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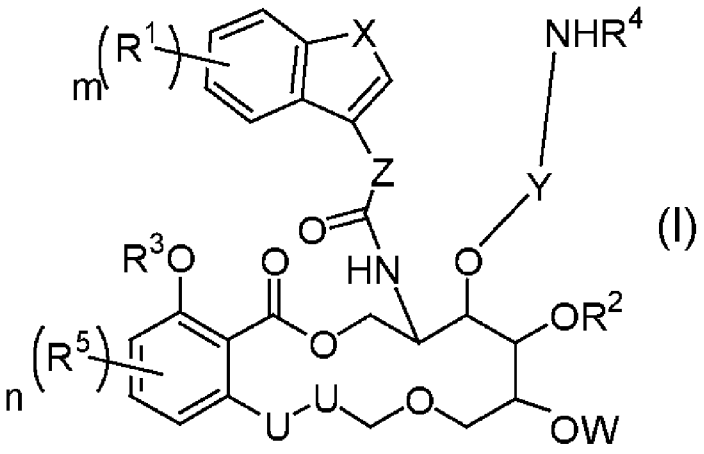
(54) **Title**: SOMATOSTATIN MIMETICS



(57) **Abstract**: Somatostatin is a tetradecapeptide that regulates, through binding to its receptors (SSTRs), a number of processes including the release of growth hormone and other pituitary hormones. Disclosed herein are a number of somatostatin mimetics that exhibit potential utility as therapeutic agents. Formula (I).

Title

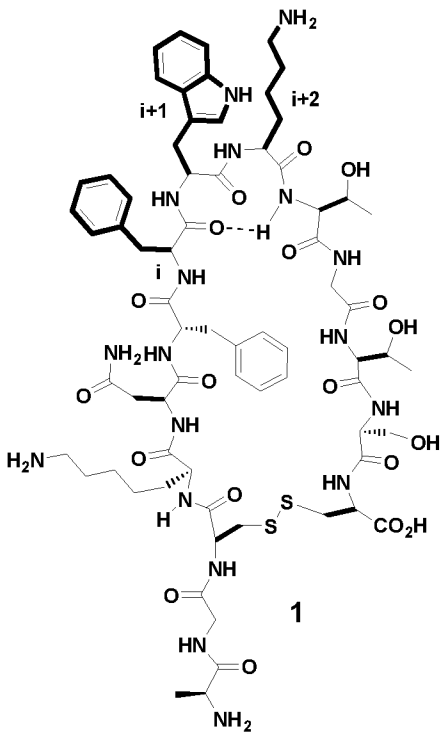
Somatostatin Mimetics

Field of the Invention

[0001] The present invention relates to novel compounds that are ligands at the Somatostatin receptors. The present invention further provides for a method of synthesis of these compounds and for the use of the compounds as therapeutic agents.

Background to the Invention

[0002] Somatostatin (SST, **1**) is a tetradecapeptide that regulates, through binding to its receptors (SSTRs), a number of processes including the release of growth hormone and other pituitary hormones. The side-chains of the Phe-Trp-Lys peptide fragment of **1** (residues i, i+1 and i+2 in Figure 1), which adopts a ß-turn conformation, are important for the recognition of SSTRs, defining an important component of its pharmacophore. The low bioavailability and poor pharmacokinetics of somatostatin has led to the synthesis of both peptide and non-peptide mimetics of this hormone.



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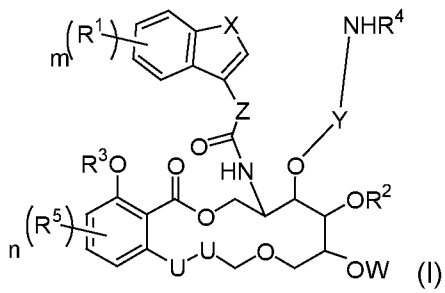
[0003] Sandostatin (D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-ol with a disulfide bridge) is a potent peptide based mimetic of somatostatin that has found clinical application. Sandostatin differs from **1** as it contains D-tryptophan instead of the L-tryptophan residue but it can be postulated that the pharmacophoric side-chains adopt a similar geometric arrangement in both sandostatin and somatostatin.

[0004] Nothwithstanding the state of the art there remains a need for alternative peptidomimetic ligands showing affinity for SSTRs.

Summary of the Invention

[0005] In a first aspect the present invention provides for a compound of the general formula (I), a pharmaceutically acceptable salt thereof, an ester thereof, a solvate thereof or a hydrate thereof:



(I)

wherein m is 0 – 4;

n is 0 – 3;

each R^1 is independently selected from the group consisting of a halogen, OH, CF_3, C_1-C_5 aliphatic, C_1-C_5 aliphatic ether, C_1-C_5 aliphatic thioether, and C_6-C_{10} aryl;

R^2 is selected from H, C_1-C_5 aliphatic, benzyl, and *p*-methoxybenzyl;

R^3 is selected from H, C_1-C_5 aliphatic, and benzyl;

R^4 is selected from H, C_1-C_{10} aliphatic, $C(O)C_1$-C_{20} aliphatic, and $C(O)C_6$-C_{20} aromatic;

each R^5 is independently selected from the group consisting of a halogen, OH, CF_3, C_1-C_5 aliphatic, C_1-C_5 aliphatic ether, C_1-C_5 aliphatic thioether, and C_6-C_{10} aryl;

W is selected from H, C_1-C_5 aliphatic, and benzyl;

X is selected from NH, NO, S, O, CH_2, and HC=CH;

Y is C_1-C_5 aliphatic;

Z is selected from C_1-C_5 aliphatic, O, NH, S, OCH_2, $NHCH_2$, and SCH_2; and

U-U is selected from CH_2-CH_2, CH=CH, C≡C, cyclopropyl, (CH-CH)O, and (CH-CH)NH.

[0006] When R^4 is $C(O)C_1$-C_{10} aliphatic or $C(O)C_6$-C_{10} aromatic the moiety NHR^4 is an aliphatic amide or an aromatic amide respectively.

[0007] The moiety (CH-CH)O represents an ethylene oxide (or oxirane) moiety. The moiety (CH-CH)NH represents an aziridine moiety.

[0008] As used herein the term ester includes aliphatic esters, aromatic esters and phosphate esters

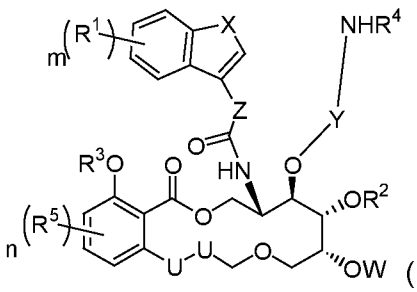
[0009] As used herein, the term C_x-C_y aliphatic refers to linear, branched, saturated and unsaturated hydrocarbon chains comprising C_x-C_y carbon atoms (and includes C_x-C_y alkyl, C_x-C_y alkenyl and C_x-C_y alkynyl).

[0010] Similarly, references to C_x-C_y alkyl, C_x-C_y alkenyl and C_x-C_y alkynyl include linear and branched C_x-C_y alkyl, C_x-C_y alkenyl and C_x-C_y alkynyl.

[0011] As used herein, the term aryl/aromatic refers to a aromatic carbocyclic structure. The term heterocycle refers to cyclic compounds having as ring members atoms of at least two different elements. The term heteroaromatic refers to an aromatic heterocyclic structure having as ring members atoms of at least two different elements.

[0012] As used herein, the term "leaving group" refers to species that departs with a pair of electrons in heterolytic bond cleavage.

[0013] The compound may have the absolute stereochemistry indicated in formula (Ia), a pharmaceutically acceptable salt thereof, an ester thereof, a solvate thereof or a hydrate thereof:



(Ia)

wherein m is 0 – 4;

n is 0 – 3;

each R^1 is independently selected from the group consisting of a halogen, OH, CF_3, C_1-C_5 aliphatic, C_1-C_5 aliphatic ether, C_1-C_5 aliphatic thioether, and C_6-C_{10} aryl;

R^2 is selected from H, C_1-C_5 aliphatic, benzyl, and *p*-methoxybenzyl;

R^3 is selected from H, C_1-C_5 aliphatic, and benzyl;

R^4 is selected from H, C_1-C_{10} aliphatic, C(O)C_1-C_{20} aliphatic, and C(O)C_6-C_{20} aromatic;

each R^5 is independently selected from the group consisting of a halogen, OH, CF_3, C_1-C_5 aliphatic, C_1-C_5 aliphatic ether, C_1-C_5 aliphatic thioether, and C_6-C_{10} aryl;

W is selected from H, C_1-C_5 aliphatic, and benzyl;

X is selected from NH, NO, S, O, CH_2, and HC=CH;

Y is C_1-C_5 aliphatic;

Z is selected from C_1-C_5 aliphatic, O, NH, S, OCH_2, $NHCH_2$, and SCH_2; and

U-U is selected from CH_2-CH_2, CH=CH, C≡C, cyclopropyl, (CH-CH)O, and (CH-CH)NH.

[0014] In one particular embodiment, the variables may be as follows: m is 0 – 4; n is 0-3; each R^1 is independently selected from the group consisting of halogen, OH, CF_3, Me, OMe and Ph; R^2 is selected from H, Me, benzyl, allyl and *p*-methoxybenzyl; R^3 is selected from H, Me, Et, C_3H_7, C_4H_9, allyl and benzyl; R^4 is selected from H, H, Me, Et, C_3H_7, C_4H_9, C(O)Me, C(O)Et, $C(O)C_3H_7$, $C(O)C_4H_9$, and C(O)Ph; each R^5 is independently selected from the group consisting of a halogen, OH, CF_3, Me, OMe and Ph; W is selected from H or benzyl; X is selected from NH, S, O, CH_2, and HC=CH; Y is selected from CH_2, CH_2CH_2, $CH_2CH_2CH_2$, $CH_2CH_2CH_2CH_2$, $CH_2CH_2CH_2CH_2CH_2$, CH_2CH=$CHCH_2$; Z is selected from CH_2, CH_2CH_2, $CH_2CH_2CH_2$, HC=$CHCH_2$, O, NH, S, OCH_2, $NHCH_2$, and SCH_2; and U-U is selected from CH_2-CH_2, and CH=CH.

[0015] In a further embodiment, the variables may be as follows: m is 0 – 4; n is 0; each R^1 is independently selected from the group consisting of halogen, OH, CF_3, Me, OMe and Ph; R^2 is selected from H, Me, benzyl, allyl and *p*-methoxybenzyl; R^3 is selected from H, Me, Et, C_3H_7, C_4H_9, allyl and benzyl; R^4 is selected from H, H, Me, Et, C_3H_7, C_4H_9, C(O)Me, C(O)Et, $C(O)C_3H_7$, $C(O)C_4H_9$, and C(O)Ph; W is selected from H or benzyl; X is selected from NH, S, O, CH_2, and HC=CH; Y is selected from CH_2, CH_2CH_2, $CH_2CH_2CH_2$, $CH_2CH_2CH_2CH_2$, $CH_2CH_2CH_2CH_2CH_2$, CH_2CH=$CHCH_2$; Z is selected from CH_2, CH_2CH_2, $CH_2CH_2CH_2$, HC=$CHCH_2$, O, NH, S, OCH_2, $NHCH_2$, and SCH_2; and U-U is selected from CH_2-CH_2, and CH=CH.

[0016] In one embodiment, m is 0 – 4; n is 0 – 3; each R^1 is independently selected from the group consisting of a halogen, OH, CF_3, and C_1-C_5 aliphatic; R^2 is selected from H, C_1-C_5 aliphatic, benzyl, and *p*-methoxybenzyl; R^3 is selected from H, C_1-C_5 aliphatic, and benzyl; R^4 is selected from H, C_1-C_{10} aliphatic, $C(O)C_1$-C_{20} aliphatic, and $C(O)C_6$-C_{20} aromatic; each R^5 is independently selected from the group consisting of a halogen, OH, CF_3, and C_1-C_5 aliphatic, W is selected from H, C_1-C_5 aliphatic, and benzyl; X is selected from NH, NO, S, O, CH_2, and HC=CH; Y is C_1-C_5 aliphatic; Z is selected from C_1-C_5 aliphatic, O, NH, S, OCH_2, $NHCH_2$, and SCH_2; and U-U is selected from CH_2-CH_2, CH=CH, C≡C, and cyclopropyl.

[0017] In a further embodiment m is 0 – 4; n is 0; each R^1 is independently selected from the group consisting of a halogen, OH, CF_3, and C_1-C_5 aliphatic; R^2 is selected from H, C_1-C_5 aliphatic, benzyl, and *p*-methoxybenzyl; R^3 is selected from H, C_1-C_5 aliphatic, and benzyl; R^4 is selected from H, C_1-C_{10} aliphatic, $C(O)C_1$-C_{20} aliphatic, and $C(O)C_6$-C_{20} aromatic; each R^5 is

independently selected from the group consisting of a halogen, OH, CF_3, and C_1-C_5 aliphatic, W is selected from H, C_1-C_5 aliphatic, and benzyl; X is selected from NH, NO, S, O, CH_2, and HC=CH; Y is C_1-C_5 aliphatic; Z is selected from C_1-C_5 aliphatic, O, NH, S, OCH_2, $NHCH_2$, and SCH_2; and U-U is selected from CH_2-CH_2, CH=CH, C≡C, and cyclopropyl

[0018] In a further embodiment m is 0 – 4; n is 0; each R^1 is independently selected from the group consisting of a halogen, OH, CF_3, C_1-C_5 aliphatic, C_1-C_5 aliphatic ether, C_1-C_5 aliphatic thioether, and C_6-C_{10} aryl; R^2 is selected from H, C_1-C_5 aliphatic, benzyl, and *p*-methoxybenzyl; R^3 is selected from H, C_1-C_5 aliphatic, and benzyl; R^4 is selected from H, C_1-C_{10} aliphatic, $C(O)C_1$-C_{20} aliphatic, and $C(O)C_6$-C_{20} aromatic; each R^5 is independently selected from the group consisting of a halogen, OH, CF_3, C_1-C_5 aliphatic, C_1-C_5 aliphatic ether, C_1-C_5 aliphatic thioether, and C_6-C_{10} aryl; W is selected from H, C_1-C_5 aliphatic, and benzyl; X is selected from NH, NO, S, O, CH_2, and HC=CH; Y is C_1-C_5 aliphatic; Z is selected from C_1-C_5 aliphatic, O, NH, S, OCH_2, $NHCH_2$, and SCH_2; and U-U is selected from CH_2-CH_2, CH=CH, C≡C, cyclopropyl, (CH-CH)O, and (CH-CH)NH.

[0019] In a further embodiment m is 0; n is 0; each R^1 is independently selected from the group consisting of a halogen, OH, CF_3, C_1-C_5 aliphatic, C_1-C_5 aliphatic ether, C_1-C_5 aliphatic thioether, and C_6-C_{10} aryl; R^2 is selected from H, C_1-C_5 aliphatic, benzyl, and *p*-methoxybenzyl; R^3 is selected from H, C_1-C_5 aliphatic, and benzyl; R^4 is selected from H, C_1-C_{10} aliphatic, $C(O)C_1$-C_{20} aliphatic, and $C(O)C_6$-C_{20} aromatic; each R^5 is independently selected from the group consisting of a halogen, OH, CF_3, C_1-C_5 aliphatic, C_1-C_5 aliphatic ether, C_1-C_5 aliphatic thioether, and C_6-C_{10} aryl; W is selected from H, C_1-C_5 aliphatic, and benzyl; X is selected from NH, NO, S, O, CH_2, and HC=CH; Y is C_1-C_5 aliphatic; Z is selected from C_1-C_5 aliphatic, O, NH, S, OCH_2, $NHCH_2$, and SCH_2; and U-U is selected from CH_2-CH_2, CH=CH, C≡C, cyclopropyl, (CH-CH)O, and (CH-CH)NH.

[0020] In a further embodiment m is 0 – 4; n is 0; each R^1 is independently selected from the group consisting of a halogen, OH, CF_3, C_1-C_5 aliphatic, C_1-C_5 aliphatic ether, C_1-C_5 aliphatic thioether, and C_6-C_{10} aryl; R^2 is selected from H, C_1-C_5 aliphatic, benzyl, and *p*-methoxybenzyl; R^3 is selected from H, C_1-C_5 aliphatic, and benzyl; R^4 is selected from H, C_1-C_{10} aliphatic, $C(O)C_1$-C_{20} aliphatic, and $C(O)C_6$-C_{20} aromatic; each R^5 is independently selected from the group consisting of a halogen, OH, CF_3, C_1-C_5 aliphatic, C_1-C_5 aliphatic ether, C_1-C_5 aliphatic thioether, and C_6-C_{10} aryl; W is selected from H, C_1-C_5 aliphatic, and benzyl; X is selected from NH, NO, S, O, CH_2, and HC=CH; Y is C_1-C_5 aliphatic; Z is C_1-C_5 aliphatic; and U-U is selected from CH_2-CH_2, CH=CH, C≡C, cyclopropyl, (CH-CH)O, and (CH-CH)NH.

[0021] In a further embodiment m is 0; n is 0; each R^1 is independently selected from the group consisting of a halogen, OH, CF_3, C_1-C_5 aliphatic, C_1-C_5 aliphatic ether, C_1-C_5 aliphatic thioether, and C_6-C_{10} aryl; R^2 is selected from H, C_1-C_5 aliphatic, benzyl, and *p*-methoxybenzyl; R^3 is selected from H, C_1-C_5 aliphatic, and benzyl; R^4 is selected from H, C_1-C_{10} aliphatic, $C(O)C_1$-C_{20}

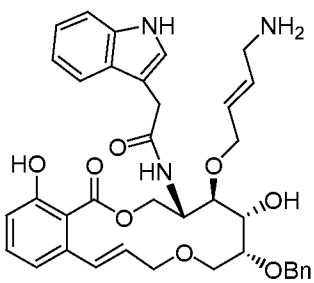
aliphatic, and C(O)C_6-C_{20} aromatic; each R^5 is independently selected from the group consisting of a halogen, OH, CF_3, C_1-C_5 aliphatic, C_1-C_5 aliphatic ether, C_1-C_5 aliphatic thioether, and C_6-C_{10} aryl; W is selected from H, C_1-C_5 aliphatic, and benzyl; X is selected from NH, NO, S, O, CH_2, and HC=CH; Y is C_1-C_5 aliphatic; Z is selected from C_1-C_5 aliphatic, O, NH, S, OCH_2, $NHCH_2$, and SCH_2; and U-U is selected from CH_2-CH_2, CH=CH, C≡C, cyclopropyl, (CH-CH)O, and (CH-CH)NH.

[0022] In yet a further embodiment, the variables may be as follows: m is 0 – 4; n is 0-3; each R^1 is independently selected from the group consisting of halogen, OH, CF_3, Me, and OMe. R^2 is selected from H, Me, benzyl, allyl and *p*-methoxybenzyl; R^3 is selected from H, Me, Et, C_3H_7, C_4H_9, allyl and benzyl; R^4 is selected from H, H, Me, Et, C_3H_7, C_4H_9, C(O)Me, C(O)Et, C(O)C_3H_7, C(O)C_4H_9, and C(O)Ph; each R^5 is independently selected from the group consisting of a halogen, OH, CF_3, Me, and OMe; W is selected from H or benzyl; X is selected from NH, S, O, CH_2, and HC=CH; Y is selected from CH_2, CH_2CH_2, $CH_2CH_2CH_2$, $CH_2CH_2CH_2CH_2$, $CH_2CH_2CH_2CH_2CH_2$, $CH_2CH=CHCH_2$; Z is selected from CH_2, CH_2CH_2, $CH_2CH_2CH_2$, $HC=CHCH_2$, O, NH, S, OCH_2, $NHCH_2$, and SCH_2; and U-U is selected from CH_2-CH_2, cyclopropyl and CH=CH.

[0023] In yet a further embodiment, the variables may be as follows: m is 0 – 4; n is 0-3; each R^1 is independently selected from the group consisting of halogen, OH, CF_3, Me, and OMe. R^2 is selected from H, Me, benzyl, allyl and *p*-methoxybenzyl; R^3 is selected from H, Me, Et, C_3H_7, C_4H_9, allyl and benzyl; R^4 is selected from H, C(O)Me, C(O)Et, C(O)C_3H_7, C(O)C_4H_9, and C(O)Ph; each R^5 is independently selected from the group consisting of a halogen, OH, CF_3, Me, and OMe; W is selected from benzyl; X is selected from NH, S, O, and CH_2; Y is selected from CH_2, CH_2CH_2, $CH_2CH_2CH_2$, $CH_2CH_2CH_2CH_2$, $CH_2CH_2CH_2CH_2CH_2$, $CH_2CH=CHCH_2$; Z is selected from CH_2, CH_2CH_2, $CH_2CH_2CH_2$, $HC=CHCH_2$, O, NH, S, OCH_2, $NHCH_2$, and SCH_2; and U-U is selected from CH_2-CH_2, cyclopropyl and CH=CH.

[0024] In one particular embodiment both n and m may be 0. In a further embodiment W may be benzyl.

[0025] The compound may be



a pharmaceutically acceptable salt thereof, an ester thereof, a solvate thereof or a hydrate thereof. The stereodescriptors indicate absolute stereochemistry.

[0026] The compound may be:

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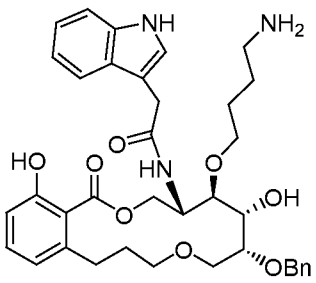


a pharmaceutically acceptable salt thereof, an ester thereof, a solvate thereof or a hydrate thereof. The stereodescriptors indicate absolute stereochemistry.

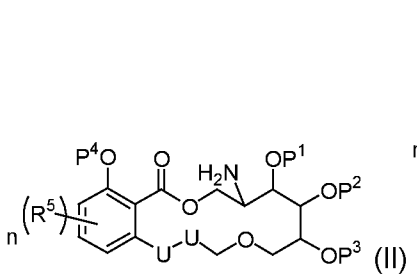
[0027] The invention further extends to pharmaceutical composition comprising a compound according to the present invention and a pharmaceutical acceptable carrier.

[0028] The compounds of the present invention may find use in the treatment of a disorder in which somatostatin receptors are implicated. For example, use in the modulation of angiogenesis. The compounds may find use in the treatment of a disorder in which neovascularisation or angiogenesis are implicated.

[0029] Suitable uses may include use in the treatment of acromegaly, cancer, arthritis, carcinoid tumours, and vasoactive intestinal peptide tumours.

[0030] In a further aspect the present invention provides for a method of preparing a compound according to the present invention, the method comprising:

i) peptide coupling a compound of formula (II) and a compound of formula (III) to provide a compound of the formula (IV):



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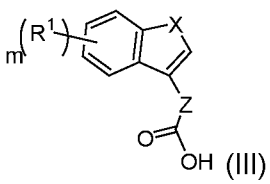

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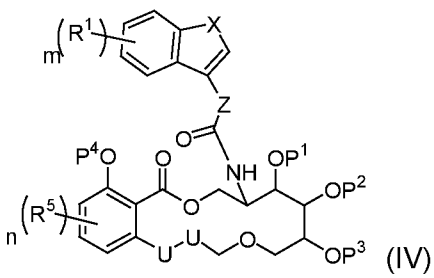


(IV)

wherein m is 0 – 4;

n is 0 – 3;

P^1-P^4 are oxygen protecting groups, such that P^2-P^4 can be the same or different and P^1 is different from each of P^2-P^4;

each R^1 is independently selected from the group consisting of a halogen, OH, CF_3, C_1-C_5 aliphatic, C_1-C_5 aliphatic ether, C_1-C_5 aliphatic thioether, and C_6-C_{10} aryl;

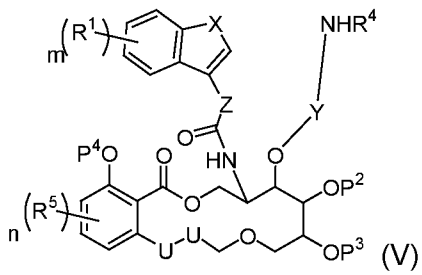
each R^5 is independently selected from the group consisting of a halogen, OH, CF_3, C_1-C_5 aliphatic, C_1-C_5 aliphatic ether, C_1-C_5 aliphatic thioether, and C_6-C_{10} aryl;

X is selected from NH, NO, S, O, CH_2, and HC=CH;

Z is selected from C_1-C_5 aliphatic, O, NH, S, OCH_2, $NHCH_2$, and SCH_2; and

U-U is selected from CH_2-CH_2, CH=CH, C≡C, cyclopropyl, (CH-CH)O, and (CH-CH)NH; and

ii) selectively removing oxygen protecting group P^1 and alkylating the free alcohol thus formed to provide a compound of the general formula (V):



(V)

wherein m is 0 – 4;

n is 0 – 3;

P^2-P^4 are the same or different and are oxygen protecting groups;

each R^1 is independently selected from the group consisting of a halogen, OH, CF_3, C_1-C_5 aliphatic, C_1-C_5 aliphatic ether, C_1-C_5 aliphatic thioether, and C_6-C_{10} aryl;

each R^5 is independently selected from the group consisting of a halogen, OH, CF_3, C_1-C_5 aliphatic, C_1-C_5 aliphatic ether, C_1-C_5 aliphatic thioether, and C_6-C_{10} aryl;

X is selected from NH, NO, S, O, CH_2, and HC=CH;

Z is selected from C_1-C_5 aliphatic, O, NH, S, OCH_2, $NHCH_2$, and SCH_2; a

U-U is selected from CH_2-CH_2, CH=CH, C≡C, cyclopropyl, (CH-CH)O, and (CH-CH)NH;

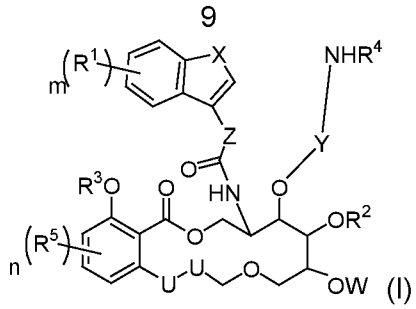
Y is C_1-C_5 aliphatic; and

R^4 is selected from H, C_1-C_{10} aliphatic, $C(O)C_1$-C_{20} aliphatic, and $C(O)C_6$-C_{20} aromatic.

[0031] As used herein the term peptide coupling refers to any direct or indirect method of forming a peptide bond between a carboxylic acid and an amine. For example, indirect coupling could be by means of first converting the acid to an acyl chloride or an activated ester/anhydride, carbodiimide coupling, HOBt coupling, or HOCt coupling.

[0032] The method may further comprising the step of:

i) selectively removing oxygen protecting groups P^2-P^4 to provide a compound of the general formula (I):



(I)

wherein m is 0 – 4;

n is 0 – 3;

each R^1 is independently selected from the group consisting of a halogen, OH, CF_3, C_1-C_5 aliphatic, C_1-C_5 aliphatic ether, C_1-C_5 aliphatic thioether, and C_6-C_{10} aryl;

R^2 is selected from H, C_1-C_5 aliphatic, benzyl, and *p*-methoxybenzyl;

R^3 is selected from H, C_1-C_5 aliphatic, and benzyl;

R^4 is selected from H, C_1-C_{10} aliphatic, $C(O)C_1$-C_{20} aliphatic, and $C(O)C_6$-C_{20} aromatic;

each R^5 is independently selected from the group consisting of a halogen, OH, CF_3, C_1-C_5 aliphatic, C_1-C_5 aliphatic ether, C_1-C_5 aliphatic thioether, and C_6-C_{10} aryl;

W is selected from H, C_1-C_5 aliphatic, and benzyl;

X is selected from NH, NO, S, O, CH_2, and HC=CH;

Y is C_1-C_5 aliphatic;

Z is selected from C_1-C_5 aliphatic, O, NH, S, OCH_2, $NHCH_2$, and SCH_2; and

U-U is selected from CH_2-CH_2, CH=CH, C≡C, cyclopropyl, (CH-CH)O, and (CH-CH)NH.

[0033] In one particular embodiment, the variables may be as follows:

m is 0 – 4;

n is 0;

each R^1 is independently selected from the group consisting of halogen, OH, CF_3, Me, OMe and Ph;

R^2 is selected from H, Me, benzyl, allyl and *p*-methoxybenzyl;

R^3 is selected from H, Me, Et, C_3H_7, C_4H_9, allyl and benzyl;

R^4 is selected from H, H, Me, Et, C_3H_7, C_4H_9, C(O)Me, C(O)Et, $C(O)C_3H_7$, $C(O)C_4H_9$, and C(O)Ph;

each R^5 is independently selected from the group consisting of a halogen, OH, CF_3, Me, OMe and Ph;

W is selected from H or benzyl;

X is selected from NH, S, O, CH_2, and HC=CH;

Y is selected from CH_2, CH_2CH_2, $CH_2CH_2CH_2$, $CH_2CH_2CH_2CH_2$, $CH_2CH_2CH_2CH_2CH_2$, $CH_2CH=CHCH_2$;

Z is selected from CH_2, CH_2CH_2, $CH_2CH_2CH_2$, $HC=CHCH_2$, O, NH, S, OCH_2, $NHCH_2$, and SCH_2; and

U-U is selected from CH_2-CH_2, and CH=CH.

[0034] In one particular embodiment both n and m may be 0. In a further embodiment W may be benzyl.

[0035] The oxygen protecting groups P^1-P^4 may be selected from benzyl, *p*-methoxybenzyl, methyl, allyl, trialkylsilyl, acetyl, tetrahydropyranyl, benzoyl, pivaloyl, substitute benzoyl, triphenyl silyl, t-butyldimethylsilyl, t-butyl-diphenylsilyl, methoxymethyl ether, methylthiomethyl ether, benzylmethoxymethyl ether, p-methoxybenzyloxymethyl, 3,4-dimethoxybenzyloxymethyl, benzyloxymethyl, t-butoxymethyl, (p-phenylphenyl)oxymethyl ether, methoxyethoxymethyl ether, 2,2,2-trichloroethoxymethyl, tetrahydrofuranyl ether, tetrahydrothiofuranyl ether, t-butyl ether, prenyl ether, p-methoxyphenyl ether, 3,4-dimethoxybenzyl, 2,6-dimethoxybenzyl, o-nitrobenzyl, p-nitrobenzyl, halobenzyl ether, dihalobenzyl ether, 2-naphthylmethyl ether, 4-acetoxybenzyl ether, diphenylmethyl ether, triphenylmethyl ether, methoxytriphenylmethyl ether, chloroacetyl, dichloroacetyl, trichloracetyl, trifluoroacetyl, phenoxyacetate, levulinate, halobenzoate, nitrobenzoate, allyloxycarbonate, methoxmethylcarbonate, benzylcarbonate, methoxybenzylcarbonate, t-butoxycarbonate, and fluorenylmethoxy carbonate.

[0036] With reference to the method of the present invention the step of alkylating the free alcohol thus formed may comprise:

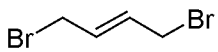
i) alkylating the free alcohol with a molecule of the formula T—Y—T', thereby liberating an anion of one of T or T', wherein Y is C_1-C_5 aliphatic;

T is Cl, Br or I;

T' is Cl, Br or I; and

ii) replacing the other of T or T' with NHR^4.

[0037] The molecule of the formula T—Y—T' may be



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[0038] The compounds of the present invention may be found or isolated in the form of esters, salts, hydrates or solvates - all of which are embraced by the present invention.

[0039] Where suitable, it will be appreciated that all optional and/or preferred features of one embodiment of the invention may be combined with optional and/or preferred features of another/other embodiment(s) of the invention.

Brief Description of the Drawings

[0040] Additional features and advantages of the present invention are described in, and will be apparent from, the detailed description of the invention and from the drawings in which:

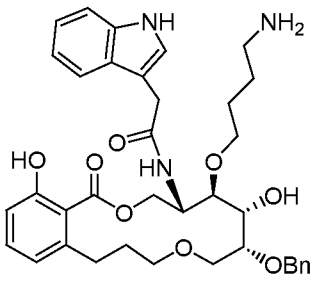
[0041] **Figure 1** illustrates the overlap of target compound **10** with the solution structure of sandostatin.

Detailed Description of the Invention

[0042] It should be readily apparent to one of ordinary skill in the art that the examples disclosed herein below represent generalised examples only, and that other arrangements and methods capable of reproducing the invention are possible and are embraced by the present invention.

Molecular Modelling Studies

[0043] A model of the target compound **10** was built with the spatial arrangement of the indole and butylamine groups found in sandostatin preserved.



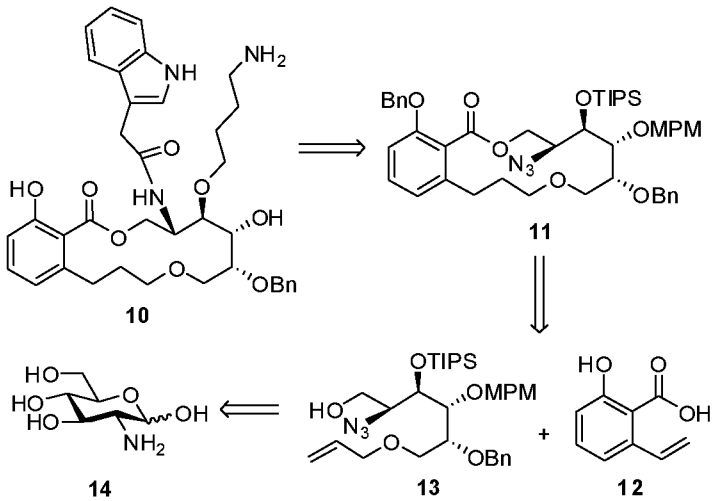
10

[0044] This was then subjected to a MonteCarlo conformational search in Macromodel 8.5 ® which was used to generate low energy conformational isomers wherein the spatial arrangement between the indole and butylamine groups was constrained whilst allowing the conformation of the remainder of the molecule to be varied during the simulation. Subsequently the indole and butylamine groups of the lowest energy conformer of **10** generated during this search (the structure on the left hand side in **Figure 1**) was overlayed with those groups in the sandostatin solution structure (the light grey structure on the right hand side in **Figure 1**).

[0045] The outcome of this procedure suggested that although the indole and butylamine groups can potentially adopt a spatial arrangement as found in sandostatin, there was not any major overlap between the peptide backbone of sandostatin and the benzomacrolactone scaffold. There was little indication in the 3-D model of any potential for the *O*-benzyl group on the scaffold to overlap with the phenylalanine residue of sandostatin.

Synthesis of protected scaffolds

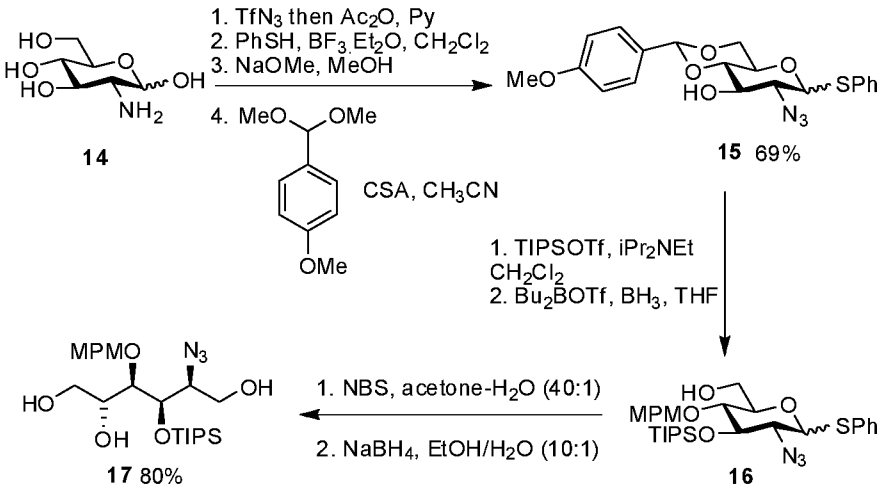
[0046] It was proposed to generate the macrolactone (Scheme 1) via **11** which was prepared via esterification of benzoic acid **12** using alcohol **13** and a subsequent ring closure metathesis (RCM). Precursor **13** was envisaged from D-glucosamine **14.** The choice of having an azide, OTIPS and OMPM (methoxyphenyl methyl) groups onto the scaffold was based on the potential of both chemoselective and regioselective functionalisation at these sites.



Scheme 1 Retrosynthetic analysis

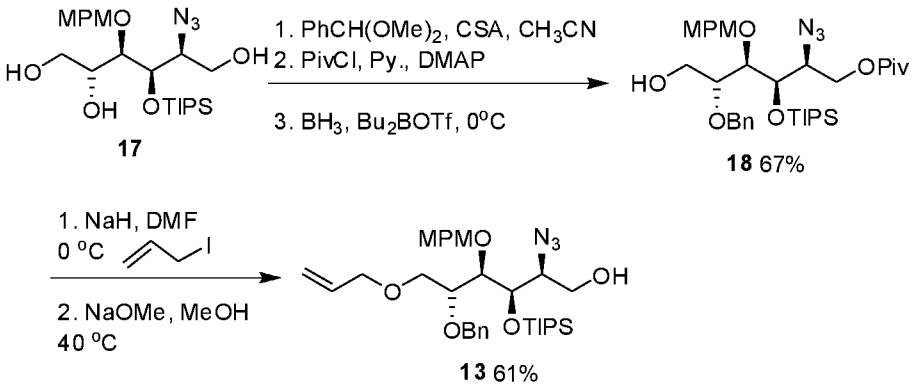
[0047] The synthesis of the orthogonally protected precursor **13** commenced as shown in Scheme 2. Starting from the commercially available glucosamine **4**, the fully acetylated 2-azido-2-deoxy-D-glucose intermediate was obtained as a mixture of anomers (α:β, 2:1) after a diazo transfer reaction and subsequent per-*O*-acetylation. A thioglycoside **6** was then obtained (α:β-mixture, 3:1) by reaction of the peracetylated product with thiophenol in the presence of $BF_3.OEt_2$. De-*O*-acetylation and subsequent reaction of the triol intermediate with dimethylanisaldehyde acetal in the presence of CSA gave the thioglycoside **15** (α:β-mixture, 1.8:1). A TIPS ether protecting group was then introduced using TIPSOTf and DIPEA as base and the partial regioselective reduction of the methoxybenzylidene group of the intermediate was next achieved by treatment with Bu_2BOTf in $BH_3.THF$ at 0 °C; this gave alcohol **16**. The structure of **16** was confirmed by NMR experiments on the α-anomer; the 2D-HMBC spectrum showed a correlation between C-4 and the CH_2 protons of the PMB group as well as a correlation between the methylene carbon of the PMB group and H-4. For this transformation the $BH_3.THF$-Bu_2BOTf system was found to be the most suitable in order to obtain the desired 4-*O*-methoxybenzyl product; the use of $Cu(OTf)_2$, $BF_3.OEt_2$, TMSOTf or TfOH as the promoters were less satisfactory and only lower yields and poor selectivity resulted. The next steps were hydrolysis of the thioglycoside and the subsequent reduction of the resulting hemiacetal in order to get the acyclic amino-deoxy-D-sorbitol derivatives. The thioglycoside **16** was hydrolyzed firstly using NBS in acetone-H_2O (v/v, 40:1, α/β-mixture, 1:2.4; 96%). The reaction time and

acetone:H_2O ratio seemed be very important. A higher proportion of water led to decomposition and a lower yield. The hemiacetal intermediate was next treated portionwise with $NaBH_4$ in EtOH-H_2O to give **17**. Lithium borohydride in THF was also investigated for this reduction reaction but the yields were found to be lower. Overall the triol **17** was obtained in 55% yield from **14** after 8 steps.



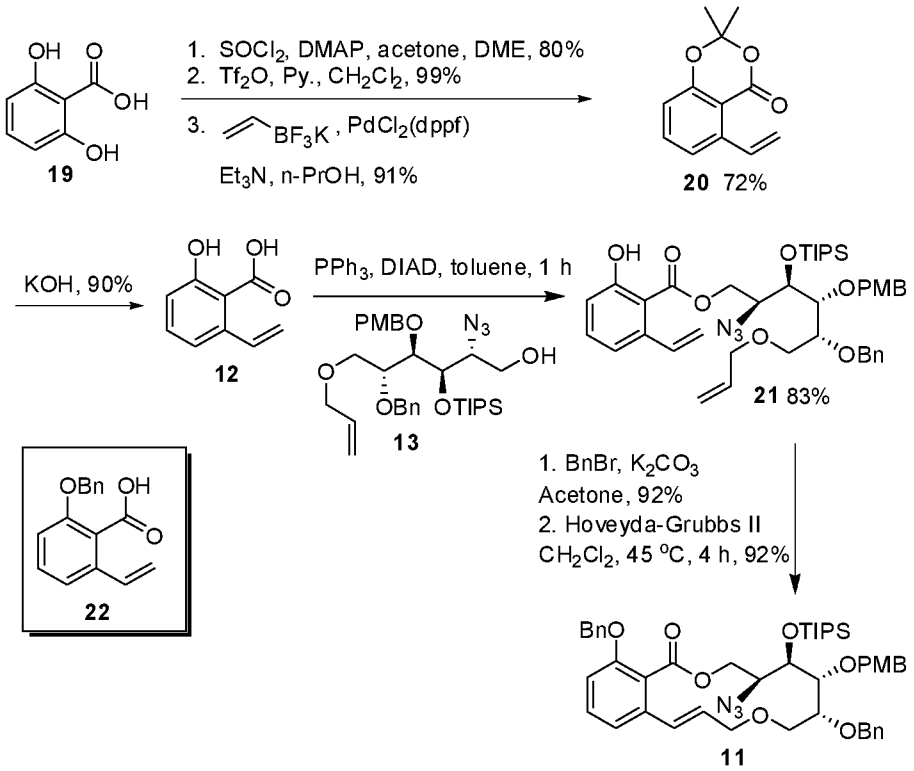
Scheme 2

[0048] Next the 1,2-diol group of **17** was protected as a benzylidene acetal in order to leave the hydroxyl group closest to the azide free; the treatment of **17** with benzaldehyde dimethylacetal in the presence of CSA gave an intermediate acetal as a mixture of diastereoisomers (86%). A pivaloyl group was next introduced at the free alcohol group and subsequent partial regioselective reductive cleavage of the benzylidene acetal gave **18**. The allylation of the free alcohol was next carried out using sodium hydride (1.4 eq) and allyl iodide; there was some evidence for some TIPS protecting group migration to the primary alcohol under these conditions. The quenching procedure after the allylation reaction involved the use of satd NH_4Cl; addition of methanol instead led to the premature removal of the pivalate. The pivaloyl group was then removed selectively by using freshly prepared MeONa to get the desired precursor **13** (61% in two steps from **18**).



Scheme 3

[0049] Preparation of the aromatic precursor **12** was next carried out (Scheme 4). The acetonide of 6-vinyl salicylic acid **20** was synthesized in three steps from commercially available 2,6-dihydroxybenzoic acid **19**; formation of the acetonide was first carried out, then the free was converted to its triflate and a subsequent palladium-catalyzed coupling between the triflate and potassium vinyltrifluoroborate gave **20** (71% from **19**). Other palladium-catalyzed ($Pd(PPh_3)_4$, LiCl) couplings such as a reaction between the triflate and a vinyl tin reagent was also investigated but the vinyl product was obtained in only 50% yield. The acetonide of **20** was then hydrolyzed using KOH to give **12** (90%). The salicylic acid **12** was then converted to key macrocyclic intermediate **11**. Reaction of **12** with the sorbitol derivative **13** by a Mitsunobu esterification promoted by triphenylphosphine in the presence of DIAD gave **21**. It is worth noting that the yield from the esterification decreased dramatically (from 83% to 45%) if the coupling was carried out starting from the benzyl ether **22**. The pKa of **12** is most likely lower than that of **22** due to intramolecular H-bonding in **12;** the pKa value of salicylic acid is ~2.98 while the pKa value of the corresponding methoxy ether of salicylic acid is ~ 4.10).

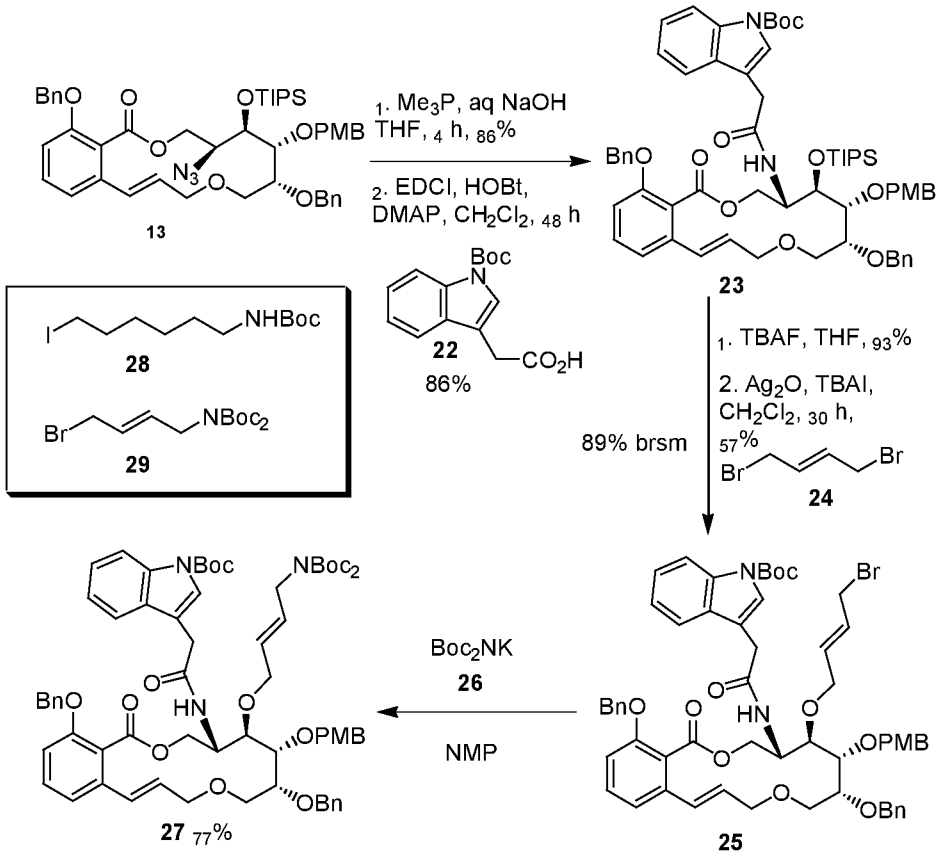


Scheme 4

[0050] The number of equivalents of PPh_3 used in the Mitsunobu reaction should be slightly less than that of DIAD; this prevents the Staudinger reaction of the azide and phosphine from occurring and prevents a loss in yield of **21**. The phenol was then converted to its benzyl ether and then ring closure metathesis (RCM) using the Hoyveda-Grubbs II catalyst in CH_2Cl_2 under argon gave **11** (85% from **21**); the optimum conditions for the RCM were established after investigation of a variety of conditions where solvent and temperature were varied and the use of additives such as 2,6-dichloro-1,4-benzoquinone were also investigated. Also the Hoveyda-Grubbs II catalyst, a phosphine-free catalyst, was chosen as it was envisaged that a catalyst containing a phosphine ligand could react with the azide. If compound **21** was subjected to RCM reaction using the Hoveyda-Grubbs II catalyst, the yield of the ring closed product was significantly lower (~40%). This explains the preparation of the benzyl ether precursor. It was also noticed that separation of the metathesis catalyst from the product was difficult. Finally chromatography using toluene-CH_3CN (200:1) as a solvent led to isolation of the pure **13** in high yield (92%).

[0051] In order to obtain the desired peptidomimetics, the side chains of the Trp-Lys dipeptide fragment, which are important for the recognition to somatostatin receptors, needed to be next installed onto the scaffold. This required: 1. the removal of the TIPS group followed by introduction of an alkyl amine and 2. reduction of the azide and subsequent coupling with 3-indole acetic acid. A number of attempts were investigated to achieve this goal and the

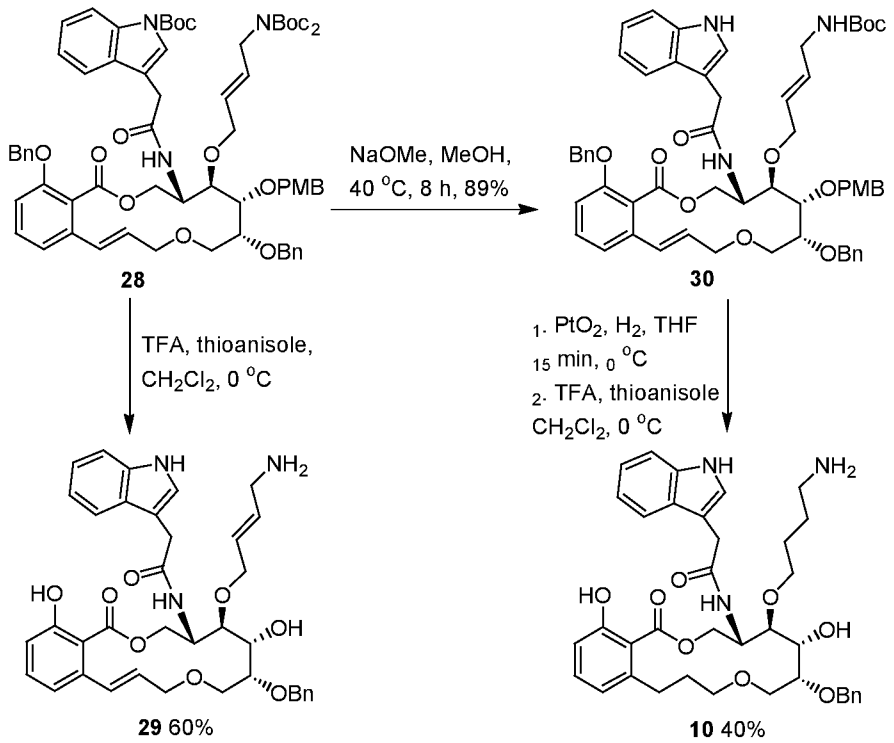
sequences shown in Scheme 5 and 6 were finally successful. It was necessary to first reduce the azide of **13** which was achieved using the Staudinger reaction. The less sterically hindered PMe_3 was found more effective than the other phosphines (PBu_3, PPh_3). The resulting amine was then coupled with indol-3-ylacetic acid **22** to give compound **23** in good yield. Next the TIPS group was removed using TBAF in THF and the resulting free hydroxyl group was then alkylated using 1,4-dibromo- *trans*-2-butene **24** to give **25**. Alkylations of the *N*-protected alkyl halides **28** and **29** with related substrates were investigated under a wide range of conditions (e.g. from **24** using NaH, K_2CO_3, Ag_2O, Ag_2CO_3 in a variety of solvents) but all attempts to alkylate the secondary hydroxyl group using **28/29** failed. For the formation of **25** it was found that the use of Ag_2O to promote the alkylation gave the best result (57% with unreacted **25** also recovered); the use of stronger bases (e.g NaH caused decomposition. These observations indicated that strong basic conditions needed to be avoided in subsequent steps. With the bromide compound **25** in hand, the amine surrogate then needed to be introduced. Usually, amines can be prepared using the Gabriel reagent (Potassium phthalimide) but strongly basic condition are later needed for removal of the phthalimide. N-benzyl derivatives were also considered but investigations with these derivatives were unsuccessful and thus thus another analogue of the Gabriel reagent that could be readily deprotected to give a primary amino group under acidic conditions was therefore required. The potassium salt of the less exploited potassium *bis-(t*-butoxycarbonyl)amine **26** (Boc_2NK) fitted these requirements extremely well and its reaction with **24** gave **26** in 77% yield in NMP as solvent. A main side product in this step was the exchange of the bromide for a hydroxyl group, which is presumably due to the presence of small amounts of KOH in the crude Boc_2NK reagent (Scheme 5).



Scheme 5

[0052] Deprotection strategies combined with reduction of the alkene groups using **27** were next investigated in order to give peptidomimetics. In order to minimize the number of deprotection steps, trifluoroacetic acid (TFA) was first chosen as the deprotection reagent as it could potentially remove the benzyl group from the phenol, the Boc and PMB protecting groups in a one-pot manner. Firstly the deprotection was investigated without any scavenger but the desired product was not obtained. The reaction with TFA in the presence of a series of cation scavengers (PhSH, anisole, thioanisole) were then screened and finally it was found that the use of thioanisole as a co-solvent with TFA was optimum and led to the formation of **29** (Scheme 6, 60%). Next reduction of the alkene group of **28** was investigated. A number of different hydrogenation conditions (5% or 10% Pd-C with AcOH or HCl in MeOH; 5% $Pd(OH)_2$, AcOH-MeOH; Wilkinson's catalyst EtOH etc.) led to decomposition. Moreover, it was also found for some reagents that reduction of the indole ring of **28** (as evidenced by MS analysis) was a problem; this could have been due to the presence of Boc group on the indole. Hence a variety of conditions were screened (H_2O, refluxing; Cs_2CO_3, imidazole, CH_3CN; MeONa, MeOH) in order to selectively remove the Boc group from the indole. Finally, it was found that this Boc group together with one of the Boc groups from the aminobutylene group were selectively removed under the Zemplen conditions to give **30**. Subsequent attempts at hydrogenation were

still problematic when Pd-C or $Pd(OH)_2$ were used as catalysts. Fortunately, hydrogenation using PtO_2 gave the desired product; treatment of the intermediate with TFA and thioanisole gave the final product and the initial target compound **10**. Purification of final products was difficult as side products, resulted from a Friedel-Craft reaction of carbocations generated with the indole ring, were difficult to separate from the target compounds using chromatographic methods. However sufficient material was obtained for biological tests.



Scheme 6

Biological evaluation

[0053] Somatostatin regulates the endocrine system and affects neurotransmission and cell proliferation via interaction with G-protein-coupled somatostatin receptors. There are five known human somatostatin receptor subtypes (hSSTR1-5). The benzomacrolactone derivatives **10** and **29** were evaluated for their binding to four of the human somatostatin repector subtypes and the results are summarized in Table 1. In general the fully reduced compound **10** was found to be more potent than alkene derivative **29**. Compound **10** inhibited binding of somatostatin to each receptor subtype; Ki values ranged from 1.1 to 10 μM. This indicates that the salicylic acid scaffold can be utilized in peptidomimetic design.

Table 1: Binding of benzomacrolactone derivatives at somatostatin receptors

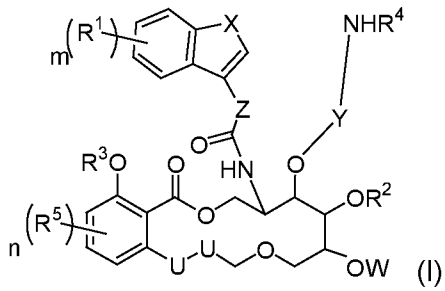
Compound	hSSTR1 (Ki, μM)	hSSTR 2 (Ki, μM)	hSSTR4 (Ki, μM)	hSSTR5 (Ki, μM)
10	8.4	10	1.1	2
29	33	50	1.5	6

[0054] The words “comprises/comprising” and the words “having/including” when used herein with reference to the present invention are used to specify the presence of stated features, integers, steps or components but do not preclude the presence or addition of one or more other features, integers, steps, components or groups thereof.

[0055] It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable sub-combination.

Claims

1. A compound of the general formula (I), a pharmaceutically acceptable salt thereof, an ester thereof, a solvate thereof or a hydrate thereof:



(I)

wherein m is 0 – 4;

n is 0 – 3;

each R^1 is independently selected from the group consisting of a halogen, OH, CF_3, C_1-C_5 aliphatic, C_1-C_5 aliphatic ether, C_1-C_5 aliphatic thioether, and C_6-C_{10} aryl;

R^2 is selected from H, C_1-C_5 aliphatic, benzyl, and *p*-methoxybenzyl;

R^3 is selected from H, C_1-C_5 aliphatic, and benzyl;

R^4 is selected from H, C_1-C_{10} aliphatic, $C(O)C_1$-C_{20} aliphatic, and $C(O)C_6$-C_{20} aromatic;

each R^5 is independently selected from the group consisting of a halogen, OH, CF_3, C_1-C_5 aliphatic, C_1-C_5 aliphatic ether, C_1-C_5 aliphatic thioether, and C_6-C_{10} aryl;

W is selected from H, C_1-C_5 aliphatic, and benzyl;

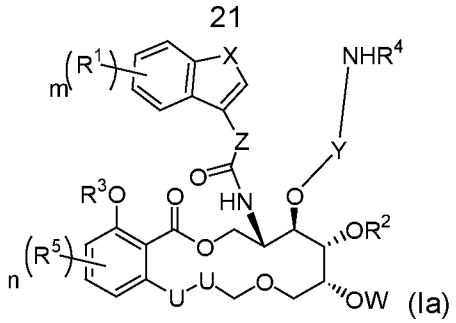
X is selected from NH, NO, S, O, CH_2, and HC=CH;

Y is C_1-C_5 aliphatic;

Z is selected from C_1-C_5 aliphatic, O, NH, S, OCH_2, $NHCH_2$, and SCH_2; and

U-U is selected from CH_2-CH_2, CH=CH, C≡C, cyclopropyl, (CH-CH)O, and (CH-CH)NH.

2. A compound according to Claim 1 of the formula (Ia), a pharmaceutically acceptable salt thereof, an ester thereof, a solvate thereof or a hydrate thereof:



(Ia)

wherein m is 0 – 4;

n is 0 – 3;

each R^1 is independently selected from the group consisting of a halogen, OH, CF_3, C_1-C_5 aliphatic, C_1-C_5 aliphatic ether, C_1-C_5 aliphatic thioether, and C_6-C_{10} aryl;

R^2 is selected from H, C_1-C_5 aliphatic, benzyl, and *p*-methoxybenzyl;

R^3 is selected from H, C_1-C_5 aliphatic, and benzyl;

R^4 is selected from H, C_1-C_{10} aliphatic, $C(O)C_1$-C_{20} aliphatic, and $C(O)C_6$-C_{20} aromatic;

each R^5 is independently selected from the group consisting of a halogen, OH, CF_3, C_1-C_5 aliphatic, C_1-C_5 aliphatic ether, C_1-C_5 aliphatic thioether, and C_6-C_{10} aryl;

W is selected from H, C_1-C_5 aliphatic, and benzyl;

X is selected from NH, NO, S, O, CH_2, and HC=CH;

Y is C_1-C_5 aliphatic;

Z is selected from C_1-C_5 aliphatic, O, NH, S, OCH_2, $NHCH_2$, and SCH_2; and

U-U is selected from CH_2-CH_2, CH=CH, C≡C, cyclopropyl, (CH-CH)O, and (CH-CH)NH.

3. A compound according to any preceding Claim wherein

m is 0 – 4;

n is 0;

each R^1 is independently selected from the group consisting of halogen, OH, CF_3, Me, OMe and Ph;

R^2 is selected from H, Me, benzyl, allyl and *p*-methoxybenzyl;

R^3 is selected from H, Me, Et, C_3H_7, C_4H_9, allyl and benzyl;

R^4 is selected from H, H, Me, Et, C_3H_7, C_4H_9, C(O)Me, C(O)Et, $C(O)C_3H_7$, $C(O)C_4H_9$, and C(O)Ph;

each R^5 is independently selected from the group consisting of a halogen, OH, CF_3, Me, OMe and Ph;

W is selected from H or benzyl;

X is selected from NH, S, O, CH_2, and HC=CH;

Y is selected from CH_2, CH_2CH_2, $CH_2CH_2CH_2$, $CH_2CH_2CH_2CH_2$, $CH_2CH_2CH_2CH_2CH_2$, $CH_2CH=CHCH_2$;

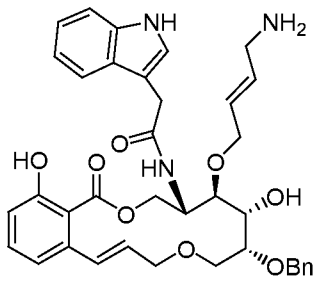
Z is selected from CH_2, CH_2CH_2, $CH_2CH_2CH_2$, $HC=CHCH_2$, O, NH, S, OCH_2, $NHCH_2$, and SCH_2; and

U-U is selected from CH_2-CH_2, and CH=CH.

4. A compound according to Claim 3 wherein m is 0.

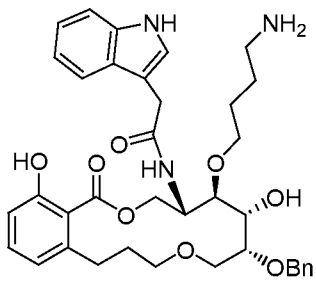
5. A compound according to any preceding Claim wherein W is benzyl.

6. A compound according to any preceding Claim wherein the compound is



a pharmaceutically acceptable salt thereof, an ester thereof, a solvate thereof or a hydrate thereof.

7. A compound according to any preceding Claim wherein the compound is



a pharmaceutically acceptable salt thereof, an ester thereof, a solvate thereof or a hydrate thereof.

8. A pharmaceutical composition comprising a compound according to any preceding Claim and a pharmaceutical acceptable carrier.

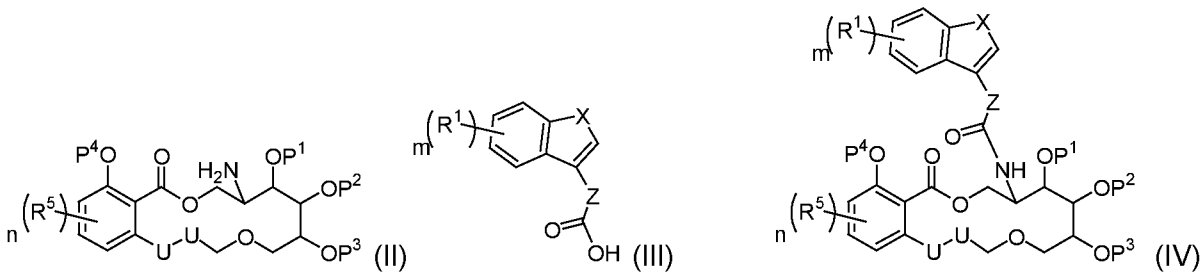
9. A compound according to any preceding Claim for use in the treatment of a disorder in which somatostatin receptors are implicated.

10. A compound according to any preceding Claim for use in the modulation of angiogenesis.

11. A compound according to any preceding Claim for use in the treatment of acromegaly, cancer, arthritis, carcinoid tumours, and vasoactive intestinal peptide tumours.

12. A method of preparing a compound according to any one of Claims 1 to 7 comprising:

i) peptide coupling a compound of formula (II) and a compound of formula (III) to provide a compound of the formula (IV):



(II) (III) (IV)

wherein m is 0 – 4;

n is 0 – 3;

P^1-P^4 are oxygen protecting groups, such that P^2-P^4 can be the same or different and P^1 is different from each of P^2-P^4;

each R^1 is independently selected from the group consisting of a halogen, OH, CF_3, C_1-C_5 aliphatic, C_1-C_5 aliphatic ether, C_1-C_5 aliphatic thioether, and C_6-C_{10} aryl;

each R^5 is independently selected from the group consisting of a halogen, OH, CF_3, C_1-C_5 aliphatic, C_1-C_5 aliphatic ether, C_1-C_5 aliphatic thioether, and C_6-C_{10} aryl;

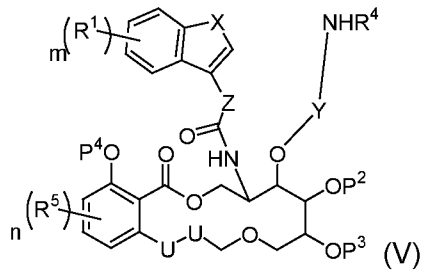
X is selected from NH, NO, S, O, CH_2, and HC=CH;

Z is selected from C_1-C_5 aliphatic, O, NH, S, OCH_2, $NHCH_2$, and SCH_2; and

U-U is selected from CH_2-CH_2, CH=CH, C≡C, cyclopropyl, (CH-CH)O, and (CH-CH)NH;

and

ii) selectively removing oxygen protecting group P^1 and alkylating the free alcohol thus formed to provide a compound of the general formula (V):



(V)

wherein m is 0 – 4;

n is 0 – 3;

P^2-P^4 are the same or different and are oxygen protecting groups;

each R^1 is independently selected from the group consisting of a halogen, OH, CF_3, C_1-C_5 aliphatic, C_1-C_5 aliphatic ether, C_1-C_5 aliphatic thioether, and C_6-C_{10} aryl;

each R^5 is independently selected from the group consisting of a halogen, OH, CF_3, C_1-C_5 aliphatic, C_1-C_5 aliphatic ether, C_1-C_5 aliphatic thioether, and C_6-C_{10} aryl;

X is selected from NH, NO, S, O, CH_2, and HC=CH;

Z is selected from C_1-C_5 aliphatic, O, NH, S, OCH_2, $NHCH_2$, and SCH_2; a

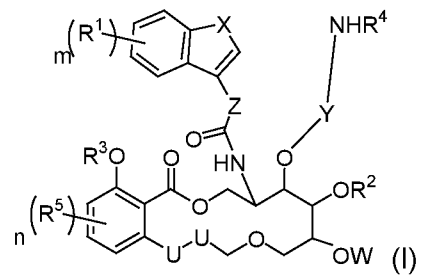
U-U is selected from CH_2-CH_2, CH=CH, C≡C, cyclopropyl, (CH-CH)O, and (CH-CH)NH;

Y is C_1-C_5 aliphatic; and

R^4 is selected from H, C_1-C_{10} aliphatic, $C(O)C_1$-C_{20} aliphatic, and $C(O)C_6$-C_{20} aromatic.

13. A method according to Claim 12 further comprising the step of:

iii) selectively removing oxygen protecting groups P^2-P^4 to provide a compound of the general formula (I):



(I)

wherein m is 0 – 4;

n is 0 – 3;

each R^1 is independently selected from the group consisting of a halogen, OH, CF_3, C_1-C_5 aliphatic, C_1-C_5 aliphatic ether, C_1-C_5 aliphatic thioether, and C_6-C_{10} aryl;

R^2 is selected from H, C_1-C_5 aliphatic, benzyl, and *p*-methoxybenzyl;

R^3 is selected from H, C_1-C_5 aliphatic, and benzyl;

R^4 is selected from H, C_1-C_{10} aliphatic, $C(O)C_1$-C_{20} aliphatic, and $C(O)C_6$-C_{20} aromatic;

each R^5 is independently selected from the group consisting of a halogen, OH, CF_3, C_1-C_5 aliphatic, C_1-C_5 aliphatic ether, C_1-C_5 aliphatic thioether, and C_6-C_{10} aryl;

W is selected from H, C_1-C_5 aliphatic, and benzyl;

X is selected from NH, NO, S, O, CH_2, and HC=CH;

Y is C_1-C_5 aliphatic;

Z is selected from C_1-C_5 aliphatic, O, NH, S, OCH_2, $NHCH_2$, and SCH_2; and

U-U is selected from CH_2-CH_2, CH=CH, C≡C, cyclopropyl, (CH-CH)O, and (CH-CH)NH.

14. A method according to anyone of Claims 12 to 13 wherein

m is 0 – 4;

n is 0;

each R^1 is independently selected from the group consisting of halogen, OH, CF_3, Me, OMe and Ph;

R^2 is selected from H, Me, benzyl, allyl and *p*-methoxybenzyl;

R^3 is selected from H, Me, Et, C_3H_7, C_4H_9, allyl and benzyl;

R^4 is selected from H, H, Me, Et, C_3H_7, C_4H_9, C(O)Me, C(O)Et, $C(O)C_3H_7$, $C(O)C_4H_9$, and C(O)Ph;

each R^5 is independently selected from the group consisting of a halogen, OH, CF_3, Me, OMe and Ph;

W is selected from H or benzyl;

X is selected from NH, S, O, CH_2, and HC=CH;

Y is selected from CH_2, CH_2CH_2, $CH_2CH_2CH_2$, $CH_2CH_2CH_2CH_2$, $CH_2CH_2CH_2CH_2CH_2$, $CH_2CH=CHCH_2$;

Z is selected from CH_2, CH_2CH_2, $CH_2CH_2CH_2$, $HC=CHCH_2$, O, NH, S, OCH_2, $NHCH_2$, and SCH_2; and

U-U is selected from CH_2-CH_2, and CH=CH.

15. A method according to Claim 12 wherein m is 0.

16. A method according to any one of Claims 13 to 15 wherein W is benzyl.

17. A method according to Claim 12 wherein oxygen protecting groups P^1-P^4 are selected from benzyl, *p*-methoxybenzyl, methyl, allyl, trialkylsilyl, acetyl, tetrahydropyranyl, benzoyl, pivaloyl, substitute benzoyl, triphenyl silyl, t-butyldimethylsilyl, t-butyl-diphenylsilyl, methoxymethyl ether, methylthiomethyl ether, benzylmethoxymethyl ether, p-methoxybenzyloxymethyl, 3,4-dimethoxybenzyloxymethyl, benzyloxymethyl, t-butoxymethyl, (p-phenylphenyl)oxymethyl ether, methoxyethoxymethyl ether, 2,2,2-trichloroethoxymethyl, tetrahydrofuranyl ether, tetrahydrothiofuranyl ether, t-butyl ether, prenyl ether, p-methoxyphenyl ether, 3,4-dimethoxybenzyl, 2,6-dimethoxybenzyl, o-nitrobenzyl, p-nitrobenzyl, halobenzyl ether, dihalobenzyl ether, 2-naphthylmethyl ether, 4-acetoxybenzyl ether, diphenylmethyl ether, triphenylmethyl ether, methoxytriphenylmethyl ether, chloroacetyl, dichloroacetyl, trichloracetyl, trifluoroacetyl, phenoxyacetate, levulinate, halobenzoate, nitrobenzoate, allyloxycarbonate, methoxmethylcarbonate, benzylcarbonate, methoxybenzylcarbonate, t-butoxycarbonate, and fluorenylmethoxy carbonate.

18. A method according to Claim 12 wherein the step of alkylating the free alcohol thus formed comprises:

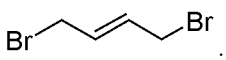
iii) alkylating the free alcohol with a molecule of the formula T—Y—T', thereby liberating an anion of one of T or T', wherein Y is C_1-C_5 aliphatic;

T is Cl, Br or I;

T' is Cl, Br or I; and

iv) replacing the other of T or T' with NHR^4.

19. A method according to Claim 18 wherein the molecule of the formula T—Y—T' is



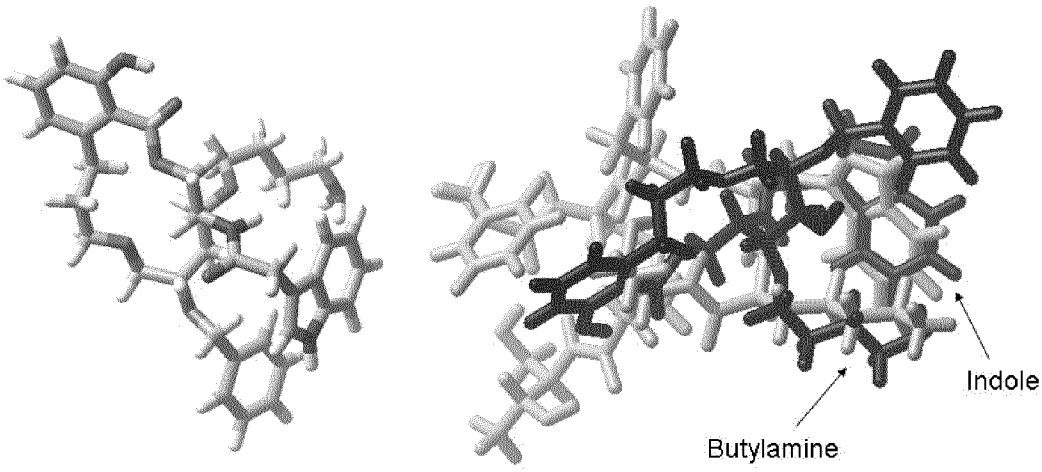


Figure 1

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2012/055900

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D405/12 A61K31/4025
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K

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

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

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	ZHOU, JIAN ET AL: "Synthesis of a Benzomacrolactone-Based Somatostatin Mimetic", ORGANIC LETTERS , 13(21), 5716-5719 CODEN: ORLEF7; ISSN: 1523-7052, 2011, XP002680921, the whole document ----- -/--	1-19

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 July 2012	10/08/2012

Name and mailing address of the ISA/	Authorized officer
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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ZHAO Y ET AL: "Biological study of a somatostatin mimetic based on the 1-deoxynojrimycin scaffold", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, ELSEVIER SCIENCE, GB, vol. 21, no. 2, 15 January 2011 (2011-01-15), pages 824-828, XP027593567, ISSN: 0960-894X, DOI: 10.1016/J.BMCL.2010.11.088 [retrieved on 2011-01-07] page 824; figure 1	1-19
A	SOUERS A J ET AL: "Optimization of a somatostatin mimetic via constrained amino acid and backbone incorporation", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, ELSEVIER SCIENCE, GB, vol. 10, no. 24, 18 December 2000 (2000-12-18), pages 2731-2733, XP027377546, ISSN: 0960-894X [retrieved on 2000-12-18] page 2732; compound 10	1-19
A	US 6 001 960 A (HIRSCHMANN RALPH F [US] ET AL) 14 December 1999 (1999-12-14) claims 1,9,10	1-19
A	MATOS, MARIE-CHRISTINE ET AL: "Synthesis of Macrolide-Saccharide Hybrids by Ring-Closing Metathesis of Precursors Derived from Glycitols and Benzoic Acids", JOURNAL OF ORGANIC CHEMISTRY , 72(5), 1803-1806 CODEN: JOCEAH; ISSN: 0022-3263, 2007, XP002680922, page 1803; compounds 9-12	1-19

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2012/055900

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6001960 A	14-12-1999	NONE	