indolin-2(R/S)-carbonsäure-2,2,2-trifluorethylamid-trifluoracetat
- 1-[2(S)-Aminobutyryl]-benz[f]-indolin-2-(R/S)-carbonsäure-2,2,2-trifluorethylamid-trifluoracetathemihydrat
- 1-[2(S)-Phenylalanyl]-5-Cl-indolin-2(R/S)-carbonsäure-2,2,2-trifluorethylamid-trifluoracetat
- 1-[2(S)-Aminobutyryl]-4-methoxyindolin-2(S)-carbonsäure-2,2,2-trifluorethylamid-trifluoracetat
- 1-[2-Glycyl]-5-chloroindolin-2(R/S)-carbonsäure-2,2,2-trifluorethylamid-trifluoracetat
- 1-[2-Alanyl]-5-chloroindolin-2(R/S)-carbonsäure-2,2,2-trifluorethylamid-trifluoracetat
- 1-[2-Norvalyl]-5-chloroindolin-2(R/S)-carbonsäure-2,2,2-trifluorethylamid-trifluoracetat
- 1-[2-(S)-Methionyl]-5-chloroindolin-2(R/S)-carbonsäure-2,2,2-trifluorethylamid-trifluoracetat
- 1-[2(S)-Aminobutyryl]-4-methylindolin-2(R/S)-carbonsäure-2,2,2-trifluorethylamid-trifluoracetat
- 1-[2(S)-Aminobutyryl]-4,5-dimethoxyindolin-2(R/S)-carbonsäure-2,2,2-trifluorethylamid-trifluoracetat
- 1-[2(S)-Aminobutyryl]-4,5-methylendioxindolin-2(R/S)-carbonsäure-2,2,2-trifluorethylamid-trifluoracetat
- 1-[2(S)-Aminobutyryl]-5-ethyindolin-2(R/S)-carbonsäure-2,2,2-trifluorethylamid-trifluoracetathydrat.

21. Verfahren zur Herstellung einer Verbindung der Formel I, wobei das Verfahren umfasst

a) Umsetzen einer Verbindung der allgemeinen Formel II:

\[
\begin{align*}
\text{R}^1 \quad & \quad \text{NH} \quad \text{COOCH}^3
\end{align*}
\]
mit einer wahlweise geschützten Aminosäure R^3CH(NHR^{10})COOH (III), worin n, R^1 und R^3 wie oben definiert sind und R^{10} H oder eine Schutzgruppe darstellt, um eine Verbindung der allgemeinen Formel IV zu erhalten:

\[
\begin{align*}
\text{(IV)}
\end{align*}
\]

worin R' Methoxy darstellt,

b) wahlweise Hydrolysieren des Esters (IV) zu der entsprechenden Säure,

c) Umsetzen der Säure oder des Esters (IV) mit einem Amin der Formel R^2NH_2, und
d) wahlweise Entfernen der Schutzgruppe R^{10} und wahlweise Umwandeln des auf diese Weise erhaltenen Produkts in ein Salz.

22. Verfahren zur Herstellung der Verbindung der Formel I, wobei das Verfahren umfasst

e) Umsetzen einer Verbindung der Formel V:

\[
\begin{align*}
\text{(V)}
\end{align*}
\]

mit einer wahlweise geschützten Aminosäure der Formel (III) R^3CH(NHR^{10})COOH, worin n, R^1, R^2, R^3 und R^{10} wie oben definiert sind, um eine Verbindung der allgemeinen Formel (IV) zu erhalten:

\[
\begin{align*}
\text{(IV)}
\end{align*}
\]

worin R' NHR^2 ist, wahlweise Entfernen der Schutzgruppe R^{10} und wahlweise Umwandeln des auf diese Weise
erhaltenen Produkts in ein Salz.

23. Arzneimittel, welches als ein Inhibitor der CCK-inaktivierenden Peptidasetripeptidylpeptidase (TPP II) wirkt, welches eine therapeutisch wirksame Menge einer Verbindung nach einem der Ansprüche 1 bis 20 umfasst.


27. Arzneimittel zur Behandlung von psychotischen Syndromen und damit verbundenen psychiatrischen Erkrankungen, welches eine therapeutische wirksame Menge einer Verbindung nach einem der Ansprüche 1 bis 20 umfasst.

28. Arzneimittel nach einem der Ansprüche 23 bis 25 und 27, welches eine wirksame Dosierung einer Verbindung I umfasst, die für die Verabreichung von 0,001 bis 10 mg, vorzugsweise 0,01 bis 1 mg pro Kilogramm Körpergewicht pro Tag geeignet ist.

29. Pharmazeutische Zusammensetzung, umfassend eine therapeutisch wirksame Menge einer Verbindung nach einem der Ansprüche 1 bis 20, zusammen mit pharmazeutisch annehmbaren Trägern oder Verdünnungsmitteln.

30. Verwendung einer Verbindung nach einem der Ansprüche 1 bis 21 in der Herstellung eines Arzneimittels zur Inhibition der CCK-inaktivierenden Peptidasetripeptidylpeptidase (TPP II).

31. Verwendung nach Anspruch 30 zur Herstellung eines Arzneimittels für die Behandlung einer Esserkrankung.

32. Verwendung nach Anspruch 30 oder 31 zur Herstellung eines Arzneimittels für die Behandlung von Fettleibigkeit.


34. Verwendung nach Anspruch 30 zur Herstellung eines Arzneimittels für die Behandlung von psychotischen Syndromen und damit verbundenen psychiatrischen Erkrankungen.

35. Kosmetische Zusammensetzung, umfassend eine Verbindung nach einem der Ansprüche 1 bis 19, zusammen mit einem physiologisch annehmbaren Träger oder Verdünnungsmittel.


37. Verfahren zur Verbesserung der Körperscheinung von Mensch oder Tier, umfassend die Verabreichung einer wirksamen Menge einer Verbindung nach einem der Ansprüche 1 bis 20, wahlweise mit einem physiologisch annehmbaren Träger oder Verdünnungsmittel, zur Unterstützung des Abnehmens.

Revendications

1. Composé de formule I suivante :
Un composé selon la revendication 1, dans lequel :

2. Composé selon la revendication 1 ou 2, dans lequel :

   chaque R1 peut être identique ou différent; et est choisi parmi un atome d’halogène; OH; un groupe alkyle en C1-C6, alcényle en C2-C6 ou alcynyle en C2-C6, éventuellement substitué par au moins un atome d’halogène, OH ou des mélanges de ceux-ci; un groupe X(alkyle en C1-C6), dans lequel X est S, O ou OCO, et le groupe alkyle est éventuellement substitué par au moins un atome d’halogène, OH ou des mélanges de ceux-ci; un groupe SO2(alkyle en C1-C6), éventuellement substitué par au moins un atome d’halogène; ou YSO2H, YSO2(alkyle en C1-C6), dans lesquels Y est O ou NH et le groupe alkyle est éventuellement substitué par au moins un atome d’halogène; un biradical-X1-(alkyle en C1-C2)-X1- dans lequel X1 est O ou S; un cycle benzène fusionné au cycle indoline ;

   n vaut de 0 à 4;

   R2 est CH2R4, dans lequel R4 est un groupe alkyle en C1-C6 substitué par au moins un atome d’halogène; (CH2)pZ(CH2)qCH3, dans lequel Z est O ou S, p vaut de 0 à 5 et q vaut de 0 à 5, à condition que p + q vaille de 0 à 5; un groupe alkyle en C2-C6 insaturé; un groupe cycloalkyle en C3-C6;

   ou R2 est un groupe alkyle en C1-C6 éventuellement substitué par au moins un atome d’halogène; R3 est H; un groupe alkyle en C1-C6 éventuellement substitué par au moins un atome d’halogène; (CH2)pZR dans lequel p vaut de 1 à 3, Z est O ou S et R5 est H ou un groupe alkyle en C1-C6; un groupe benzyle; ou un sel d’addition d’acide pharmaceutiquement acceptable de celui-ci; à condition que:

   lorsque n = 0 ou lorsque n ne vaut pas 0, R1 représentant un atome d’halogène ou un groupe O(alkyle en C1-C4), OH ou alkyle en C1-C4, alors R2 ne puisse pas être un groupe alkyle en C1-C6 ou CH2R4 avec R4 étant (CH2)2SCH3, -(CH2)2OH ou un groupe cyclohexyle, R3 représentant un atome d’hydrogène ou un groupe alkyle en C1-C4.

3. Composé selon la revendication 1 ou 2, dans lequel R3 est un atome d’hydrogène, un groupe méthyle ou éthyle, de préférence un groupe éthyle.

4. Composé selon la revendication 1 ou 2, dans lequel R3 est un groupe alkyle en C1-C6 éventuellement substitué par au moins un atome d’halogène; (CH2)pZR où p, Z et R5 sont tels que définis dans la revendication 1; ou un groupe benzyle.

5. Composé selon la revendication 4, dans lequel R3 est -(CH2)2SCH3.

6. Composé selon l’une quelconque des revendications 1 à 5, dans lequel R2 est CH2R4, R4 étant un groupe alkyle
Composé selon l'une quelconque des revendications 1 à 9, dans lequel n ne vaut pas 0 et R.

7. Composé selon l'une quelconque des revendications 1 à 6, dans lequel R² est CH₃R⁴, R⁴ étant CH₂OCH₃, CH₂SCH₃, SCH₃, CH=CH₂, C=CH ou un groupe cyclopropyle, de préférence CH₂OCH₃, CH₂SCH₃, ou R² est HCH₃.

8. Composé selon l'une quelconque des revendications 1 à 7, dans lequel R² contient au moins un atome d'halogène, de préférence choisi entre un atome de fluor et de chlore.

9. Composé selon la revendication 8, dans lequel R² est CH₂R⁴ avec R⁴ représentant CHF₂, CF₃, CF₂CF₃, CH₂F, et CH₂Cl, de préférence CF₃ ou CF₂CF₃ et de façon plus préférée CF₃.

10. Composé selon l'une quelconque des revendications 1 à 9, dans lequel n vaut 0.

11. Composé selon l'une quelconque des revendications 1 à 9, dans lequel n ne vaut pas 0 et R¹ est un groupe alkyle en C₁-C₆ substitué par au moins un atome d'halogène, OH ou des mélanges de ceux-ci ; un groupe X(alkyle en C₁-C₆) dans lequel X est S ou OCO, éventuellement substitué par au moins un atome d'halogène, OH ou des mélanges de ceux-ci ; un groupe O(alkyle en C₁-C₆) substitué par au moins un atome d'halogène, OH ou des mélanges de ceux-ci ; un groupe SO₂(alkyl en C₁-C₆), éventuellement substitué par au moins un atome d'halogène ; ou YSO₃H, YSO₂(alkyle en C₁-C₆) dans lesquels Y est O ou NH éventuellement substitué par au moins un atome d'halogène.

12. Composé selon l'une quelconque des revendications 1 à 9 et 11, dans lequel R¹ est CH₃, OCH₃, Cl, F, OH, OCF₃, OSO₃H, OSO₂CH₃, OCOCH₃, OSO₂CF₃, SO₂CH₃, SCH₃, NHSO₂CH₃ ou CF₃, de préférence OCH₃, OH, Cl ou F.

13. Composé selon l'une quelconque des revendications 1 à 9, dans lequel n ne vaut pas 0 et R¹ est un groupe alcényle en C₂-C₆ ou alcynyle en C₂-C₆.

14. Composé selon la revendication 13, dans lequel R¹ est -C=CH₂.

15. Composé selon l'une quelconque des revendications 1 à 9, dans lequel n vaut 1 et R¹ est un biradical -X⁺-(alkyle en C₁-C₂)-X⁺, où X⁺ est tel que défini dans la revendication 1, de préférence lié au cycle indoline aux positions 4,5 ou aux positions 5,6.

16. Composé selon la revendication 15, dans lequel R¹ est -OCH₂O⁻.

17. Composé selon l'une quelconque des revendications 1 à 9, dans lequel n vaut 1 et R¹ est un cycle benzène fusionné au cycle indoline de préférence aux positions 4,5 ou aux positions 5,6.

18. Composé selon l'une quelconque des revendications 1 à 9 et 11 à 14, dans lequel n vaut 1 ou 2, de préférence 2.

19. Composé selon l'une quelconque des revendications 1 à 18, qui est :

le (2,2,2-trifluoroéthyl)amide de l'acide 1-(2(S)-aminobutyryl)-5-chloroindoline-2(S)-carboxylique,
le 2-chloroéthylamide de l'acide 1-(2(S)-aminobutyryl)-5-chloroindoline-2(S)-carboxylique,
le [2-méthylthioéthyl]amide de l'acide 1-(2(S)-aminobutyryl)-indoline-2(S)-carboxylique,
le N-cyclopropylméthyl)amide de l'acide 1-(2(S)-aminobutyryl)-indoline-2(S)-carboxylique,
le (2,2,2-trifluoréthyl)amide de l'acide 1-(2(S)-aminobutyryl)-indoline-2(S)-carboxylique,
le (2,2,2-trifluoréthyl)amide de l'acide 1-(2(S)-aminobutyryl)-5-hydroxyindoline-2(R/Sa)-carboxylique,
le (2,2,2-trifluoréthyl)amide de l'acide 1-(2(S)-aminobutyryl)-4-chloroindoline-2(R/S)-carboxylique,
le (2,2,2-trifluoréthyl)amide de l'acide 1-(2(S)-aminobutyryl)-4-fluoroindoline-2(R/S)-carboxylique,
le (2,2,2-trifluoréthyl)amide de l'acide 1-(2(S)-aminobutyryl)-5-méthoxyindoline-2(R/S)-carboxylique,
le (2,2,2-trifluoréthyl)amide de l'acide 1-(2(S)-aminobutyryl)-5-trifluorométhoxyindoline-2(R/S)-carboxylique,

ou les sels pharmaceutiquement acceptables de ceux-ci.

20. Composé selon l'une quelconque des revendications 1 à 18, qui est :
le trifluoroacétate de 2,2,2-trifluoroéthylamide de l’acide 1-[2-(S)-aminobutyryl]-4,5-dichloro-indoline-2-(S)-carboxylique,
le trifluoroacétate de 2,2,2-trifluoroéthylamide de l’acide 1-[2-(S)-aminobutyryl]-5,6-dichloro-indoline-2-(S)-carboxylique,
le trifluoroacétate de 2,2,2-trifluoroéthylamide de l’acide 1-[2-(S)-aminobutyryl]-benz[e]-indoline-2-(S)-carboxylique,
le trifluoroacétate de butyl amide de l’acide 1-[2-(S)-aminobutyryl]-5-O-sulfato-indoline-2-(R/S)-carboxylique,
le trifluoroacétate de butyl amide de l’acide 1-[2-(S)-aminobutyryl]-benz[f]-indoline-2-(R/S)-carboxylique,
le trifluoroacétate de trifluoroéthylamide de l’acide 1-[2-(S)-aminobutyryl]-5-O-sulfato-indoline-2(R/S)-carboxylique,
le trifluoroacétate de 2,2,2-trifluoroéthylamide de l’acide 1-[2-(S)-aminobutyryl]-5-(R/S)-carboxylique,
le trifluoroacétate de trifluoroéthylamide de l’acide 1-[2-(S)-aminobutyryl]-5-(R/S)-carboxylique, hémihydrate,
le trifluoroacétate de (2,2,2-trifluoroéthyl)amide de l’acide 1-[2-(S)-alanyl]-5-(R/S)-carboxylique,
le trifluoroacétate de (2,2,2-trifluoroéthyl)amide de l’acide 1-[2-(S)-méthionyl]-5-(R/S)-carboxylique,
le trifluoroacétate de (2,2,2-trifluoroéthyl)amide de l’acide 1-[2-(S)-norvalyl]-5-(R/S)-carboxylique,
le trifluoroacétate de (2,2,2-trifluoroéthyl)amide de l’acide 1-[2-(S)-norvalyl]-5-(R/S)-carboxylique, hydrate.

\[ \text{EP 1 042 288 B1} \]

21. Procédé de préparation d’un composé de formule I, lequel procédé comprend

a) la réaction d’un composé de formule II suivante :

\[ \text{with an acid amine eventually protected } R^3\text{CH(NH} R^{10}\text{)}\text{COOH (III), where } n, R^1 \text{ and } R^3 \text{ are as defined above and } R^{10} \text{ is } H \text{ or a protective group, to obtain a compound of formula IV as follows :} \]
dans laquelle \( R' \) est un groupe méthoxy,
b) l'hydrolyse éventuelle de l'ester (IV) en l'acide correspondant,
c) la réaction de l'acide ou de l'ester (IV) avec une amine de formule \( R_2^2 \text{NH}_2 \), et
d) l'élimination éventuelle du groupe de protection \( R_{10}^2 \), et la conversion éventuelle du produit ainsi obtenu en un sel.

22. Procédé de préparation d'un composé de formule I, lequel procédé comprend
e) la réaction d'un composé de formule V :

avec un acide aminé éventuellement protégé de formule (III) \( R_3^3 \text{CH}(\text{NHR}_{10}^2)\text{COOH} \), dans laquelle \( n, R_1^1, R_2^2, R_3^3 \) et \( R_{10}^2 \) sont tels que définis ci-dessus, pour obtenir un composé de formule (IV) suivante :

\[
\text{(IV)}
\]

dans laquelle \( R^1 \) est \( \text{NHR}_2^2 \), en éliminant éventuellement le groupe protecteur \( R_{10}^2 \), et en convertissant éventuellement le produit ainsi obtenu en un sel.

23. Médicament agissant comme un inhibiteur de la tripeptidyl peptidase inactivant la CCK (TPP II), qui comprend une quantité thérapeutiquement efficace d'un composé selon l'une quelconque des revendications 1 à 20.

24. Médicament destiné au traitement d'un trouble de l'alimentation, qui comprend une quantité thérapeutiquement efficace d'un composé selon l'une quelconque des revendications 1 à 20.

25. Médicament de la revendication 24, destiné au traitement de l'obésité.
26. Médicament selon l’une quelconque des revendications 24 et 25, comprenant en outre un composé efficace dans le traitement de l’obésité, par exemple choisi parmi un agoniste du récepteur β₃ adrénergique, un antagoniste du récepteur H₃ de l’histamine, un antagoniste du récepteur du neuropeptide Y (NPY-5), un composé agissant sur le récepteur de l’amyline ou un composé qui fait augmenter les niveaux de noradrénaline, de dopamine ou de sérotonine dans le cerveau, par exemple la dexfenfuramine, la sibutramine ou la fluoxétine.

27. Médicament destiné au traitement de syndromes psychotiques et de troubles psychiatriques associés, qui comprend une quantité thérapeutiquement efficace d’un composé selon l’une quelconque des revendications 1 à 20.

28. Médicament selon l’une quelconque des revendications 23 à 25 et 27, qui comprend une dose efficace d’un composé I adapté pour une administration de 0,001 à 10 mg, de préférence de 0,01 à 1mg par kg de poids corporel par jour.

29. Composition pharmaceutique comprenant une quantité thérapeutiquement efficace d’un composé selon l’une quelconque des revendications 1 à 20, conjointement à un véhicule ou un diluant pharmaceutiquement acceptable.

30. Utilisation d’un composé selon l’une quelconque des revendications 1 à 21, dans la fabrication d’un médicament destiné à inhiber la tripeptidyl peptidase inactivant la CCK (TPP II).

31. Utilisation selon la revendication 30, pour la fabrication d’un médicament destiné au traitement d’un trouble de l’alimentation.

32. Utilisation selon la revendication 30 ou 31, pour la fabrication d’un médicament destiné au traitement de l’obésité.

33. Utilisation selon l’une quelconque des revendications 30 à 32, en combinaison avec un composé efficace dans le traitement de l’obésité, par exemple choisi parmi un agoniste du récepteur β₃ adrénergique, un antagoniste du récepteur H₃ de l’histamine, un antagoniste du récepteur du neuropeptide Y (NPY-5), un composé agissant sur le récepteur de l’amyline ou un composé qui fait augmenter les niveaux de noradrénaline, de dopamine ou de sérotonine dans le cerveau, par exemple la dexfenfuramine, la sibutramine ou la fluoxétine.

34. Utilisation selon la revendication 30, pour la fabrication d’un médicament destiné au traitement des syndromes psychotiques et des troubles psychiatriques associés.

35. Composition cosmétique comprenant un composé selon l’une quelconque des revendications 1 à 19, conjointement à un véhicule ou un diluant physiologiquement acceptables.

36. Composition cosmétique selon la revendication 35, destinée à aider à l’amincissement.

37. Procédé d’amélioration de l’apparence corporelle d’un humain ou d’un animal, qui comprend l’administration d’une quantité efficace d’un composé selon l’une quelconque des revendications 1 à 20, éventuellement avec un véhicule ou un diluant physiologiquement acceptable, destiné à aider à l’amincissement.
REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader’s convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- WO 9635805 A [0011] [0206]

Non-patent literature cited in the description

- J. HETEROCYCLIC CHEM. J. Heterocyclic Chem, 1993, vol. 30, 217 [0141] [0142] [0143]