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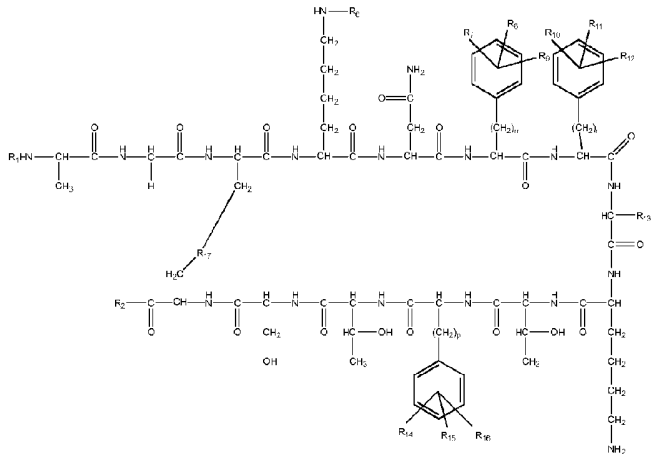
(54) Title: PEPTIDE LIGANDS OF SOMATOSTATIN RECEPTORS



(I)

(57) Abstract: The invention relates to peptide derivatives of general formula (I), their stereoisomers, mixtures thereof and/or their pharmaceutically acceptable salts, a method of obtaining them, pharmaceutical compositions containing them and the use thereof for the treatment, prevention and/or diagnosis of those conditions, disorders and/or pathologies in which the sstrl, sstr2, sstr3, sstr4 and/or sstr5 somatostatin receptors are expressed.

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PEPTIDE LIGANDS OF SOMATOSTATIN RECEPTORS

Field of the Invention

This invention is within the field of biomedical chemistry. The invention particularly encompasses new peptide ligands of somatostatin receptors. These peptide ligands have a potential application in preventive and/or curative therapies, applied to pathologies in which the somatostatin receptors are expressed, as well as in the diagnosis of diseases in which said receptors are expressed.

Background of the Invention

Somatostatin is a cyclic tetradecapeptide originally isolated in the hypothalamus [Burgus *et al.*, Proc. Natl. Acad. Sci. USA, 1973, 70, 684-688]. The somatostatin regulating mechanism commences by means of binding to the G protein-coupled sstr1, sstr2, sstr3, sstr4 and sstr5 somatostatin receptors [Patel *et al.*, Front. Neuroendocrinol., 1999, 20, 157-198]. They all bind to somatostatin with nanomolar affinity [Patel *et al.*, Endocrinology, 1994, 135, 2814-2817]. The five somatostatin receptors differ in their distribution in tissue and pharmacological properties. The first known action of somatostatin is the inhibition of secretion of the growth hormone via the sstr2 and sstr5 receptors. Furthermore, somatostatin inhibits glucagon secretion through sstr2 and insulin secretion via sstr5 [Strowski *et al.*, 2000, Endocrinology, 141(1), 111-117]. The sstr3, and to a lesser extent, sstr2 receptors seem to be involved in induction of cell apoptosis [Qiu *et al.*, 2006, World Gastroenterol., 12(13), 2011-2015]. In addition, sstr1 and sstr5 have an inhibitory effect on the cell cycle and sstr1 could modulate angiogenesis [Bocci *et al.*, Eur. J. Clin. Invest., 2007, 37(9), 700-708]. The function of sstr4 has been studied less, although recent studies have shown its potential as a therapeutic target in hepatic diseases and prostate cancer [Jung *et al.*, Laboratory Investigation, 2006, 86, 477-489; Hansson *et al.*, Prostate, 2002, 53(1), 50-59].

In clinical practice, somatostatin is used as therapy for the treatment of gastrointestinal bleeding due to esophagogastric varices and as an adjuvant in the treatment of secreting pancreatic fistulae. The lack of side effects is its greatest advantage. Despite its biological profile, one of the drawbacks of somatostatin is its short blood half-life (less than 3 min), which makes continuous endovenous infusion necessary and restricts its use to a hospital level.

The short half-life of somatostatin brought about the development of analogs that present greater stability against enzymatic degradation. Somatostatin analogs which maintain the structure of the original molecule can be found in the state of the art. For example, patent US 4,211,693 A describes somatostatin analogs in which any of the phenylalanine amino acids has been substituted with para-halogenated or para-methoxylated phenylalanine, and patent US 4,133,782 A describes somatostatin analogs in which the tryptophan amino acid in position 8 is the D-stereoisomer. Brown *et al.* also describe primarily analogs with D-amino acids [Brown *et al.* J Physiol. 1978, 277, 1-14]. Besides these initial proposals for somatostatin analogs from the original molecule, most of the works known in the state of the art relate to analogs of 8 or fewer amino acids [Janecka *et al.* 2001, J. Pept. Res., 58(2), 91-107; Pawlikowski *et al.*, 2004, Curr. Opin. Pharmacol., 4(6), 608-613].

Octreotide was the first analog developed in clinical practice. It has a structure with a 6-amino acid cycle. Other octreotide analogs which maintain a common structure with a 6-amino acid cycle (lanreotide, vapreotide, pasireotide) can be found in the state of the art. The reduction of the original 12-amino acid cycle of somatostatin to a 6-amino acid cycle restricts the flexibility of the original molecule by limiting interaction with some receptors of the family of sstr1-sstr5 receptors. While somatostatin binds with nanomolar affinity to each of its sstr1, sstr2, sstr3, sstr4 and sstr5 receptors, octreotide, lanreotide and vapreotide only bind with high

affinity to the sstr2 receptor, with moderate affinity to the sstr5 receptor, and with moderate-low affinity to sstr3 and they do not bind to the sstr1 and sstr4 receptors [Patel *et al.*, Endocrinology, 1994, 135(6), 2814-2817]. In the example of pasireotide, the interaction with the sstr4 receptor is lost and the affinity for the sstr2 receptor is an order of magnitude lower [Weckbecker *et al.*, Endocrinology, 2002, 143, 4123-4130].

The identification of different expression profiles of the five somatostatin receptors in target organs of somatostatin explains the limited efficacy of treatments with octreotide, lanreotide and vapreotide in pathologies in which the sstr2 receptor is under-expressed [Khare *et al.*, Faseb J., 1999, 13(2), 387-394].

The use of these 3 analogs has been approved only for a limited number of clinical applications, such as acromegaly, metastatic carcinoid tumor, VIPomas, diarrhea, bleeding of esophageal varices and perioperative protection in pancreatic surgery. Taking into account the wide range of pathologies in which the expression of somatostatin receptors has been identified [Pawlikowski *et al.*, Neuro Endocrinol Lett, 2003, 24 (1-2), 21-27; Vaysse *et al.*, Curr. Med. Chem., 2005, 4, 91-104; Reubi *et al.*, Endocr. Rev., 2003, 24(4), 389-427; Kumar *et al.*, Neuroscience, 2005, 134(2), 525-538] these known analogs solve a small area of possible applications.

In this context of clinical interest for new somatostatin analogs with a high affinity for several or all the receptors thereof and of new applications of somatostatin and its analogs [Tulipano *et al.*, Eur. J. Endocrinol., 2007, 156 Suppl 1, S3-S11; Lamberts *et al.*, Eur. J. Endocrinol., 2002, 146(5), 701-705], the heterogeneous expression of the sstr2 and sstr5 receptors in secreting adenomas of the growth hormone and their treatment with bispecific analogs has demonstrated better control of growth hormone hypersecretion with respect to treatment with octreotide and lanreotide, with preferential affinity for the sstr2 receptor, with an inhibitory concentration IC_{50} of 12 to 18 times greater than sstr5 [Savenau

et al., J. Clin. Endocrinol. Metab., 2001, 86, 140-145].

Therefore, there is still a need to find new synthetic somatostatin analogs for the treatment of those pathologies which present expressed somatostatin receptors sstr1, sstr2, sstr3, sstr4 or sstr5 and which present greater stability in blood than somatostatin.

The new somatostatin analogs must present a broader profile of interaction with the somatostatin receptors, if possible a universal profile of interaction with the 5 sstr1 to sstr5 receptors, or which is at least specific for those receptors with which the analogs already known in the state of the art do not interact, such as the sstr1, sstr4, and sstr3 receptors.

Description of the Invention

The present invention provides a solution to the aforementioned problems. It has surprisingly been found that certain modifications with non-natural or derivatized amino acids improve the selectivity or maintain a profile of universal interaction with the sstr1, sstr2, sstr3, sstr4 and sstr5 receptors. It has particularly been found that the substitution of phenylalanine of the original sequence with aromatic synthetic amino acids with alkyl substituents, the derivatization of the amino group of the lysine side chain, the substitution of cysteines with allylglycines or the substitution of tryptophan with quinolylalanine cause the resulting peptides with one or several of these modifications to present stabilities in serum, gastric fluid and intestinal fluid that are greater than the stabilities of somatostatin and to interact with the 5 sstr1 to sstr5 receptors or combinations of several of these receptors. The peptides of the present invention are also useful for the treatment, prevention and/or diagnosis of those conditions, disorders and/or pathologies in which the sstr1 to sstr5 somatostatin receptors are expressed.

Definitions

The meanings of some terms and expressions as they are used in the context of the invention are included for the purpose of aiding understanding of the present invention.

In the present description, the abbreviations used for amino acids follow the rules of the IUPAC-IUB Joint Commission on Biochemical Nomenclature specified in Eur. J. Biochem., 1984, 138:9-37 and in J. Biol. Chem., 1989, 264:633-673.

Thus, for example, Gly represents NH_2-CH_2-COOH, Gly- represents NH_2-CH_2-CO-, -Gly represents -NH-CH_2-COOH and -Gly- represents -NH-CH_2-CO-. Therefore, the dash, which represents the peptide bond, eliminates the OH from the 1-carboxyl group of the amino acid (represented herein in the conventional non-ionized form) when it is located to the right of the symbol, and it eliminates the H from the 2-amino group of the amino acid when it is located to the left of the symbol; both modifications can be applied to one and the same symbol.

The term "non-cyclic aliphatic group" is used in the present invention to include linear or branched alkyl, alkenyl and alkynyl groups.

The term "alkyl group" relates to a linear or branched saturated group having between 1 and 24, preferably between 1 and 16, more preferably between 1 and 14, even more preferably between 1 and 12, still more preferably 1, 2, 3, 4, 5 or 6 carbon atoms and which is bound to the rest of the molecule by means of a single bond, including, by way of non-limiting example, methyl, ethyl, isopropyl, isobutyl, *tert*-butyl, heptyl, octyl, decyl, dodecyl, lauryl, hexadecyl, octadecyl, amyl, 2-ethylhexyl, 2-methylbutyl, 5-methylhexyl and the like.

The term "alkenyl group" relates to a linear or branched group having between 2 and 24, preferably between 2 and 16, more preferably between 2 and 14, even more preferably between 2 and 12, still more preferably 2, 3, 4, 5 or 6 carbon atoms, with one or more carbon-carbon double bonds, preferably with 1, 2 or 3 conjugated or unconjugated carbon-carbon double bonds, which is bound to the rest of the molecule by means of a single bond, including, by way of non-limiting example, vinyl (-CH_2=CH_2), allyl (-CH_2-CH=CH_2), oleyl, linoleyl group and the like.

The term "alkynyl group" relates to a linear or branched group having between 2 and 24, preferably between 2 and 16, more

preferably between 2 and 14, even more preferably between 2 and 12, still more preferably 2, 3, 4, 5 or 6 carbon atoms with one or more carbon-carbon triple bonds, preferably 1, 2 or 3 conjugated or unconjugated carbon-carbon triple bonds, which is bound to the rest of the molecule by means of a single bond, including, by way of non-limiting example, the ethinyl group, 1-propinyl group, 2-propinyl group, 1-butinyl group, 2-butinyl group, 3-butinyl group, pentinyl group, for example 1-pentinyl group, and the like. The alkynyl groups can also contain one or more carbon-carbon double bonds, including by way of non-limiting example, the but-1-en-3-inyl, pent-4-en-1-inyl group and the like.

The term "alicyclic group" is used in the present invention to include, by way of non-limiting example, cycloalkyl or cycloalkenyl or cycloalkynyl groups.

The term "cycloalkyl" relates to a saturated mono- or polycyclic aliphatic group having between 3 and 24, preferably between 3 and 16, more preferably between 3 and 14, even more preferably between 3 and 12, still more preferably 3, 4, 5 or 6 carbon atoms and which is bound to the rest of the molecule by means of a single bond, including, by way of non-limiting example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, methyl cyclohexyl, dimethyl cyclohexyl, octahydroindene, decahydronaphthalene, dodecahydrophenalene and the like.

The term "cycloalkenyl" relates to a non-aromatic mono- or polycyclic aliphatic group having between 5 and 24, preferably between 5 and 16, more preferably between 5 and 14, even more preferably between 5 and 12, still more preferably 5 or 6 carbon atoms, with one or more carbon-carbon double bonds, preferably 1, 2 or 3 conjugated or unconjugated carbon-carbon double bonds, and which is bound to the rest of the molecule by means of a single bond, including, by way of non-limiting example, the cyclopent-1-en-1-yl group and the like.

The term "cycloalkynyl" relates to a non-aromatic mono- or polycyclic aliphatic group having between 8 and 24, preferably

between 8 and 16, more preferably between 8 and 14, even more preferably between 8 and 12, still more preferably 8 or 9 carbon atoms, with one or more carbon-carbon triple bonds, preferably 1, 2 or 3 conjugated or unconjugated carbon-carbon triple bonds, and which is bound to the rest of the molecule by means of a single bond, including, by way of non-limiting example, the cyclooct-2-en-1-yl group and the like. The cycloalkynyl groups can also contain one or more carbon-carbon double bonds, including by way of non-limiting example, the cyclooct-4-in-2-inyl group and the like

The term "aryl group" relates to an aromatic group having between 6 and 30, preferably between 6 and 18, more preferably between 6 and 10, even more preferably 6 or 10 carbon atoms, comprising 1, 2, 3 or 4 aromatic rings, linked by means of a carbon-carbon bond or fused, including, by way of non-limiting example, phenyl, naphthyl, diphenyl, indenyl, phenanthryl or anthranyl among others; or to an aralkyl group.

The term "aralkyl group" relates to an alkyl group substituted with an aromatic group, having between 7 and 24 carbon atoms and including, by way of non-limiting example, $-(CH_2)_{1-6}$-phenyl, $-(CH_2)_{1-6}$-(1-naphthyl), $-(CH_2)_{1-6}$-(2-naphthyl), $-(CH_2)_{1-6}$-CH(phenyl)$_2$ and the like.

The term "heterocyclyl group" relates to a hydrocarbon ring having 3-10 members, in which one or more of the atoms of the ring, preferably 1, 2 or 3 of the atoms of the ring, is an element other than carbon, such as for example nitrogen, oxygen or sulfur and which can be saturated or unsaturated. For the purposes of this invention, the heterocycle can be a cyclic, monocyclic, bicyclic or tricyclic system, which can include fused ring systems; and the nitrogen, carbon or sulfur atoms can optionally be oxidized in the heterocyclyl radical; the nitrogen atom can optionally be quaternized; and the heterocyclyl radical can be partially or completely saturated or can be aromatic. More preferably, the term heterocyclic relates to a ring having 5 or 6 members. Examples of saturated heterocyclyl groups are dioxane, piperidine, piperazine, pyrrolidine, morpholine and

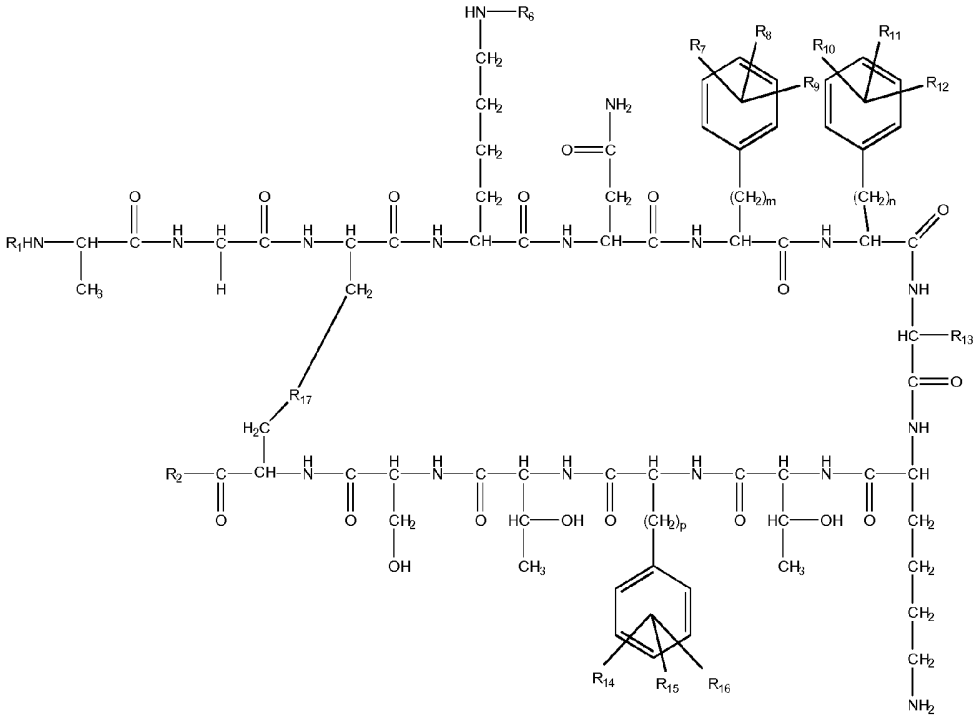
thiomorpholine. Examples of aromatic heterocyclyl groups, also known as heteroaromatic groups, are pyridine, pyrrole, furan, thiophene, benzofuran, imidazoline, quinoleine, quinoline, pyridazine and naphthyridine.

The term "heteroarylalkyl group" relates to an alkyl group substituted with a substituted or unsubstituted aromatic heterocyclyl group, the alkyl group having from 1 to 6 carbon atoms and the aromatic heterocyclyl group between 2 and 24 carbon atoms and from 1 to 3 atoms other than carbon and including, by way of non-limiting example, $-(CH_2)_{1-6}$-imidazolyl, $-(CH_2)_{1-6}$-triazolyl, $-(CH_2)_{1-6}$-thienyl, $-(CH_2)_{1-6}$-furyl, $-(CH_2)_{1-6}$-pyrrolidinyl and the like.

As is understood in this technical field, there can be a certain degree of substitution in the previously defined groups. Therefore, there can be substitution in the groups of the present invention where this is explicitly indicated. The references herein to substituted groups in the groups of the present invention indicate that the specified radical can be substituted in one or more available positions with one or more substituents, preferably in 1, 2 or 3 positions, more preferably in 1 or 2 positions, still more preferably in 1 position. Said substituents include, by way of non-limiting example, C_1-C_4 alkyl; hydroxyl; C_1-C_4 alcoxyl; amino; C_1-C_4 aminoalkyl; C_1-C_4 carbonyloxyl; C_1-C_4 oxycarbonyl; halogen such as fluorine, chlorine, bromine and iodine; cyano; nitro; azido; C_1-C_4 alkylsulfonyl; thiol; C_1-C_4 alkylthio; aryloxyl such as phenoxyl; $-NR_b(C=NR_b)NR_bR_c$; where R_b and R_c are independently selected from the group consisting of H, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_3-C_{10} cycloalkyl, C_6-C_{18} aryl, C_7-C_{17} aralkyl, heterocyclyl having 3-10 members or a protecting group of the amino group.

Compounds of the Invention

The compounds of the invention are defined by general formula (I)



(I)

their stereoisomers, mixtures thereof and/or their pharmaceutically acceptable salts, wherein:

R_1 is selected from the group consisting of H, a substituted or unsubstituted non-cyclic aliphatic group, a substituted or unsubstituted alicyclyl group, a substituted or unsubstituted heterocyclyl group, a substituted or unsubstituted heteroarylalkyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted aralkyl group, a polyethylene glycol polymer, a chelating agent and R_5-CO-;

R_2 is selected from the group consisting of $-NR_3R_4$, $-OR_3$ and $-SR_3$;

R_6 is selected from the group consisting of H, acetyl, trifluoroacetyl, isopropyl, palmitoyl, allyloxycarbonyl, 2-chlorobenzyl, formyl, *N*-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethyl] and benzyloxycarbonyl;

R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{14}, R_{15} and R_{16} are selected independently from one another from the group consisting of H and a non-cyclic aliphatic group;

m is an integer selected from between 0 and 6 with the

condition that when R_7, R_8 and R_9 are H, then m is different from 0;

n is an integer selected from between 0 and 6 with the condition that when R_{10}, R_{11} and R_{12} are H, then n is different from 0;

p is an integer selected from between 0 and 6 with the condition that when R_{14}, R_{15} and R_{16} are H, then p is different from 0;

R_{13} is selected from the group consisting of L-(3-quinolyl)methyl, D-(3-quinolyl)methyl, L-(3-indolyl)methyl and D-(3-indolyl)methyl;

R_{17} is selected from the group consisting of -S-S-, $-CH_2-CH_2-$ and -CH=CH-;

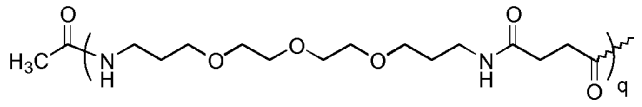
R_3 and R_4 are independently selected from the group consisting of H, a substituted or unsubstituted non-cyclic aliphatic group, a substituted or unsubstituted alicyclyl group, a substituted or unsubstituted heterocyclyl group, a substituted or unsubstituted heteroarylalkyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted aralkyl group and a polymer;

R_5 is selected from the group consisting of H, a substituted or unsubstituted non-cyclic aliphatic group, a substituted or unsubstituted alicyclyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted aralkyl group, a substituted or unsubstituted heterocyclyl group and a substituted or unsubstituted heteroarylalkyl group;

with the condition that when R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{14}, R_{15} and R_{16} are all equal to H, n, m and p are equal to 1 and R_{13} is equal to L-(3-indolyl)methyl or to D-(3-indolyl)methyl, R_{17} is not equal to -S-S-.

The R_1 and R_2 groups are bound at the amino-terminal (*N*-terminal) and carboxy-terminal (*C*-terminal) ends of the peptide sequences, respectively.

According to a preferred embodiment of the present invention R_1 is selected from the group consisting of H, a polymer of general formula (II)



(II)

where q ranges between 1 and 5, and R_5-CO-, where R_5 is selected from the group consisting of substituted or unsubstituted C_1-C_{24} alkyl radical, substituted or unsubstituted C_2-C_{24} alkenyl radical, substituted or unsubstituted C_2-C_{24} alkynyl radical, substituted or unsubstituted C_3-C_{24} cycloalkyl radical, substituted or unsubstituted C_5-C_{24} cycloalkenyl radical, substituted or unsubstituted C_8-C_{24} cycloalkynyl radical, substituted or unsubstituted C_6-C_{30} aryl radical, substituted or unsubstituted C_7-C_{24} aralkyl radical, a substituted or unsubstituted heterocyclyl radical having 3-10 ring members, a substituted or unsubstituted heteroarylalkyl radical having 2 to 24 carbon atoms and having 1 to 3 atoms other than carbon where the alkyl chain is of 1 to 6 carbon atoms. More preferably, R_1 is selected from H, acetyl, *tert*-butanoyl, hexanoyl, 2-methylhexanoyl, cyclohexanecarboxyl, octanoyl, decanoyl, lauroyl, myristoyl, palmitoyl, stearoyl, behenyl, oleoyl and linoleoyl. Even more preferably, R_1 is H, acetyl, hexanoyl, octanoyl, lauroyl, myristoyl or palmitoyl.

According to another preferred embodiment, R_1 is a chelating agent optionally complexed with a detectable element or a radiotherapeutic element. Chelating agent is understood as a group that is capable of forming coordination complexes with the detectable element or the radiotherapeutic element. Preferably, the chelating agent is a group capable of forming complexes with metal ions, more preferably selected from the group consisting of DOTA, DTPA, TETA or derivatives thereof. The chelating agent can be bound directly or through a linker.

Detectable element is understood as any element, preferably a metal ion, displaying a detectable property in an *in vivo* diagnostic technique. Radiotherapeutic element is understood as any element emitting α radiation, β radiation, or γ radiation.

According to another preferred embodiment, R_2 is -NR_3R_4,

$-OR_3$ or $-SR_3$ where R_3 and R_4 are independently selected from the group consisting of H, substituted or unsubstituted C_1-C_{24} alkyl, substituted or unsubstituted C_2-C_{24} alkenyl, substituted or unsubstituted C_2-C_{24} alkynyl, substituted or unsubstituted C_3-C_{24} cycloalkyl, substituted or unsubstituted C_5-C_{24} cycloalkenyl, substituted or unsubstituted C_8-C_{24} cycloalkynyl, substituted or unsubstituted C_6-C_{30} aryl, substituted or unsubstituted C_7-C_{24} aralkyl, a substituted or unsubstituted heterocyclyl having 3-10 ring members, and a substituted or unsubstituted heteroarylalkyl group having 2 to 24 carbon atoms and having 1 to 3 atoms other than carbon where the alkyl chain is of 1 to 6 carbon atoms and a polymer of general formula (II) where q ranges between 1 and 5. Optionally, R_3 and R_4 can be bound by means of a saturated or unsaturated carbon-carbon bond, forming a cycle with the nitrogen atom. More preferably, R_2 is $-NR_3R_4$ or $-OR_3$, where R_3 and R_4 are independently selected from the group consisting of H, substituted or unsubstituted C_1-C_{24} alkyl, substituted or unsubstituted C_2-C_{24} alkenyl, substituted or unsubstituted C_2-C_{24} alkynyl, substituted or unsubstituted C_3-C_{15} cycloalkyl, substituted or unsubstituted C_6-C_{15} aryl and a substituted or unsubstituted heterocyclyl of 3-10 members, a substituted or unsubstituted heteroarylalkyl group with a ring having 3 to 10 members and an alkyl chain of 1 to 6 carbon atoms and a polymer of general formula (II) where q ranges between 1 and 5. More preferably, R_3 and R_4 are selected from the group consisting of H, methyl, ethyl, hexyl, dodecyl or hexadecyl. Even more preferably, R_3 is H and R_4 is selected from the group consisting of H, methyl, ethyl, hexyl, dodecyl or hexadecyl. According to an even more preferred embodiment, R_2 is selected from -OH and $-NH_2$.

According to another preferred embodiment, R_7, R_8 and R_9 are equal to one another and are in an ortho-, para-, ortho- configuration or a meta-, para-, meta- configuration, R_{10}, R_{11} and R_{12} are equal to one another and are in an ortho-, para-, ortho- configuration or a meta-, para-, meta- configuration, and R_{14}, R_{15} and R_{16} are equal to one another and are in an ortho-,

para-, ortho- configuration or a meta-, para-, meta-configuration, more preferably, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{14}, R_{15} and R_{16} are selected from the group consisting of H and C_1-C_{24} alkyl, even more preferably they are selected from the group consisting of H and C_1-C_6 alkyl, and still more preferably they are selected from the group consisting of H, methyl and ethyl.

According to another embodiment of the present invention, R_1 is selected from the group consisting of H, acetyl, lauroyl, myristoyl, palmitoyl or a polymer of general formula (II) where q ranges between 1 and 5, R_2 is $-NR_3R_4$ or $-OR_3$ where R_3 and R_4 are independently selected from H, methyl, ethyl, hexyl, dodecyl and hexadecyl, R_6 is H, R_7, R_8 and R_9 are methyl and are in an ortho-, para-, ortho- configuration or a meta-, para-, meta-configuration, m is 0 or 1, R_{10}, R_{11}, R_{12}, R_{14}, R_{15} and R_{16} are H, n and p are equal to 1, R_{13} is selected from the group consisting of L-(3-indolyl)methyl and D-(3-indolyl)methyl and R_{17} is -S-S-.

According to another embodiment of the present invention, R_1 is selected from the group consisting of H, acetyl, lauroyl, myristoyl, palmitoyl or a polymer of general formula (II) where q ranges between 1 and 5, R_2 is $-NR_3R_4$ or $-OR_3$ where R_3 and R_4 are independently selected from H, methyl, ethyl, hexyl, dodecyl and hexadecyl, R_6 is H, R_{10}, R_{11} and R_{12} are methyl and are in an ortho-, para-, ortho- configuration or a meta-, para-, meta-configuration, n is 0 or 1, R_7, R_8, R_9, R_{14}, R_{15} and R_{16} are H, m and p are equal to 1, R_{13} is selected from the group consisting of L-(3-indolyl)methyl and D-(3-indolyl)methyl and R_{17} is -S-S-.

According to another embodiment of the present invention, R_1 is selected from the group consisting of H, acetyl, lauroyl, myristoyl, palmitoyl or a polymer of general formula (II) where q ranges between 1 and 5, R_2 is $-NR_3R_4$ or $-OR_3$ where R_3 and R_4 are independently selected from H, methyl, ethyl, hexyl, dodecyl and hexadecyl, R_6 is H, R_{14}, R_{15} and R_{16} are methyl and are in an ortho-, para-, ortho- configuration or a meta-, para-, meta-configuration, p is 0 or 1, R_7, R_8, R_9, R_{10}, R_{11} and R_{12} are H, m and n are equal to 1, R_{13} is selected from the group consisting of L-(3-indolyl)methyl and D-(3-indolyl)methyl and R_{17} is -S-S-.

According to another embodiment of the present invention, R_1 is selected from the group consisting of H, acetyl, lauroyl, myristoyl, palmitoyl or a polymer of general formula (II) where q ranges between 1 and 5, R_2 is $-NR_3R_4$ or $-OR_3$ where R_3 and R_4 are independently selected from H, methyl, ethyl, hexyl, dodecyl and hexadecyl, R_6 is H, R_7, R_8, R_9, R_{10}, R_{11} and R_{12} are methyl and are in an ortho-, para-, ortho- configuration or a meta-, para-, meta- configuration, m and n are 0 or 1, R_{14}, R_{15} and R_{16} are H, p is equal to 1, R_{13} is selected from the group consisting of L-(3-indolyl)methyl and D-(3-indolyl)methyl and R_{17} is -S-S-.

According to another embodiment of the present invention, R_1 is selected from the group consisting of H, acetyl, lauroyl, myristoyl, palmitoyl or a polymer of general formula (II) where q ranges between 1 and 5, R_2 is $-NR_3R_4$ or $-OR_3$ where R_3 and R_4 are independently selected from H, methyl, ethyl, hexyl, dodecyl and hexadecyl, R_6 is H, R_7, R_8, R_9, R_{14}, R_{15} and R_{16} are methyl and are in an ortho-, para-, ortho- configuration or a meta-, para-, meta- configuration, m and p are 0 or 1, R_{10}, R_{11} and R_{12} are H, n is equal to 1, R_{13} is selected from the group consisting of L-(3-indolyl)methyl and D-(3-indolyl)methyl and R_{17} is -S-S-.

According to another embodiment of the present invention, R_1 is selected from the group consisting of H, acetyl, lauroyl, myristoyl, palmitoyl or a polymer of general formula (II) where q ranges between 1 and 5, R_2 is $-NR_3R_4$ or $-OR_3$ where R_3 and R_4 are independently selected from H, methyl, ethyl, hexyl, dodecyl and hexadecyl, R_6 is H, R_{10}, R_{11}, R_{12}, R_{14}, R_{15} and R_{16} are methyl and are in an ortho-, para-, ortho- configuration or a meta-, para-, meta- configuration, n and p are 0 or 1, R_7, R_8 and R_9 are H, m is equal to 1, R_{13} is selected from the group consisting of L-(3-indolyl)methyl and D-(3-indolyl)methyl and R_{17} is -S-S-.

According to another embodiment of the present invention, R_1 is selected from the group consisting of H, acetyl, lauroyl, myristoyl, palmitoyl or a polymer of general formula (II) where q ranges between 1 and 5, R_2 is $-NR_3R_4$ or $-OR_3$ where R_3 and R_4 are independently selected from H, methyl, ethyl, hexyl, dodecyl and hexadecyl, R_6 is selected from the group consisting of acetyl,

palmitoyl, trifluoroacetyl, isopropyl, allyloxycarbonyl, 2-chlorobenzyl, *N*-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethyl], R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{14}, R_{15} and R_{16} are H, m, n and p are equal to 1, R_{13} is selected from the group consisting of L-(3-indolyl)methyl and D-(3-indolyl)methyl and R_{17} is -S-S-.

According to another embodiment of the present invention, R_1 is selected from the group consisting of H, acetyl, lauroyl, myristoyl, palmitoyl or a polymer of general formula (II) where q ranges between 1 and 5, R_2 is $-NR_3R_4$ or $-OR_3$ where R_3 and R_4 are independently selected from H, methyl, ethyl, hexyl, dodecyl and hexadecyl, R_6 is H, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{14}, R_{15} and R_{16} are H, m, n and p are equal to 1, R_{13} is selected from the group consisting of L-(3-quinolyl)methyl and D-(3-quinolyl)methyl and R_{17} is -S-S-.

According to another embodiment of the present invention, R_1 is selected from the group consisting of H, acetyl, lauroyl, myristoyl, palmitoyl or a polymer of general formula (II) where q ranges between 1 and 5, R_2 is $-NR_3R_4$ or $-OR_3$ where R_3 and R_4 are independently selected from H, methyl, ethyl, hexyl, dodecyl and hexadecyl, R_6 is H, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{14}, R_{15} and R_{16} are H, m, n and p are equal to 1, R_{13} is selected from the group consisting of L-(3-indolyl)methyl and D-(3-indolyl)methyl and R_{17} is -CH=CH-.

The compounds of the present invention can exist as stereoisomers or mixtures of stereoisomers; for example, the amino acids forming them can have an L-, D- configuration, or can be racemic independently of one another. Therefore, it is possible to obtain isomeric mixtures, as well as racemic mixtures or diastereomeric mixtures, or pure diastereomers or enantiomers, depending on the number of asymmetric carbons and on which isomers or isomeric mixtures are present. The preferred structures of the compounds of the invention are pure isomers, i.e., a single enantiomer or diastereomer.

For example, unless otherwise indicated, it is understood that the amino acid is L or D, or racemic or non-racemic mixtures of both. The preparation processes described in the

present document allow the person skilled in the art to obtain each of the stereoisomers of the compound of the invention by means of choosing the amino acid with the suitable configuration.

The pharmaceutically acceptable salts of the compounds provided in the present invention are also within the scope thereof. The term "pharmaceutically acceptable salts" means a salt that is recognized for use in animals and more particularly in humans, and it includes the salts used to form addition salts of bases, inorganic bases, such as, by way of non-limiting example, lithium, sodium, potassium, calcium, magnesium, manganese, copper, zinc or aluminum, among others, or organic bases, such as, by way of non-limiting example, ethylamine, diethylamine, ethylenediamine, ethanolamine, diethanolamine, arginine, lysine, histidine or piperazine among others, or addition salts of acids, organic acids, such as by way of non-limiting example, acetate, citrate, lactate, malonate, maleate, tartrate, fumarate, benzoate, aspartate, glutamate, succinate, oleate, trifluoroacetate, oxalate, pamoate or gluconate among others, or inorganic acids, such as by way of non-limiting example, chloride, sulfate, borate or carbonate, among others. The nature of the salt is not critical provided that it is pharmaceutically acceptable. The pharmaceutically acceptable salts of the peptides of the invention can be obtained by conventional methods well-known in the state of the art [Berge S.M. *et al.*, J. Pharm. Sci. 1977, 66, 1-19].

Another aspect of the present invention relates to a compound of general formula (I), their stereoisomers, mixtures thereof and/or their pharmaceutically acceptable salts, as described in the present invention, for the treatment, prevention and/or diagnosis of those conditions, disorders and/or pathologies in which the sstr1, sstr2, sstr3, sstr4 and/or sstr5 somatostatin receptors are expressed.

In a more particular aspect, the present invention relates to a compound of general formula (I), their stereoisomers, mixtures thereof and/or their pharmaceutically acceptable salts,

as described in the present invention, for the treatment, prevention and/or diagnosis of those conditions, disorders and/or pathologies selected from the group consisting of acromegaly, symptomatic treatment of gastroenteropancreatic neuroendocrine tumors, diarrhea, cancer, tumors, neurodegenerative diseases, ocular diseases, immune system pathologies, inflammation, infections, esophageal varices, pain, wound healing, tissue regeneration, chronic pancreatitis, hypertrophic pulmonary osteoarthropathy and thyrotrophic adenoma.

In a more particular aspect, the present invention relates to a compound of general formula (I), their stereoisomers, mixtures thereof and/or their pharmaceutically acceptable salts, as described in the present invention, for the treatment, prevention and/or diagnosis of those conditions, disorders and/or pathologies selected from the group consisting of acromegaly, inflammation, infections, esophageal varices, neuropathic pain, wound healing, tissue regeneration, chronic pancreatitis, hypertrophic pulmonary osteoarthropathy, thyrotrophic adenoma, grade 3-4 diarrhea, diarrhea associated with radiotherapy and/or chemotherapy treatment, symptomatic treatment of carcinoid syndrome or VIPomas, endocrine cancer, pancreatic cancer, colorectal cancer, breast cancer, ovarian cancer, prostate cancer, thyroid cancer, lung cancer, gastric cancer, hepatocellular carcinoma, Alzheimer's disease, arthritis, allergies, Lupus erythematosus, lymphoproliferative disorder, diabetic retinopathy, macular edema, Graves' ophthalmopathy, Cushing's syndrome, restenosis, angiogenesis, hyperthyroidism, hypothyroidism, hyperinsulinemia, psoriasis, hypercalcemia, Paget's disease, caquexia, and Zollinger-Ellison syndrome.

In a more particular aspect, the treatment, prevention and/or diagnosis with the compounds of the present invention is performed by means of a local or systemic application, such as, by way of non-limiting example by topical, oral or parenteral route. In the context of the present invention, the term

"parenteral" includes nasal, auricular, ophthalmic, vaginal, rectal route, subcutaneous, intradermal, intravascular injections, such as, for example, intravenous, intramuscular, intravitreous, intraspinal, intracranial, intraarticular, intrathecal and intraperitoneal injections, as well as any other similar injection or infusion technique.

Preparation Processes

The compounds of the invention, their stereoisomers or their pharmaceutically acceptable salts can be synthesized according to conventional methods known in the state of the art.

In an embodiment of the present invention, the compounds are synthesized by means of solution or solid phase peptide synthesis methods.

The solid phase synthesis methods are described for example in [Stewart J.M. and Young J.D., 1984, "Solid Phase Peptide Synthesis, 2nd edition" Pierce Chemical Company, Rockford, Illinois; Bodanzsky M., and Bodanzsky A., 1984 "The practice of Peptide Synthesis" Springer Verlag, New Cork; Lloyd-Williams P., Albericio F. and Giralt E. (1997) "Chemical Approaches to the Synthesis of Peptides and Proteins" CRC, Boca Raton, FL, USA]. Solution synthesis methods and combinations of the solution and solid phase synthesis methods or enzymatic synthesis are described in [Kullmann W. *et al.*, J.Biol.Chem., 1980, 255, 8234-8238].

In an embodiment of the present invention, the compounds of formula (I) are prepared by means of a method comprising the steps of:

1. Solid phase synthesis
2. Cleaving the peptide from the polymer support, preferably by means of acid treatment
3. Cycling the peptide in solution
4. If needed, eliminating the protecting groups, preferably with trifluoroacetic acid

or alternatively

1. Solid phase synthesis
2. Solid phase cycling

3. Cleaving the peptide from the polymer support and simultaneously eliminating the protecting groups, preferably by means of treatment with trifluoroacetic acid.

Preferably, the *C*-terminal end is bound to a solid support and the process is developed in solid phase and therefore comprises coupling an amino acid with the *N*-terminal end protected and the *C*-terminal end free on an amino acid with the *N*-terminal end free and the *C*-terminal end bound to a polymer support; eliminating the protecting group from the *N*-terminal end; and repeating this sequence as many times as needed to thus obtain a tetradecapeptide, followed finally by cleaving the synthesized peptide from the original polymer support.

The functional groups of the amino acid side chains are maintained suitably protected with temporary or permanent protecting groups throughout synthesis, and they can be deprotected simultaneously or orthogonally to the process of cleaving the peptide from the polymer support.

Alternatively, the solid phase synthesis can be performed by means of a convergent strategy by coupling a peptide fragment on the polymer support or on a peptide fragment previously bound to the polymer support. Convergent synthesis strategies are well known by persons skilled in the art and are described by Lloyd-Williams P. *et al.* in Tetrahedron 1993, 49, 11065-11133.

The process can comprise the additional steps of deprotecting the *N*-terminal and *C*-terminal ends and/or cleaving the peptide from the polymer support in an indistinct order, using standard processes and conditions known in the art, after which the functional groups of said ends can be modified. The optional modification of the *N*-terminal and *C*-terminal ends can be performed with the peptide of formula (I) anchored to the polymer support or once the peptide has been cleaved from the polymer support.

Optionally, R_1 can be introduced by means of reacting the *N*-terminal end of the peptide of the invention with an R_1-Z compound, where R_1 has the meaning described above and Z is a leaving group, such as, by way of non-limiting example, the

tosyl group, the mesyl group and halogen groups, among others; by means of a nucleophilic substitution reaction, in the presence of a suitable base and solvent and where said fragments present the functional groups which do not participate in the formation of the N-C bond suitably protected with temporary or permanent protecting groups. R_1 can also be introduced by means of reacting the *N*-terminal end of the compound of the invention with an R_5COOH group or the esters, acid halides or anhydride thereof.

Optionally and/or additionally, the R_2 radicals can be introduced by means of reacting an HR_2 compound, where R_2 is $-OR_3$, $-NR_3R_4$ or $-SR_3$, with a complementary fragment corresponding with the peptide of formula (I) in which R_2 is -OH in the presence of a suitable solvent and a base such as, for example, *N,N*-diisopropylethylamine (DIEA) or triethylamine or an additive such as, for example, 1-hydroxybenzotriazole (HOBt) or 1-hydroxyazabenzotriazole (HOAt) and a dehydrating agent, such as for example a carbodiimide, a uronium salt, a phosphonium salt or an amidinium salt, among others, to thus obtain a peptide according to the invention of general formula (I), where said fragments present the functional groups which do not participate in the formation of the N-C, O-C or S-C bond suitable protected with temporary or permanent protecting groups, or alternatively other R_2 radicals can be introduced by means of incorporating simultaneously to the process of cleaving the peptide from the polymer support.

A person skilled in the art will easily understand that the steps of deprotecting/cleaving the *C*-terminal and *N*-terminal ends and the subsequent derivatization thereof can be performed in an indistinct order, according to processes known in the art [Smith M. B. and March J., 1999 "March's Advanced Organic Chemistry Reactions, Mechanisms and Structure", 5th Edition, John Wiley & Sons, 2001].

The term "protecting group" relates to a group which blocks an organic functional group and which can be removed under controlled conditions. The protecting groups, their relative

reactivities and the conditions in which they remain inert are known by the person skilled in the art.

Examples of representative protecting groups for the amino group are the amides, such as amide acetate, amide benzoate, amide pivalate; carbamates, such as benzyloxycarbonyl (Cbz or Z), 2-chlorobenzyl (ClZ), *para*-nitrobenzyloxycarbonyl (pNZ), *tert*-butyloxycarbonyl (Boc), 2,2,2-trichloroethoxycarbonyl (Troc), 2-(trimethylsilyl)ethoxycarbonyl (Teoc), 9-fluorenylmethoxycarbonyl (Fmoc) or allyloxycarbonyl (Alloc), trityl (Trt), methoxytrityl (Mtt), 2,4-dinitrophenyl (Dnp), *N*-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethyl] (Dde), 1-(4,4-dimethyl-2,6-dioxo-cyclohexylidene)-3-methyl-butyl (ivDde), 1-(1-adamantyl)-1-methylethoxy-carbonyl (Adpoc), among others; preferably, Boc or Fmoc.

Examples of representative protecting groups for the carboxyl group are the esters, such as the *tert*-butyl (tBu) ester, allyl (All) ester, triphenylmethyl ester (trityl ester, Trt), cyclohexyl (cHx) ester, benzyl (Bzl) ester, *ortho*-nitrobenzyl ester, *para*-nitrobenzyl ester, *para*-methoxybenzyl ester, trimethylsilylethyl ester, 2-phenylisopropyl ester, fluorenylmethyl (Fm) ester, 4-(*N*-[1-(4,4-dimethyl-2,6-dioxocyclohexylidene)-3-methylbutyl]amino)benzyl (Dmab) ester, among others; preferred protecting groups of the invention are All, tBu, cHex, Bzl and Trt esters.

The trifunctional amino acids can be protected during the synthetic process with temporary or permanent protecting groups orthogonal to the protecting groups of the *N*-terminal and *C*-terminal ends. The amino group protecting groups described above are used to protect the amino group of the lysine side chain, the tryptophan side chain can be protected with any of the amino group protecting groups described above, or it may not be protected, the serine and threonine side chain is protected with *tert*-butyl (tBu) ester, the cysteine side chain is protected with a protecting group selected from the group consisting of trityl and acetamidomethyl and the asparagine side

chain can be protected with a protecting group selected from the group consisting of methoxytrityl, trityl and xanthyl or it may not be protected. Preferred trifunctional amino acid protecting groups of the invention are tBu esters in the serine and threonine side chains; Boc in the lysine side chains, Trt in the cysteine side chains and Fmoc or Boc as a temporary protecting group of the *N*-terminal end.

Examples of these and other additional protecting groups, their introduction and their removal, are described in the literature [Greene T.W. and Wuts P.G.M., (1999) "Protective groups in organic synthesis" John Wiley & Sons, New York; Atherton B. and Sheppard R.C. (1989) "Solid Phase Peptide Synthesis: A practical approach" IRL Oxford University Press]. The term "protecting groups" also includes the polymer supports used in the solid phase synthesis.

When the synthesis is performed partially or entirely in solid phase, the polystyrene, polyethyleneglycol grafted in polystyrene supports and the like, can be mentioned as solid supports to be used in the process of the invention such as, by way of non-limiting example, *p*-methylbenzhydrylamine (MBHA) resins [Matsueda G.R. *et al.*, Peptides 1981, 2, 45-50], 2-chlorotrityl resins [Barlos K. *et al.* 1989 Tetrahedron Lett. 30:3943-3946; Barlos K. *et al.*, 1989 Tetrahedron Lett. 30, 3947-3951], TentaGel® resins (Rapp Polymere GmbH), ChemMatrix® resins (Matrix Innovation, Inc) and the like, which may or may not include a labile linker, such as 5-(4-aminomethyl-3,5-dimethoxyphenoxy)valeric acid (PAL) [Albericio F. *et al.*, 1990, J. Org. Chem. 55, 3730-3743], the 2-[4-aminomethyl-(2,4-dimethoxyphenyl)]phenoxyacetic acid (AM) [Rink H., 1987, Tetrahedron Lett. 28, 3787-3790], Wang [Wang S.S., 1973, J. Am. Chem. Soc. 95, 1328-1333] and the like, which allow cleaving the semi-protected peptide and forming the cycle in solution with a step of deprotecting in solution or solid phase cycling and subsequently deprotecting and simultaneously cleaving the peptide.

Pharmaceutical compositions

The compounds of the invention can be administered by any means which causes contacting the compounds with the action site thereof in the body of a mammal, preferably the body of a human, and in the form of a composition containing them.

In this sense, another aspect of the invention is a pharmaceutical composition comprising a pharmaceutically effective amount of at least one compound of general formula (I), their stereoisomers, mixtures thereof and/or their pharmaceutically acceptable salts, and at least one pharmaceutically acceptable excipient. The number and the nature of the pharmaceutically acceptable excipients depend on the desired dosage form. The pharmaceutically acceptable excipients are known by the person skilled in the art [Faulí i Trillo C. (1993) "Tratado de Farmacia Galénica", Luzán 5, S.A. Ediciones, Madrid]. Said compositions can be prepared by means of conventional methods known in the state of the art ["Remington: The Science and Practice of Pharmacy", 20th (2003) Genaro A.R., ed., Lippincott Williams & Wilkins, Philadelphia, US].

The pharmaceutical compositions containing the compounds of the invention, their stereoisomers, mixtures thereof and/or their pharmaceutically acceptable salts, can be administered through any suitable type of route, for example by topical, oral or parenteral route, for which purpose they will include the pharmaceutically acceptable excipients necessary for the formulation of the desired dosage form.

Uses

Another aspect of the present invention relates to the use of a compound of general formula (I), their stereoisomers, mixtures thereof and/or their pharmaceutically acceptable salts, in the preparation of a pharmaceutical composition for the treatment, prevention and/or diagnosis of those conditions, disorders and/or pathologies in which the sstr1, sstr2, sstr3, sstr4 and/or sstr5 somatostatin receptors are expressed.

In a more particular aspect, the present invention relates to the use of a compound of general formula (I), their stereoisomers, mixtures thereof and/or their pharmaceutically

acceptable salts, in the preparation of a pharmaceutical composition for the treatment, prevention and/or diagnosis of those conditions, disorders and/or pathologies selected from the group consisting of acromegaly, symptomatic treatment of gastroenteropancreatic neuroendocrine tumors, diarrhea, cancer, tumors, neurodegenerative diseases, ocular diseases, immune system pathologies, inflammation, infections, esophageal varices, pain, wound healing, tissue regeneration, chronic pancreatitis, hypertrophic pulmonary osteoarthropathy and thyrotrophic adenoma.

In a more particular aspect, the present invention relates to the use of a compound of general formula (I), their stereoisomers, mixtures thereof and/or their pharmaceutically acceptable salts, in the preparation of a pharmaceutical composition for the treatment, prevention and/or diagnosis of those conditions, disorders and/or pathologies selected from the group consisting of acromegaly, inflammation, infections, esophageal varices, neuropathic pain, wound healing, tissue regeneration, chronic pancreatitis, hypertrophic pulmonary osteoarthropathy, thyrotrophic adenoma, grade 3-4 diarrhea, diarrhea associated with radiotherapy and/or chemotherapy treatment, symptomatic treatment of carcinoid syndrome or VIPomas, endocrine cancer, pancreatic cancer, colorectal cancer, breast cancer, ovarian cancer, prostate cancer, thyroid cancer, lung cancer, gastric cancer, hepatocellular carcinoma, Alzheimer's disease, arthritis, allergies, Lupus erythematosus, lymphoproliferative disorder, diabetic retinopathy, macular edema, Graves' ophthalmopathy, Cushing's syndrome, restenosis, angiogenesis, hyperthyroidism, hypothyroidism, hyperinsulinemia, psoriasis, hypercalcemia, Paget's disease, caquexia and Zollinger-Ellison syndrome.

Definitions

The abbreviations used in the present description have the following meanings:

Ac_2O, acetic anhydride; AcOH, acetic acid; Adpoc, 1-(1-adamantyl)-1-methylethoxy-carbonyl; All, allyl; Alloc,

allyloxycarbonyl; Boc, *tert*-butoxycarbonyl; Bzl, benzyl; Cbz, benzyloxycarbonyl; cHx, cyclohexyl; ClZ, 2-chlorobenzyl; DCM, dichloromethane; Dde, *N*-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethyl]; DIEA, N,N'-diisopropylethylamine; DIPCDI, diisopropylcarbodiimide; Dmab, 4-(*N*-[1-(4,4-dimethyl-2,6-dioxocyclohexylidene)-3-methylbutyl]amino)benzyl; DMF, N,N-dimethylformamide; Dnp, 2,4-dinitrophenyl; DOTA, 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid; DTPA, diethylenetriaminepentaacetic acid; ESI-MS, electrospray ionization mass spectrometry; Fm, fluorenylmethyl; Fmoc, 9-fluorenylmethoxycarbonyl; HF, hydrofluoric acid; HOBT, N-hydroxybenzotriazole; HPLC, High Performance Liquid Chromatography; IC_{50}, 50% maximal inhibitory concentration of a substance; ivDde, 1-(4,4-dimethyl-2,6-dioxo-cyclohexylidene)-3-methyl-butyl; Ki, inhibition constant of a drug; M, molecular mass; Mtt, methoxytrityl; µL, microliter; µmol, micromole; pNZ, *para*-nitrobenzyloxycarbonyl; RP-HPLC, reverse phase HPLC; SOM, somatostatin; tBu, *tert*-butyl; Teoc, 2-(trimethylsilyl)ethoxycarbonyl; TFA, trifluoroacetic acid; TFE, 2,2,2-trifluoroethanol; Tris, tris(hydroxymethyl)aminomethane; rt, retention time; Trt, trityl; Troc, 2,2,2-trichloroethoxycarbonyl; Z, benzyloxycarbonyl;

Amino acids:

Ala (A): Alanine

Asn (N): Asparagine

Cys (C): Cysteine

Gly (G): Glycine

Lys (K): Lysine

Lys(Ac): (N-acetyl)lysine

Lys(Alloc): (N-allyloxycarbonyl)lysine

Lys(2-Cl-Z): (N-2-chlorobenzyl)lysine

Lys(Dde): (N-1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethyl)lysine

Lys(For): (N-formyl)lysine

Lys(isopropyl): (N-isopropyl)lysine

Lys(palmitoyl): (N-palmitoyl)lysine

Lys(Tfa): (N-trifluoroacetyl)lysine

Lys(Z): (N-Benzyloxycarbonyl)lysine

Phe (F): Phenylalanine

Ser (S): Serine

Thr (T): Threonine

Trp (W): Tryptophan

Msa: 2,4,6-trimethylphenylalanine or 3-mesityl-alanine

Msg: 2,4,6-trimethyl-phenylglycine or 2-mesityl-glycine

Qla: 3-(3'-quinolyl)alanine or ß-(quinol-3-yl)-alanine

Examples

The following specific examples provided in this patent document serve to illustrate the nature of the present invention. These examples are included only for illustrative purposes and must not be interpreted as being limitations to the invention claimed herein.

Example 1: Synthesis of compound 1,

H-L-Ala-L-Gly-L-Cys-L-Lys-L-Asn-D-Msg-L-Phe-L-Trp-L-Lys-L-Thr-L-Phe-L-Thr-L-Ser-L-Cys-OH

The resin was deposited in the synthesis reactor equipped with a filtering plate and a cock. The *C*-terminal residue was incorporated to 0.3 g 2-chlorotrityl resin (1.6 mmol/g). The first amino acid Fmoc-Cys(Trt)-OH (1 eq.) was dissolved in 3 mL DCM and 0.15 mL DMF. DIEA (3 eq.) was added. The solution with amino acid and base was transferred to the reactor and stirred for 45 min. After this time 0.24 mL MeOH were added and left to react for 10 min. The filtrate was filtered out and discarded. The resin was washed with DCM and DMF. The filtrates were filtered out and discarded in each washing. 2.5 eq. Fmoc-amino acid, 2.5 eq. HOBT and 2.5 eq. DIPCDI were used for the incorporation of the next amino acids. For the coupling reaction, it was left to react 40 - 60 min and the incorporation of the amino acid was controlled with a ninhydrin test. If the ninhydrin test was positive, a reactivation step was performed for 15 - 30 min with 0.83 eq. HOBT and 0.83 eq. DIPCDI. If the ninhydrin test continued to be positive, a recoupling was performed with 1.25 eq. Fmoc-amino acid, HOBT and DIPCDI. If the

ninhydrin test was negative, the synthesis continued with the step of deprotecting the Fmoc group by means of treating with a solution of 20% piperidine in DMF twice. The peptidyl-resin was washed 5 times with DMF, filtering out and discarding the filtrates each time, and the next amino acid was then incorporated. 1.4 g peptidyl-resin were obtained.

1.4 g (0.43 mmol) peptidyl-resin were deposited in a reactor. 13.76 mL of an AcOH:TFE:DCM solution were added under magnetic stirring and left to react for 2h. It was filtered in a reactor with a filter plate and the filtrate was recovered. The resin was washed 3 times with 3.66 mL of the AcOH:TFE:DCM solution, the filtrates being recovered.

A solution of 1.12 g (10 eq.) iodine in 5.5 mL of AcOH:TFE:DCM solution was prepared. The filtrates recovered in acidolysis were transferred to the reactor that contained the iodine solution and the reaction was left under stirring. A solution of 2.34 g (22 eq.) sodium thiosulfate in 9.44 mL water was prepared and were added to the reactor once oxidation ended, complete discoloring being observed in 5 min. The stirring was stopped and the mixture was left to decant until phase separation. An extraction was performed by treating the aqueous phase 3 times with DCM and the organic phase 3 times with 5% citric acid:NaCl (v:w). The organic fractions were evaporated and the residue was vacuum dried. The solid residue was washed with water in a filter plate. 0.89 g of oxidized and protected product were obtained.

18.94 mL of the TFA:H_2O:DCM:anisole (55:5:30:10) reaction mixture were introduced in the reactor. 0.88 g of the semi-protected peptide were added to the previous solution and it was left to react for 4h. Heptane (20.1 mL) was added and it was stirred for 5 min. The stirring was stopped and it was left to decant. The aqueous phase was poured on cold ether and was left to stand for 15 - 30 min. The obtained suspension was filtered through a filter plate and the filtrates were discarded. The residue was washed with ether, discarding the filtrates in each washing. The solid was freeze dried, obtaining 0.63 g of crude

product.

The crude product was purified in a semi-preparative system equipped with an NW50 column packed with 10 micron kromasil silica. The peptide was suspended in 0.1N AcOH and DOWEX resin conditioned in 0.1N AcOH was added. The final acetate compound was recovered by filtration and was characterized by mass spectrometry in ESI-MS equipment.

Characterization:

ESI-MS: Theoretical M = 1664.7 g/mol, Experimental M: (m/z): $[M+2H]^+/2$=833.8

Analytical RP-HPLC: Gradient: 25-60% B in 20 min, rt = 14.08 min; Isocratic: 33% B in 30 min, rt =11.2 min (B= 0.07% TFA in acetonitrile).

Example 2: Synthesis of compound 2,

H-L-Ala-L-Gly-L-Cys-L-Lys-L-Asn-L-Phe-D-Msg-L-Trp-L-Lys-L-Thr-L-Phe-L-Thr-L-Ser-L-Cys-OH

The compound was prepared as described in Example 1. 0.3 g of resin were used to start and 0.54 g of crude product were obtained with the same equivalent ratios.

Characterization:

ESI-MS: Theoretical M = 1664.7 g/mol, Experimental M: (m/z): $[M+2H]^+/2$=833.8

Analytical RP-HPLC: Gradient: 25-60% B in 20 min, rt = 14.3 min; Isocratic: 33% B in 30 min, rt =12.5 min (B= 0.07% TFA in acetonitrile).

Example 3: Synthesis of compound 3,

H-L-Ala-L-Gly-L-Cys-L-Lys-L-Asn-L-Phe-L-Phe-L-Trp-L-Lys-L-Thr-D-Msg-L-Thr-L-Ser-L-Cys-OH

The compound was prepared as described in Example 1. 0.3 g of peptidyl-resin were used to start and 0.39 g of crude product were obtained with the same equivalent ratios.

Characterization:

ESI-MS: Theoretical M = 1664.7 g/mol, Experimental M: (m/z): $[M+2H]^+/2$=834.4

Analytical RP-HPLC: Gradient: 25-60% B in 20 min, rt = 12.42 min; Isocratic: 29.5% B in 30 min, rt =13.3 min (B= 0.07% TFA in

acetonitrile).

Example 4: Synthesis of compound 4,

H-L-Ala-L-Gly-L-Cys-L-Lys-L-Asn-L-Msg-L-Phe-L-Trp-L-Lys-L-Thr-L-Phe-L-Thr-L-Ser-L-Cys-OH

The compound was prepared as described in Example 1. 0.3 g of resin were used to start and 0.6 g of crude product were obtained with the same equivalent ratios.

Characterization:

ESI-MS: Theoretical M = 1664.7 g/mol, Experimental M: (m/z): $[M+2H]^+/2$=834.1

Analytical RP-HPLC: Gradient: 25-60% B in 20 min, rt = 12.5 min; Isocratic: 29.5% B in 30 min, rt =13.2 min (B= 0.07% TFA in acetonitrile).

Example 5: Synthesis of compound 5,

H-L-Ala-L-Gly-L-Cys-L-Lys-L-Asn-L-Phe-L-Msg-L-Trp-L-Lys-L-Thr-L-Phe-L-Thr-L-Ser-L-Cys-OH

The compound was prepared as described in Example 1. 0.3 g of resin were used to start and 0.49 g of crude product were obtained with the same equivalent ratios.

Characterization:

ESI-MS: Theoretical M = 1664.7 g/mol, Experimental M: (m/z): $[M+2H]^+/2$=833.8

Analytical RP-HPLC: Gradient: 25-60% B in 20 min, rt = 12.3 min; Isocratic: 29.5% B in 30 min, rt =12.3 min (B= 0.07% TFA in acetonitrile).

Example 6: Synthesis of compound 6,

H-L-Ala-L-Gly-L-Cys-L-Lys-L-Asn-L-Phe-L-Phe-L-Trp-L-Lys-L-Thr-L-Msg-L-Thr-L-Ser-L-Cys-OH

The compound was prepared as described in Example 1. 0.3 g of resin were used to start and 0.5 g of crude product were obtained with the same equivalent ratios.

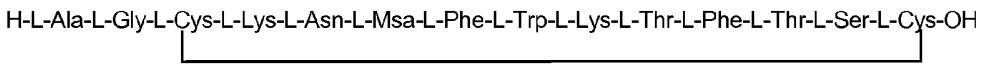
Characterization:

ESI-MS: Theoretical M = 1664.3 g/mol, Experimental M: (m/z): $[M+2H]^+/2$=833.5

Analytical RP-HPLC: Gradient: 25-60% B in 20 min, rt = 12.1 min; Isocratic: 29.5% B in 30 min, rt =11.45 min (B= 0.07% TFA in

acetonitrile).

Example 7: Synthesis of compound 7,



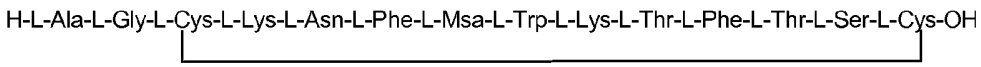
The compound was prepared as described in Example 1. 0.14 g of resin were used to start and 0.21 g of crude product were obtained with the same equivalent ratios.

Characterization:

ESI-MS: Theoretical M = 1678.7 g/mol, Experimental M: (m/z): $[M+2H]^+/2$=841.1

Analytical RP-HPLC: Gradient: 25-60% B in 20 min, rt = 14.3 min; Isocratic: 33% B in 30 min, rt =14.9 min (B= 0.07% TFA in acetonitrile).

Example 8: Synthesis of compound 8,



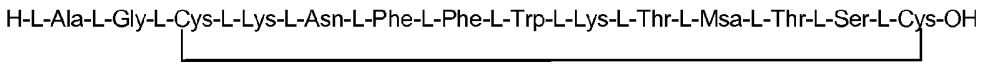
The compound was prepared as described in Example 1. 0.14 g of resin were used to start and 0.23 g of crude product were obtained with the same equivalent ratios.

Characterization:

ESI-MS: Theoretical M = 1678.7 g/mol, Experimental M: (m/z): $[M+2H]^+/2$=840.9

Analytical RP-HPLC: Gradient: 25-60% B in 20 min, rt = 14.8 min; Isocratic: 35% B in 30 min, rt =11.08 min (B= 0.07% TFA in acetonitrile).

Example 9: Synthesis of compound 9,



The compound was prepared as described in Example 1. 0.14 g of resin were used to start and 0.28 g of crude product were obtained with the same equivalent ratios.

Characterization:

ESI-MS: Theoretical M = 1678.7 g/mol, Experimental M: (m/z): $[M+2H]^+/2$=841

Analytical RP-HPLC: Gradient: 25-60% B in 20 min, rt = 14.1 min; Isocratic: 33% B in 30 min, rt =12.9 min (B= 0.07% TFA in

acetonitrile).

Example 10: Synthesis of compound 10,

H-L-Ala-L-Gly-L-Cys-L-Lys-L-Asn-D-Msa-L-Phe-L-Trp-L-Lys-L-Thr-L-Phe-L-Thr-L-Ser-L-Cys-OH

The compound was prepared as described in Example 1. 0.25 g of resin were used to start and 0.39 g of crude product were obtained with the same equivalent ratios.

Characterization:

ESI-MS: Theoretical M = 1678.7 g/mol, Experimental M: (m/z): $[M+2H]^+/2$=840.7

Analytical RP-HPLC: Gradient: 25-60% B in 20 min, rt = 14.8 min; Isocratic: 33% B in 30 min, rt =17.7 min (B= 0.07% TFA in acetonitrile).

Example 11: Synthesis of compound 11,

H-L-Ala-L-Gly-L-Cys-L-Lys-L-Asn-L-Phe-D-Msa-L-Trp-L-Lys-L-Thr-L-Phe-L-Thr-L-Ser-L-Cys-OH

The compound was prepared as described in Example 1. 0.25 g of resin were used to start and 0.47 g of crude product were obtained with the same equivalent ratios.

Characterization:

ESI-MS: Theoretical M = 1678.7 g/mol, Experimental M: (m/z): $[M+2H]^+/2$=840.7

Analytical RP-HPLC: Gradient: 25-60% B in 20 min, rt = 15.7 min; Isocratic: 36% B in 30 min, rt =12.3 min (B= 0.07% TFA in acetonitrile).

Example 12: Synthesis of compound 12,

H-L-Ala-L-Gly-L-Cys-L-Lys-L-Asn-L-Phe-L-Phe-L-Trp-L-Lys-L-Thr-D-Msa-L-Thr-L-Ser-L-Cys-OH

The compound was prepared as described in Example 1. 0.25 g of resin were used to start and 0.46 g of crude product were obtained with the same equivalent ratios.

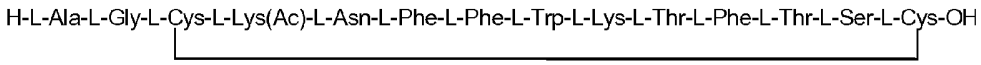
Characterization:

ESI-MS: Theoretical M = 1678.7 g/mol, Experimental M: (m/z): $[M+2H]^+/2$=840.8

Analytical RP-HPLC: Gradient: 25-60% B in 20 min, rt = 13.4 min; Isocratic: 32% B in 30 min, rt =12.03 min (B= 0.07% TFA in

acetonitrile).

Example 13: Synthesis of compound 13,



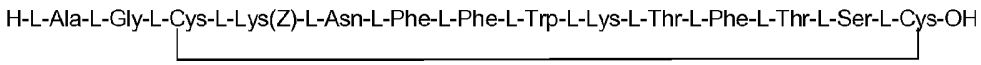
The compound was prepared as described in Example 1. 0.5 g of resin were used to start and 0.99 g of crude product were obtained with the same equivalent ratios.

Characterization:

ESI-MS: Theoretical M = 1679.05 g/mol, Experimental M: (m/z): $[M+2H]^+/2$=840.8

Analytical RP-HPLC: Gradient: 25-60% B in 20 min, rt = 12.2 min; Isocratic: 31% B in 30 min, rt =11.2 min (B= 0.07% TFA in acetonitrile).

Example 14: Synthesis of compound 14,



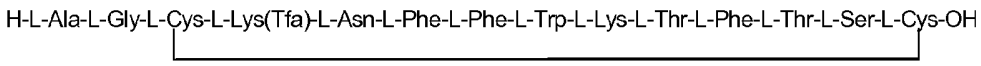
The compound was prepared as described in Example 1. 0.5 g of resin were used to start and 0.97 g of crude product were obtained with the same equivalent ratios.

Characterization:

ESI-MS: Theoretical M = 1771.7 g/mol, Experimental M: (m/z): $[M+2H]^+/2$=887.3

Analytical RP-HPLC: Gradient: 25-60% B in 20 min, rt = 15.9 min; Isocratic: 36% B in 30 min, rt =14.6 min (B= 0.07% TFA in acetonitrile).

Example 15: Synthesis of compound 15,



The compound was prepared as described in Example 1. 0.5 g of resin were used to start and 1 g of crude product was obtained with the same equivalent ratios.

Characterization:

ESI-MS: Theoretical M = 1733.6 g/mol, Experimental M: (m/z): $[M+2H]^+/2$=867.6

Analytical RP-HPLC: Gradient: 25-60% B in 20 min, rt = 14.4 min; Isocratic: 33% B in 30 min, rt =15.4 min (B= 0.07% TFA in

acetonitrile).

Example 16: Synthesis of compound 16,

H-L-Ala-L-Gly-L-Cys-L-Lys(2-Cl-Z)-L-Asn-L-Phe-L-Phe-L-Trp-L-Lys-L-Thr-L-Phe-L-Thr-L-Ser-L-Cys-OH

The compound was prepared as described in Example 1. 0.5 g of resin were used to start and 1.03 g of crude product were obtained with the same equivalent ratios.

Characterization:

ESI-MS: Theoretical M = 1806.5 g/mol, Experimental M: (m/z): $[M+2H]^+/2$=903.8

Analytical RP-HPLC: Gradient: 25-60% B in 20 min, rt = 16.7 min; Isocratic: 38% B in 30 min, rt =12.4 min (B= 0.07% TFA in acetonitrile).

Example 17: Synthesis of compound 17,

H-L-Ala-L-Gly-L-Cys-L-Lys(For)-L-Asn-L-Phe-L-Phe-L-Trp-L-Lys-L-Thr-L-Phe-L-Thr-L-Ser-L-Cys-OH

The compound was prepared as described in Example 1. 0.5 g of resin were used to start and 0.89 g of crude product were obtained with the same equivalent ratios.

Characterization:

ESI-MS: Theoretical M = 1665.67 g/mol, Experimental M: (m/z): $[M+2H]^+/2$=833.7

Analytical RP-HPLC: Gradient: 25-60% B in 20 min, rt = 12.4 min; Isocratic: 31% B in 30 min, rt =10.5 min (B= 0.07% TFA in acetonitrile).

Example 18: Synthesis of compound 18,

H-L-Ala-L-Gly-L-Cys-L-Lys(isopropyl)-L-Asn-L-Phe-L-Phe-L-Trp-L-Lys-L-Thr-L-Phe-L-Thr-L-Ser-L-Cys-OH

The compound was prepared as described in Example 1. 0.5 g of resin were used to start and 1.05 g of crude product were obtained with the same equivalent ratios.

Characterization:

ESI-MS: Theoretical M = 1679.2 g/mol, Experimental M: (m/z): $[M+2H]^+/2$=840.7

Analytical RP-HPLC: Gradient: 25-60% B in 20 min, rt = 11.75 min; Isocratic: 29% B in 30 min, rt =13.7 min (B= 0.07% TFA in acetonitrile).

Example 19: Synthesis of compound 19,

H-L-Ala-L-Gly-L-Cys-L-Lys(Alloc)-L-Asn-L-Phe-L-Phe-L-Trp-L-Lys-L-Thr-L-Phe-L-Thr-L-Ser-L-Cys-OH

The compound was prepared as described in Example 1. 0.5 g of resin were used to start and 0.95 g of crude product were obtained with the same equivalent ratios.

Characterization:

ESI-MS: Theoretical M = 1721.09 g/mol, Experimental M: (m/z): $[M+2H]^{+}/2$=861.8

Analytical RP-HPLC: Gradient: 25-60% B in 20 min, rt = 13.3 min; Isocratic: 34% B in 30 min, rt =12.1 min (B= 0.07% TFA in acetonitrile).

Example 20: Synthesis of compound 20,

H-L-Ala-L-Gly-L-Cys-L-Lys(Dde)-L-Asn-L-Phe-L-Phe-L-Trp-L-Lys-L-Thr-L-Phe-L-Thr-L-Ser-L-Cys-OH

The compound was prepared as described in Example 1. 0.5 g of resin were used to start and 1.02 g of crude product were obtained with the same equivalent ratios.

Characterization:

ESI-MS: Theoretical M = 1801.7 g/mol, Experimental M: (m/z): $[M+2H]^{+}/2$=901.7

Analytical RP-HPLC: Gradient: 25-60% B in 20 min, rt = 14.8 min; Isocratic: 34% B in 30 min, rt =13.5 min (B= 0.07% TFA in acetonitrile).

Example 21: Synthesis of compound 21,

H-L-Ala-L-Gly-L-Cys-L-Lys(palmitoyl)-L-Asn-L-Phe-L-Phe-L-Trp-L-Lys-L-Thr-L-Phe-L-Thr-L-Ser-L-Cys-OH

The compound was prepared as described in Example 1. 0.5 g of resin were used to start and 1.01 g of crude product were obtained with the same equivalent ratios.

Characterization:

ESI-MS: Theoretical M = 1875.4 g/mol, Experimental M: (m/z): $[M+2H]^{+}/2$=939.4

Analytical RP-HPLC: Gradient: 5-100% B in 20 min, rt = 19.1 min; Isocratic: 55% B in 30 min, rt =13.8 min (B= 0.07% TFA in acetonitrile).

Example 22: Synthesis of compound 22,

H-L-Ala-L-Gly-L-Cys-L-Lys-L-Asn-L-Phe-L-Phe-L-Qla-L-Lys-L-Thr-L-Phe-L-Thr-L-Ser-L-Cys-OH

The compound was prepared as described in Example 1. 0.3 g of resin were used to start and 0.58 g of crude product were obtained with the same equivalent ratios.

Characterization:

ESI-MS: Theoretical M = 1649.9 g/mol, Experimental M: (m/z): $[M+2H]^{+}/2$=825.6

Analytical RP-HPLC: Gradient: 25-60% B in 20 min, rt = 8.3 min; Isocratic: 24% B in 30 min, rt =12.2 min (B= 0.07% TFA in acetonitrile).

Example 23: Synthesis of compound 23,

H-L-Ala-L-Gly-L-Cys-L-Lys-L-Asn-L-Phe-L-Phe-D-Qla-L-Lys-L-Thr-L-Phe-L-Thr-L-Ser-L-Cys-OH

The compound was prepared as described in Example 1. 0.3 g of resin were used to start and 0.63 g of crude product were obtained with the same equivalent ratios.

Characterization:

ESI-MS: Theoretical M = 1649.9 g/mol, Experimental M: (m/z): $[M+2H]^{+}/2$=825.6

Analytical RP-HPLC: Gradient: 25-60% B in 20 min, rt = 8.9 min; Isocratic: 25% B in 30 min, rt =11.1 min (B= 0.07% TFA in acetonitrile).

Example 24: Synthesis of compound 24,

H-L-Ala-L-Gly-L-Cys-L-Lys-L-Asn-L-Msa-L-Phe-D-Trp-L-Lys-L-Thr-L-Phe-L-Thr-L-Ser-L-Cys-OH

The compound was prepared as described in Example 1. 0.4 g of resin were used to start and 0.71 g of crude product were obtained with the same equivalent ratios.

Characterization:

ESI-MS: Theoretical M = 1678.7 g/mol, Experimental M: (m/z): $[M+2H]^{+}/2$=840.4

Analytical RP-HPLC: Gradient: 25-60% B in 20 min, rt = 16.1 min; Isocratic: 36% B in 30 min, rt =11.4 min (B= 0.07% TFA in acetonitrile).

Example 25: Synthesis of compound 25,

H-L-Ala-L-Gly-L-Cys-L-Lys-L-Asn-L-Phe-L-Msa-D-Trp-L-Lys-L-Thr-L-Phe-L-Thr-L-Ser-L-Cys-OH

The compound was prepared as described in Example 1. 0.4 g of resin were used to start and 0.66 g of crude product were obtained with the same equivalent ratios.

Characterization:

ESI-MS: Theoretical M = 1678.7 g/mol, Experimental M: (m/z): $[M+2H]^{+}/2$=840.6

Analytical RP-HPLC: Gradient: 25-60% B in 20 min, rt = 16.05 min; Isocratic: 36% B in 30 min, rt =11.3 min (B= 0.07% TFA in acetonitrile).

Example 26: Synthesis of compound 26,

H-L-Ala-L-Gly-L-Cys-L-Lys-L-Asn-L-Phe-L-Phe-D-Trp-L-Lys-L-Thr-L-Msa-L-Thr-L-Ser-L-Cys-OH

The compound was prepared as described in Example 1. 0.4 g of resin were used to start and 0.61 g of crude product were obtained with the same equivalent ratios.

Characterization:

ESI-MS: Theoretical M = 1678.7 g/mol, Experimental M: (m/z): $[M+2H]^{+}/2$=840.5

Analytical RP-HPLC: Gradient: 25-60% B in 20 min, rt = 15.6 min; Isocratic: 34% B in 30 min, rt =14.6 min (B= 0.07% TFA in acetonitrile).

Example 27: Synthesis of compound 27,

H-L-Ala-L-Gly-L-Cys-L-Lys-L-Asn-L-Msa-L-Msa-L-Trp-L-Lys-L-Thr-L-Phe-L-Thr-L-Ser-L-Cys-OH

The compound was prepared as described in Example 1. 0.1 g of resin were used to start and 0.12 g of crude product were obtained with the same equivalent ratios.

Characterization:

ESI-MS: Theoretical M = 1721.1 g/mol, Experimental M: (m/z): $[M+2H]^{+}/2$=861.5

Analytical RP-HPLC: Gradient: 25-60% B in 20 min, rt = 16.5 min; Isocratic: 37% B in 30 min, rt =16.6 min (B= 0.07% TFA in acetonitrile).

Example 28: Synthesis of compound 28,

H-L-Ala-L-Gly-L-Cys-L-Lys-L-Asn-L-Msa-L-Phe-L-Trp-L-Lys-L-Thr-L-Msa-L-Thr-L-Ser-L-Cys-OH

The compound was prepared as described in Example 1. 0.1 g of resin were used to start and 0.1 g of crude product were obtained with the same equivalent ratios.

Characterization:

ESI-MS: Theoretical M = 1721.1 g/mol, Experimental M: (m/z): $[M+2H]^{+}/2$=861.4

Analytical RP-HPLC: Gradient: 25-60% B in 20 min, rt = 15.38 min; Isocratic: 37% B in 30 min, rt =9.8 min (B= 0.07% TFA in acetonitrile).

Example 29: Synthesis of compound 29,

H-L-Ala-L-Gly-L-Cys-L-Lys-L-Asn-L-Phe-L-Msa-L-Trp-L-Lys-L-Thr-L-Msa-L-Thr-L-Ser-L-Cys-OH

The compound was prepared as described in Example 1. 0.1 g of resin were used to start and 0.12 g of crude product were obtained with the same equivalent ratios.

Characterization:

ESI-MS: Theoretical M = 1721.1 g/mol, Experimental M: (m/z): $[M+2H]^{+}/2$=861.5

Analytical RP-HPLC: Gradient: 25-60% B in 20 min, rt = 16.4 min; Isocratic: 37% B in 30 min, rt =15.4 min (B= 0.07% TFA in acetonitrile).

Example 30: Synthesis of compound 30,

H-L-Ala-L-Gly-L-Cys-L-Lys-L-Asn-L-Msa-L-Msa-L-Trp-L-Lys-L-Thr-L-Msa-L-Thr-L-Ser-L-Cys-OH

The compound was prepared as described in Example 1. 0.1 g of resin were used to start and 0.1 g of crude product were obtained with the same equivalent ratios.

Characterization:

ESI-MS: Theoretical M = 1762.9 g/mol, Experimental M: (m/z): $[M+2H]^{+}/2$=882.6

Analytical RP-HPLC: Gradient: 25-60% B in 20 min, rt = 18.3 min; Isocratic: 40% B in 30 min, rt =17.8 min (B= 0.07% TFA in acetonitrile).

Example 31: Synthesis of compound 31,

H-L-Ala-L-Gly-L-Gly-L-Lys-L-Asn-L-Phe-L-Phe-L-Trp-L-Lys-L-Thr-L-Phe-L-Thr-L-Ser-L-Gly-NH2

CH_2-CH=CH-CH_2

The compound was synthesized following the general protocol described for the synthesis of the previous analogs starting from 1 g of Rink amide resin (0.45 mmol/g). The peptidyl-resin (200 mg, 0.09 mmol) was suspended in 1 mL DCM and 0.1 mL 0.4 M LiCl in DMF in a high pressure reactor. 15 mg (0.018 mmol) second generation Grubbs' catalyst were added and left to react for 1h irradiating at 100°C in a CEM Discovery microwave equipment. Once the metathesis reaction ended, the peptidyl-resin is passed to a reactor equipped with a filter plate and is washed with DMF, DCM, MeOH and ether. The peptidyl-resin was treated with a mixture of TFA:TIS:H_2O for 1h and the compound was isolated by means of filtration. The filtrates were precipitated with ether. The obtained suspension was filtered through a filter plate and the filtrates were discarded. The residue was washed with ether, discarding the filtrates in each washing. The solid was freeze dried, obtaining 40 mg of crude product.

Characterization:

ESI-MS: Theoretical M = 1597.8 g/mol, Experimental M: (m/z): $[M+H^+]$=1597.8

Analytical RP-HPLC: Gradient: 20-35% B in 6 min, rt = 1.74 min (B= 0.07% TFA in acetonitrile).

Example 32: sstr1, sstr2, sstr3, sstr4 and sstr 5 receptor binding assay.

The sstr1, sstr2, sstr3, sstr4 and sstr 5 receptor binding assay were performed using membranes from CHO-K1 cells (ATCC, American Type Culture Collection) in which the sstr1, sstr2, sstr3, sstr4 or sstr5 somatostatin receptors (Invitrogen plasmids) were selectively transfected. ^{125}I-Tyr^{11}-somatostatin 14 was used as a radioactive ligand and somatostatin-14 as a cold ligand. The transfected cells were isolated by centrifugation and the pellet was resuspended in Tris buffer, and proteins were determined by the Bradford method. Dose-effect curves were elaborated to determine the IC_{50} and Ki with those somatostatin

analogs that displaced ^{125}I-Tyr^{11}-somatostatin 14 to a concentration of 10 µM. Membranes from the clones expressed by the various receptors were incubated with a fixed concentration of tracer (0.1 nM) in the presence of increasing concentrations of somatostatin-14 and analogs, from 1 pM up to 1 µM. The mixture was incubated in 96-well plates for 1h at 30°C, and after this time it was filtered in a Harvester to separate the bound radioactivity from the unbound radioactivity. The filter, which contained the membranes that had bound ^{125}I-Tyr^{11}-somatostatin 14, was coated with of scintillation fluid and was counted in a MicroBeta counter. The radioactivity obtained in the absence of somatostatin-14 is considered as the total binding and the radioactivity obtained in the presence of 1 µM of somatostatin-14 is considered as the nonspecific binding. The specific binding is considered the difference between the total and nonspecific binding. The percentage of specific binding at each point was calculated. Tables 1-5 show the results of % specific binding of the somatostatin analogs to the 1-5 somatostatin receptors with respect to the somatostatin.

Table 1: Percentage of specific binding to the sstr1 receptor with respect to somatostatin.

SSTR1 Concentration (M)	Compound 1 % specific binding	Compound 2 % specific binding	Compound 3 % specific binding	Compound 4 % specific binding	Compound 5 % specific binding	Compound 6 % specific binding
-13	100.0	100.0	100.0	100.0	100.0	100.0
-12	94.0	102.7	98.4	100.5	119.9	100.0
-11	100.1	92.0	97.1	92.5	109.7	87.1
-10	100.9	95.1	94.6	99.7	114.9	89.2
-9	95.7	92.9	96.2	89.6	127.1	97.5
-8	94.2	83.4	86.8	91.2	111.9	99.3
-7	74.5	64.3	76.3	76.4	87.6	65.2
-6	40.5	22.0	20.0	27.4	25.0	13.0

SSTR1 Concentration (M)	Compound 7 % specific binding	Compound 8 % specific binding	Compound 9 % specific binding	Compound 11 % specific binding	Compound 13 % specific binding	Compound 14 % specific binding
-13	100.0	100.0	100.0	100.0	100.0	100.0
-12	101.6	105.2	107.9	95.8	94.2	77.0
-11	99.0	85.5	94.8	90.0	88.1	79.2
-10	101.1	82.0	88.7	83.8	88.5	79.2
-9	76.1	67.7	89.8	72.6	70.5	66.4
-8	41.8	38.9	55.8	68.0	42.0	43.2
-7	19.2	18.0	25.6	29.6	12.5	18.0
-6	4.6	0.6	11.1	5.2	1.7	1.2

SSTR1 Concentration (M)	Compound 15 % specific binding	Compound 16 % specific binding	Compound 17 % specific binding	Compound 18 % specific binding	Compound 19 % specific binding	Compound 20 % specific binding
-13	100.0	100.0	100.0	100.0	100.0	100.0
-12	87.2	97.5	104.1	89.2	93.7	95.3
-11	92.6	100.9	101.3	81.2	90.5	99.9
-10	93.6	92.4	99.4	76.8	94.1	95.5

-9	86.7	89.9	88.2	53.2	77.0	86.9
-8	46.1	79.2	52.4	22.7	40.9	47.6
-7	23.1	38.4	29.5	1.3	19.3	20.1
-6	9.1	13.9	17.2	-2.8	4.5	6.6

SSTR1 Concentration (M)	Compound 21 % specific binding	Compound 22 % specific binding	Compound 23 % specific binding	Compound 24 % specific binding	Compound 25 % specific binding	Compound 26 % specific binding
-13	100.0	100.0	100.0	100.0	100.0	100.0
-12	94.1	101.1	98.2	101.3	100.8	106.9
-11	102.0	103.7	107.9	96.7	97.9	98.2
-10	88.6	87.4	99.0	94.3	80.1	97.7
-9	78.8	67.8	89.0	78.2	53.5	81.1
-8	70.4	41.8	64.8	50.8	42.2	54.8
-7	40.0	26.9	31.8	35.2	31.8	42.1
-6	20.1	18.1	10.1	23.8	25.1	24.7

SSTR1 Concentration (M)	Compound 29 % specific binding	Compound 31 % specific binding
-13	100.0	100.0
-12	104.0	96.0
-11	103.9	91.5
-10	91.7	75.6
-9	91.4	48.6
-8	86.2	33.6
-7	57.1	30.4
-6	14.0	16.9

Table 2: Percentage of specific binding to the sstr2 receptor with respect to somatostatin.

SSTR2 Concentration (M)	Compound 1 % specific binding	Compound 2 % specific binding	Compound 3 % specific binding	Compound 4 % specific binding	Compound 5 % specific binding	Compound 6 % specific binding
-13	100.0	100.0	100.0	100.0	100.0	100.0
-12	100.9	101.1	106.9	104.4	96.5	93.8
-11	97.4	96.4	100.6	106.0	101.7	98.1
-10	97.0	95.2	99.5	104.7	101.3	97.7
-9	98.3	96.0	99.0	104.4	101.7	98.1
-8	88.9	82.7	97.0	97.4	97.7	94.3
-7	62.8	49.8	72.7	64.4	55.9	72.1
-6	12.1	10.0	13.3	6.5	8.4	17.2

SSTR2 Concentration (M)	Compound 7 % specific binding	Compound 8 % specific binding	Compound 9 % specific binding	Compound 11 % specific binding	Compound 12 % specific binding	Compound 13 % specific binding
-13	100.0	100.0	100.0	100.0	100.0	100.0
-12	96.9	66.6	72.8	99.2	99.0	100.6
-11	93.9	57.4	61.2	93.4	95.9	90.1
-10	83.7	43.0	50.1	92.6	90.9	68.1
-9	60.7	23.1	24.8	78.9	82.2	30.3
-8	33.7	9.9	6.6	33.9	42.9	9.8
-7	23.0	3.7	2.0	5.5	9.8	4.0
-6	11.1	1.8	2.3	0.5	2.4	1.3

SSTR2 Concentration (M)	Compound 14 % specific binding	Compound 15 % specific binding	Compound 16 % specific binding	Compound 17 % specific binding	Compound 18 % specific binding	Compound 19 % specific binding
-13	100.0	100.0	100.0	100.0	100.0	100.0
-12	52.9	70.9	69.1	104.8	78.2	47.9
-11	46.5	53.6	64.2	88.0	59.8	35.4
-10	39.5	39.3	57.8	59.6	41.8	20.1

-9	24.2	19.3	42.3	28.6	15.1	10.9		
-8	9.0	5.8	14.8	10.6	6.0	3.5		
-7	3.3	1.5	4.9	3.1	-0.2	1.7		
-6	1.1	0.5	2.0	1.1	-2.0	1.0		

SSTR2	Compound 20	Compound 21	Compound 23	Compound 24	Compound 25	Compound 26
Concentration (M)	% specific binding	% specific binding	% specific binding	% specific binding	% specific binding	% specific binding
-13	100.0	100.0	100.0	100.0	100.0	100.0
-12	60.3	88.1	103.3	100.7	68.4	91.1
-11	53.6	90.3	100.8	98.0	40.0	84.3
-10	44.1	81.3	91.0	96.1	18.8	68.4
-9	22.3	56.7	68.3	79.9	6.1	27.0
-8	8.0	22.6	35.6	52.7	4.6	7.1
-7	2.9	7.6	14.3	17.6	3.3	3.3
-6	2.3	3.6	4.7	3.7	0.6	1.4

SSTR2	Compound 27	Compound 29	Compound 31
Concentration (M)	% specific binding	% specific binding	% specific binding
-13	100.0	100.0	100.0
-12	98.0	98.6	98.0
-11	96.7	93.9	87.4
-10	95.9	86.9	71.6
-9	94.7	71.3	50.8
-8	73.5	24.3	19.4
-7	22.5	4.7	9.2
-6	2.2	1.6	4.6

Table 3: Percentage of specific binding to the sstr3 receptor with respect to somatostatin.

SSTR3 Concentration (M)	Compound 6 % specific binding	Compound 7 % specific binding	Compound 9 % specific binding	Compound 10 % specific binding	Compound 13 % specific binding	Compound 14 % specific binding
-13	100.0	100.0	100.0	100.0	100.0	100.0
-12	104.6	93.2	90.2	94.6	96.5	82.9
-11	100.8	92.5	87.9	92.6	92.0	81.4
-10	98.6	77.6	75.7	92.2	86.7	78.0
-9	79.6	55.0	67.3	90.7	71.0	62.8
-8	65.6	26.7	33.9	73.8	43.1	36.2
-7	41.3	9.9	14.5	30.4	14.5	8.3
-6	10.0	1.6	5.3	4.8	3.4	-1.1

SSTR3 Concentration (M)	Compound 15 % specific binding	Compound 16 % specific binding	Compound 17 % specific binding	Compound 18 % specific binding	Compound 19 % specific binding	Compound 20 % specific binding
-13	100.0	100.0	100.0	100.8	100.0	100.0
-12	93.3	99.1	100.1	91.8	92.4	94.9
-11	87.7	92.8	96.9	84.8	82.2	87.7
-10	82.4	88.4	89.3	65.0	70.7	81.7
-9	65.6	76.5	79.9	31.8	64.5	62.8
-8	36.5	45.2	42.5	9.8	30.7	31.7
-7	11.8	14.6	14.8	-0.3	5.9	5.3
-6	4.6	3.8	3.8	-1.7	-1.0	-3.2

SSTR3 Concentration (M)	Compound 21 % specific binding	Compound 22 % specific binding	Compound 23 % specific binding	Compound 24 % specific binding	Compound 25 % specific binding	Compound 26 % specific binding
-13	100.0	100.0	100.0	100.0	100.0	100.0
-12	100.7	87.6	87.9	82.3	93.2	79.6
-11	101.4	83.4	82.1	70.2	87.3	73.7
-10	95.8	75.5	65.2	63.5	81.7	67.0

-9	82.7	56.8	34.7	40.8	74.6	47.1
-8	56.6	26.3	9.4	11.0	48.9	14.3
-7	23.0	3.2	-0.3	-0.2	21.3	-1.4
-6	4.8	-5.3	-5.3	-3.8	4.3	-6.7

SSTR3

Concentration (M)	Compound 28 % specific binding	Compound 31 % specific binding
-13	100.0	100.0
-12	96.5	94.5
-11	92.3	86.3
-10	88.2	83.5
-9	86.4	71.1
-8	58.5	40.9
-7	19.6	13.6
-6	1.5	2.2

Table 4: Percentage of specific binding to the sstr4 receptor with respect to somatostatin.

SSTR4 Concentration (M)	Compound 3 % specific binding	Compound 6 % specific binding	Compound 7 % specific binding	Compound 8 % specific binding	Compound 9 % specific binding	Compound 13 % specific binding
-13	100.0	100.0	100.0	100.0	100.0	100.0
-12	99.9	101.1	91.7	99.3	93.8	94.0
-11	106.6	110.2	89.3	103.2	94.9	95.3
-10	107.9	95.8	90.3	98.8	96.9	91.7
-9	101.9	94.7	70.5	94.6	79.6	84.4
-8	98.7	86.2	31.0	71.1	42.1	49.6
-7	78.6	53.6	1.3	25.3	4.9	13.6
-6	32.3	7.1	-7.1	-3.7	-5.7	2.7

SSTR4 Concentration (M)	Compound 14 % specific binding	Compound 15 % specific binding	Compound 16 % specific binding	Compound 17 % specific binding	Compound 18 % specific binding	Compound 19 % specific binding
-13	100.0	100.0	100.0	100.0	100.0	100.0
-12	82.8	86.6	91.3	93.8	99.3	96.7
-11	84.1	93.1	87.5	93.4	93.2	93.0
-10	81.3	86.1	81.1	91.9	93.0	90.2
-9	70.6	76.4	72.0	78.6	76.5	67.9
-8	36.2	42.6	46.7	45.2	33.0	29.8
-7	13.5	14.0	15.2	12.7	7.8	9.3
-6	1.8	2.2	4.1	4.1	-0.4	1.1

SSTR4 Concentration (M)	Compound 20 % specific binding	Compound 21 % specific binding	Compound 24 % specific binding	Compound 31 % specific binding
-13	100.0	100.0	100.0	100.0
-12	93.3	101.3	99.9	90.1
-11	94.9	94.0	95.2	94.3
-10	90.0	90.7	91.7	87.0

-9	81.3	62.7	76.1	65.0
-8	51.3	32.8	41.3	27.9
-7	11.1	15.2	17.0	16.4
-6	2.4	7.5	3.5	7.7

Table 5: Percentage of specific binding to the sstr5 receptor with respect to somatostatin.

SSTR5 Concentration (M)	Compound 6 % specific binding	Compound 7 % specific binding	Compound 9 % specific binding	Compound 13 % specific binding	Compound 14 % specific binding	Compound 15 % specific binding
-13	100.0	100.0	100.0	100.0	100.0	100.0
-12	97.6	92.4	100.3	102.5	88.6	90.1
-11	102.1	90.3	100.8	97.4	77.6	88.8
-10	99.6	79.5	89.7	94.5	77.3	79.2
-9	95.3	54.7	71.0	78.3	62.9	57.0
-8	80.3	17.6	24.7	39.4	31.3	22.7
-7	44.7	4.2	6.1	9.3	5.2	4.6
-6	9.3	-1.4	0.9	-0.6	-1.1	-0.6

SSTR5 Concentration (M)	Compound 16 % specific binding	Compound 17 % specific binding	Compound 18 % specific binding	Compound 19 % specific binding	Compound 20 % specific binding	Compound 21 % specific binding
-13	100.0	100.0	100.0	100.0	100.0	100.0
-12	90.2	100.5	100.1	94.2	96.5	97.5
-11	87.2	104.2	94.6	86.7	89.1	95.9
-10	84.4	95.6	87.3	79.2	87.9	86.5
-9	73.8	80.4	62.9	62.1	74.1	69.0
-8	35.0	35.1	26.5	30.5	46.1	28.3
-7	7.0	7.6	5.0	7.3	14.6	8.1
-6	-0.8	-1.0	-2.2	0.5	1.7	1.2

SSTR5 Concentration (M)	Compound 23 % specific binding	Compound 24 % specific binding	Compound 25 % specific binding	Compound 26 % specific binding	Compound 28 % specific binding	Compound 31 % specific binding
-13	100.0	100.0	100.0	100.0	100.0	102.1
-12	102.9	92.9	102.7	93.7	97.3	95.4
-11	104.3	86.1	103.0	86.8	92.3	83.8

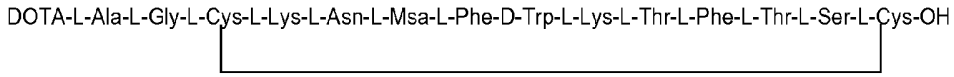
-10	95.8	72.5	101.9	75.7	91.4	61.7
-9	86.1	38.3	97.0	49.2	85.5	31.1
-8	58.9	8.6	76.2	12.2	57.2	7.2
-7	25.6	1.0	31.0	1.1	11.1	-1.4
-6	3.5	-0.6	2.9	-0.2	0.1	-4.2

Example 33: Stability

The new compounds were incubated with 90% human serum at 37°C. Aliquots were extracted at different incubation times. Acetonitrile was added to precipitate the proteins from the serum, it was centrifuged and the supernatant was filtered and injected in the RP-HPLC (Grad: 20-80% B in 30 min, B= 0.07% TFA in acetonitrile). The disappearance of the initial product was analyzed using the area corresponding to the initial product and the half-life time was calculated.

The new compounds have a half-life time greater than that of somatostatin. Compound 8 has a half-life time of 5.2h. Compounds 10 and 11 have half-life times of 10.5h and 8.1h, respectively. Compound 21 has a half-life time of 41.7h. Compounds 24, 25 and 26 have half-life times of 26.2, 24.6 and 41h, respectively. Compound 27 has a half-life time of 43.9h and compound 30 has a half-life time of 93.3h.

Example 34: Synthesis of compound 32



The incorporation of the C-terminal residue was performed as described in Example 1 starting from 1 g of 2-chlorotrityl resin. The incorporation of the next 7 amino acids (fragment 7-14) was performed in an automatic synthesis reactor Liberty-CEM with an initial functionalization of 1.6 meq/g, scale 1 mM and 3 eq. Fmoc-amino acid, 3 eq. HOBT and 3 eq. DIPCDI. The incorporation of the last 6 amino acids was performed on 1.887 g of peptidyl-resin as described in Example 1, with the same ratio of equivalents. The incorporation of tri(tBu)-DOTA-OH was performed using 2.5 eq. tri(tBu)-DOTA-OH, 2.5 eq. benzotriazole-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate, 2.5 eq. HOBt and 5 eq. DIEA in DMF during 60 min. The incorporation of DOTA was controlled with a ninhydrin test. 0.8454 g peptidyl-resin were obtained.

The subsequent oxidation and deprotection treatments were performed as described in Example 1 and 0.383 g of crude product were obtained.

The crude product was purified in a semi-preparative system equipped with an NW50 column packed with 10 micron kromasil silica, obtaining 0.103 g of purified product.

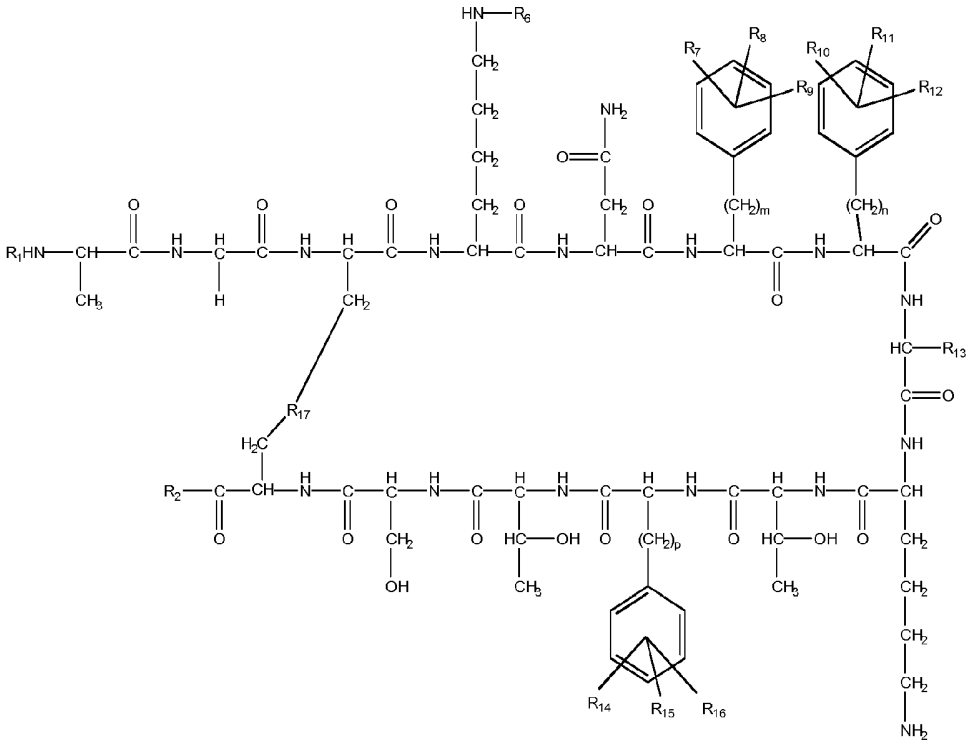
Characterization:

ESI-MS: Theoretical M = 2065.7 g/mol, Experimental M: (m/z): $[M+2H]^+/2$=1034.6

Analytical RP-HPLC: Gradient: 25-60% B in 20 min, rt = 13.1 min; Isocratic: 32% B in 30 min, rt = 12.5 min (B = 0.07% TFA in acetonitrile).

CLAIMS

1. A compound of general formula (I)



(I)

their stereoisomers, mixtures thereof and/or their pharmaceutically acceptable salts, wherein:

R_1 is selected from the group consisting of H, a substituted or unsubstituted non-cyclic aliphatic group, a substituted or unsubstituted alicyclyl group, a substituted or unsubstituted heterocyclyl group, a substituted or unsubstituted heteroarylalkyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted aralkyl group, a polyethylene glycol polymer, a chelating agent and R_5-CO-;

R_2 is selected from the group consisting of $-NR_3R_4$, $-OR_3$ and $-SR_3$;

R_6 is selected from the group consisting of H, acetyl, trifluoroacetyl, isopropyl, palmitoyl, allyloxycarbonyl, 2-chlorobenzyl, formyl, *N*-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-

ylidene)ethyl] and benzyloxycarbonyl;

R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{14}, R_{15} and R_{16} are selected independently from one another from the group consisting of H and a non-cyclic aliphatic group;

m is an integer selected from between 0 and 6 with the condition that when R_7, R_8 and R_9 are H, then m is different from 0;

n is an integer selected from between 0 and 6 with the condition that when R_{10}, R_{11} and R_{12} are H, then n is different from 0;

p is an integer selected from between 0 and 6 with the condition that when R_{14}, R_{15} and R_{16} are H, then p is different from 0;

R_{13} is selected from the group consisting of L-(3-quinolyl)methyl, D-(3-quinolyl)methyl, L-(3-indolyl)methyl and D-(3-indolyl)methyl;

R_{17} is selected from the group consisting of -S-S-, $-CH_2-CH_2-$ and -CH=CH-;

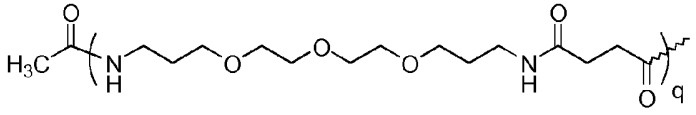
R_3 and R_4 are independently selected from the group consisting of H, a substituted or unsubstituted non-cyclic aliphatic group, a substituted or unsubstituted alicyclyl group, a substituted or unsubstituted heterocyclyl group, a substituted or unsubstituted heteroarylalkyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted aralkyl group and a polymer;

R_5 is selected from the group consisting of H, a substituted or unsubstituted non-cyclic aliphatic group, a substituted or unsubstituted alicyclyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted aralkyl group, a substituted or unsubstituted heterocyclyl group and a substituted or unsubstituted heteroarylalkyl group;

with the condition that when R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{14}, R_{15} and R_{16} are all equal to H, n, m and p are equal to 1 and R_{13} is equal to L-(3-indolyl)methyl or to D-(3-indolyl)methyl, R_{17} is not equal to -S-S-.

2. The compound according to claim 1, wherein R_2 is

selected from the group consisting of H, a polymer of general formula (II)



(II)

where q ranges between 1 and 5, and R_5-CO-, where R_5 is selected from the group consisting of substituted or unsubstituted C_1-C_{24} alkyl radical, substituted or unsubstituted C_2-C_{24} alkenyl radical, substituted or unsubstituted C_2-C_{24} alkynyl radical, substituted or unsubstituted C_3-C_{24} cycloalkyl radical, substituted or unsubstituted C_5-C_{24} cycloalkenyl radical, substituted or unsubstituted C_8-C_{24} cycloalkynyl radical, substituted or unsubstituted C_6-C_{30} aryl radical, substituted or unsubstituted C_7-C_{24} aralkyl radical, a substituted or unsubstituted heterocyclyl radical having 3-10 ring members, a substituted or unsubstituted heteroarylalkyl radical having 2 to 24 carbon atoms and having 1 to 3 atoms other than carbon where the alkyl chain is of 1 to 6 carbon atoms.

3. The compound according to claim 2, wherein R_5 is selected from H, acetyl, *tert*-butanoyl, hexanoyl, 2-methylhexanoyl, cyclohexanecarboxyl, octanoyl, decanoyl, lauroyl, myristoyl, palmitoyl, stearoyl, behenyl, oleoyl and linoleoyl.

4. The compound according to claim 1, wherein R_1 is a chelating agent complexed with a detectable element or a radiotherapeutic element.

5. The compound according to any of the previous claims, wherein R_3 and R_4 are independently selected from the group consisting of H, substituted or unsubstituted C_1-C_{24} alkyl, substituted or unsubstituted C_2-C_{24} alkenyl, substituted or unsubstituted C_2-C_{24} alkynyl, substituted or unsubstituted C_3-C_{24} cycloalkyl, substituted or unsubstituted C_5-C_{24} cycloalkenyl, substituted or unsubstituted C_8-C_{24} cycloalkynyl, substituted or unsubstituted C_6-C_{30} aryl, substituted or unsubstituted C_7-C_{24} aralkyl, a substituted or unsubstituted heterocyclyl having 3-10

ring members, and a substituted or unsubstituted heteroarylalkyl group having 2 to 24 carbon atoms and having 1 to 3 atoms other than carbon where the alkyl chain is of 1 to 6 carbon atoms, and a polymer of general formula (II) where q ranges between 1 and 5.

6. The compound according to claim 5, wherein R_3 and R_4 are selected from the group consisting of H, methyl, ethyl, hexyl, dodecyl or hexadecyl.

7. The compound according to any of the previous claims, wherein R_7, R_8 and R_9 are equal to one another and are in an ortho-, para-, ortho- configuration or a meta-, para-, meta-configuration, R_{10}, R_{11} and R_{12} are equal to one another and are in an ortho-, para-, ortho- configuration or a meta-, para-, meta- configuration, and R_{14}, R_{15} and R_{16} are equal to one another and are in an ortho-, para-, ortho- configuration or a meta-, para-, meta- configuration.

8. The compound according to any of the previous claims, wherein R_1 is selected from the group consisting of H, acetyl, lauroyl, myristoyl, palmitoyl or a polymer of general formula (II) where q ranges between 1 and 5, R_2 is $-NR_3R_4$ or $-OR_3$ where R_3 and R_4 are independently selected from H, methyl, ethyl, hexyl, dodecyl and hexadecyl, R_6 is H, R_7, R_8 and R_9 are methyl and are in an ortho-, para-, ortho- configuration or a meta-, para-, meta- configuration, m is 0 or 1, R_{10}, R_{11}, R_{12}, R_{14}, R_{15} and R_{16} are H, n and p are equal to 1, R_{13} is selected from the group consisting of L-(3-indolyl)methyl and D-(3-indolyl)methyl and R_{17} is -S-S-.

9. The compound according to any of claims 1 to 7, wherein R_1 is selected from the group consisting of H, acetyl, lauroyl, myristoyl, palmitoyl or a polymer of general formula (II) where q ranges between 1 and 5, R_2 is $-NR_3R_4$ or $-OR_3$ where R_3 and R_4 are independently selected from H, methyl, ethyl, hexyl, dodecyl and hexadecyl, R_6 is H, R_{10}, R_{11} and R_{12} are methyl and are in an ortho-, para-, ortho- configuration or a meta-, para-, meta-configuration, n is 0 or 1, R_7, R_8, R_9, R_{14}, R_{15} and R_{16} are H, m and p are equal to 1, R_{13} is selected from the group consisting

of L-(3-indolyl)methyl and D-(3-indolyl)methyl and R_{17} is -S-S-.

10. The compound according to any of claims 1 to 7, wherein R_1 is selected from the group consisting of H, acetyl, lauroyl, myristoyl, palmitoyl or a polymer of general formula (II) where q ranges between 1 and 5, R_2 is $-NR_3R_4$ or $-OR_3$ where R_3 and R_4 are independently selected from H, methyl, ethyl, hexyl, dodecyl and hexadecyl, R_6 is H, R_{14}, R_{15} and R_{16} are methyl and are in an ortho-, para-, ortho- configuration or a meta-, para-, meta-configuration, p is 0 or 1, R_7, R_8, R_9, R_{10}, R_{11} and R_{12} are H, m and n are equal to 1, R_{13} is selected from the group consisting of L-(3-indolyl)methyl and D-(3-indolyl)methyl and R_{17} is -S-S-.

11. The compound according to any of claims 1 to 7, wherein R_1 is selected from the group consisting of H, acetyl, lauroyl, myristoyl, palmitoyl or a polymer of general formula (II) where q ranges between 1 and 5, R_2 is $-NR_3R_4$ or $-OR_3$ where R_3 and R_4 are independently selected from H, methyl, ethyl, hexyl, dodecyl and hexadecyl, R_6 is H, R_7, R_8, R_9, R_{10}, R_{11} and R_{12} are methyl and are in an ortho-, para-, ortho- configuration or a meta-, para-, meta- configuration, m and n are 0 or 1, R_{14}, R_{15} and R_{16} are H, p is equal to 1, R_{13} is selected from the group consisting of L-(3-indolyl)methyl and D-(3-indolyl)methyl and R_{17} is -S-S-.

12. The compound according to any of claims 1 to 7, wherein R_1 is selected from the group consisting of H, acetyl, lauroyl, myristoyl, palmitoyl or a polymer of general formula (II) where q ranges between 1 and 5, R_2 is $-NR_3R_4$ or $-OR_3$ where R_3 and R_4 are independently selected from H, methyl, ethyl, hexyl, dodecyl and hexadecyl, R_6 is H, R_7, R_8, R_9, R_{14}, R_{15} and R_{16} are methyl and are in an ortho-, para-, ortho- configuration or a meta-, para-, meta- configuration, m and p are 0 or 1, R_{10}, R_{11} and R_{12} are H, n is equal to 1, R_{13} is selected from the group consisting of L-(3-indolyl)methyl and D-(3-indolyl)methyl and R_{17} is -S-S-.

13. The compound according to any of claims 1 to 7, wherein R_1 is selected from the group consisting of H, acetyl, lauroyl, myristoyl, palmitoyl or a polymer of general formula (II) where q ranges between 1 and 5, R_2 is $-NR_3R_4$ or $-OR_3$ where R_3 and R_4 are independently selected from H, methyl, ethyl, hexyl, dodecyl and

hexadecyl, R_6 is H, R_{10}, R_{11}, R_{12}, R_{14}, R_{15} and R_{16} are methyl and are in an ortho-, para-, ortho- configuration or a meta-, para-, meta- configuration, n and p are 0 or 1, R_7, R_8 and R_9 are H, m is equal to 1, R_{13} is selected from the group consisting of L-(3-indolyl)methyl and D-(3-indolyl)methyl and R_{17} is -S-S-.

14. The compound according to any of claims 1 to 7, wherein R_1 is selected from the group consisting of H, acetyl, lauroyl, myristoyl, palmitoyl or a polymer of general formula (II) where q ranges between 1 and 5, R_2 is $-NR_3R_4$ or $-OR_3$ where R_3 and R_4 are independently selected from H, methyl, ethyl, hexyl, dodecyl and hexadecyl, R_6 is selected from the group consisting of acetyl, palmitoyl, trifluoroacetyl, isopropyl, allyloxycarbonyl, 2-chlorobenzyl, *N*-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethyl], R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{14}, R_{15} and R_{16} are H, m, n and p are equal to 1, R_{13} is selected from the group consisting of L-(3-indolyl)methyl and D-(3-indolyl)methyl and R_{17} is -S-S-.

15. The compound according to any of claims 1 to 7, wherein R_1 is selected from the group consisting of H, acetyl, lauroyl, myristoyl, palmitoyl or a polymer of general formula (II) where q ranges between 1 and 5, R_2 is $-NR_3R_4$ or $-OR_3$ where R_3 and R_4 are independently selected from H, methyl, ethyl, hexyl, dodecyl and hexadecyl, R_6 is H, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{14}, R_{15} and R_{16} are H, m, n and p are equal to 1, R_{13} is selected from the group consisting of L-(3-quinolyl)methyl and D-(3-quinolyl)methyl and R_{17} is -S-S-.

16. The compound according to any of claims 1 to 7, wherein R_1 is selected from the group consisting of H, acetyl, lauroyl, myristoyl, palmitoyl or a polymer of general formula (II) where q ranges between 1 and 5, R_2 is $-NR_3R_4$ or $-OR_3$ where R_3 and R_4 are independently selected from H, methyl, ethyl, hexyl, dodecyl and hexadecyl, R_6 is H, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{14}, R_{15} and R_{16} are H, m, n and p are equal to 1, R_{13} is selected from the group consisting of L-(3-indolyl)methyl and D-(3-indolyl)methyl and R_{17} is -CH=CH-.

17. The compound according to any of claims 1 to 16 for the treatment, prevention and/or diagnosis of those conditions,

disorders and/or pathologies in which the sstr1, sstr2, sstr3, sstr4 and/or sstr5 somatostatin receptors are expressed.

18. The compound according to claim 17 for the treatment, prevention and/or diagnosis of those conditions, disorders and/or pathologies selected from the group consisting of acromegaly, symptomatic treatment of gastroenteropancreatic neuroendocrine tumors, diarrhea, cancer, tumors, neurodegenerative diseases, ocular diseases, immune system pathologies, inflammation, infections, esophageal varices, pain, wound healing, tissue regeneration, chronic pancreatitis, hypertrophic pulmonary osteoarthropathy and thyrotrophic adenoma.

19. The compound according to claim 18 for the treatment, prevention and/or diagnosis of those conditions, disorders and/or pathologies selected from the group consisting of acromegaly, symptomatic treatment of gastroenteropancreatic neuroendocrine tumors, grade 3-4 diarrhea, diarrhea associated with radiotherapy and/or chemotherapy treatment, symptomatic treatment of carcinoid syndrome or VIPomas, endocrine cancer, pancreatic cancer, colorectal cancer, breast cancer, ovarian cancer, prostate cancer, thyroid cancer, lung cancer, gastric cancer, hepatocellular carcinoma, Alzheimer's disease, arthritis, allergies, Lupus erythematosus, lymphoproliferative disorder, diabetic retinopathy, macular edema, Graves' ophthalmopathy, Cushing's syndrome, neuropathic pain, restenosis, angiogenesis, hyperthyroidism, hypothyroidism, hyperinsulinemia, psoriasis, hypercalcemia, Paget's disease, caquexia and Zollinger-Ellison syndrome.

20. A process for obtaining a compound of general formula (I), their stereoisomers, mixtures thereof, or their cosmetically or pharmaceutically acceptable salts as defined in any of claims 1 to 7, which is performed in solid phase or in solution.

21. The process according to claim 20, which includes the following steps:

1. solid phase synthesis

2. cleaving the peptide from the polymer support

3. cycling the peptide in solution

4. eliminating the protecting groups

or alternatively

1. solid phase synthesis

2. solid phase cycling

3. cleaving the peptide from the polymer support and simultaneously eliminating the protecting groups.

22. A pharmaceutical composition comprising a pharmaceutically effective amount of at least one compound of general formula (I), their stereoisomers, mixtures thereof and/or their pharmaceutically acceptable salts, according to any of claims 1 to 16, and at least one pharmaceutically acceptable excipient.

23. Use of a compound according to any of claims 1 to 16 in the preparation of a pharmaceutical composition for the treatment, prevention and/or diagnosis of those conditions, disorders and/or pathologies in which the sstr1, sstr2, sstr3, sstr4 and/or sstr5 somatostatin receptors are expressed.

24. The use according to claim 23, characterized in that the conditions, disorders and/or pathologies are selected from the group consisting of acromegaly, symptomatic treatment of gastroenteropancreatic neuroendocrine tumors, diarrhea, cancer, tumors, neurodegenerative diseases, ocular diseases, immune system pathologies, inflammation, infections, esophageal varices, pain, wound healing, tissue regeneration, chronic pancreatitis, hypertrophic pulmonary osteoarthropathy and thyrotrophic adenoma.

25. The use according to claim 24, characterized in that the conditions, disorders and/or pathologies are selected from the group consisting of acromegaly, symptomatic treatment of gastroenteropancreatic neuroendocrine tumors, grade 3-4 diarrhea, diarrhea associated with radiotherapy and/or chemotherapy treatment, symptomatic treatment of carcinoid syndrome or VIPomas, endocrine cancer, pancreatic cancer, colorectal cancer, breast cancer, ovarian cancer, prostate

cancer, thyroid cancer, lung cancer, gastric cancer, hepatocellular carcinoma, Alzheimer's disease, arthritis, allergies, Lupus erythematosus, lymphoproliferative disorder, diabetic retinopathy, macular edema, Graves' ophthalmopathy, Cushing's syndrome, neuropathic pain, restenosis, angiogenesis, hyperthyroidism, hypothyroidism, hyperinsulinemia, psoriasis, hypercalcemia, Paget's disease, caquexia and Zollinger-Ellison syndrome.