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(54) Title: CYCLIC PEPTIDES ACTING AS UROTENSIN-II ANTAGONISTS

(57) Abstract: Cyclic peptides are described herein, having antagonist activity toward Urotensin-II receptor, and pharmaceutical compositions comprising such peptides, useful for the treatment of diseases associated with Urotensin-II imbalance.

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TITLE

"Cyclic peptides acting as Urotensin-II antagonists"

FIELD OF THE INVENTION

The present invention refers to cyclic peptides analogues of Urotensin-II having the formula (I) reported herein below, useful for the preparation of pharmaceutical compositions for the treatment of diseases associated with Urotensin-II imbalance.

STATE OF THE ART

Urotensin-II is a cyclic peptide originally isolated from teleost fish urophysis and sequenced more than 20 years ago (Pearson, D. et al. *Proc. Natl. Acad. Sci. USA* (1980), *77*, 5021-5024). Different structural forms of Urotensin-II were subsequently described in various species of fish and amphibians, as well as in mammals, including humans. In 1999 the Urotensin-II receptor was identified (Ames R.S. et al. *Nature* (1999), *401*, 282-286). Several publications indicate that Urotensin-II is a potent constrictor of certain isolated human artery and veins, *in vitro*. Moreover, Urotensin-II induces contraction of non-vascular smooth muscle of cardiac and respiratory systems.

Urotensin-II and its receptor were identified in human cardiac tissues and it was reported that Urotensin-II exerts a strong inotropic effects in the human heart *in vitro*. Taken together, data reported in the literature indicate that Urotensin-II modulates cardiovascular homeostasis and therefore may play a key role in certain cardiovascular pathologies (Ames R.S. et al. *Nature* (1999), *401*, 282-286). Consequently, synthetic analogues of Urotensin-II can be used to develop agonists, antagonists, and inhibitors of Urotensin-II and then for the pharmacological treatment of pathological states associated with Urotensin-II balance. For this purpose, cyclic peptides that are Urotensin-II analogues and comprise exclusively amino acid residues not containing sulphur, were developed and described in the International Patent Application No. WO 01/37856 (SmithKline Beecham Corp.).

Other cyclic peptides that are Urotensin-II analogues and have the above mentioned pharmacological use, were also described in the International Patent Application No. WO 01/37780 (SmithKline Beecham Corp.); in this case the peptides contain two cysteine residues linked by a disulphide bridge.

Cyclic peptide analogues of Urotensin-II having formula X-cyclo[M-A_w-B-C-D_z-N]-Y were described in Grieco P. et al., *J. Med. Chem.*, 2002, 45:4391-4394; in these cyclic peptides a disulphide bridge is formed between the side chains of two amino acid residues containing sulphur M and N, which are never simultaneously cystein; moreover, in the above said formula (I) w and z are 0 or 1, X is chosen among H, Ac, H-Asp, Ac-Asp, and H-Glu-Thr-Pro-Asp; Y is chosen among OH, NH_2, Val-OH, e Val-NH_2; A and D are chosen among Phe, D-Phe, Tyr, D-Tyr, Pro, D-Pro, Nal(1), D-Nal(1), Nal(2), D-Nal(2), Cha, Chg, e Bpa; B è scelto tra Trp, D-Trp, e (α-Me)Trp; e C è scelto tra Lys, Arg, Orn, e Dab.

The above mentioned Urotensin-II peptide analogues described to date in the literature, although endowed with a certain antagonist activity toward Urotensin-II receptor, nevertheless show limited specificity and sometimes a residual agonist activity which severely limits their pharmacological and therapeutic usefulness.

Therefore it is still felt the need of peptides endowed with antagonist activity toward the Urotensin-II receptor without the drawbacks reported above for the known peptides above reported, thus being useful for an effective treatment of the above mentioned pathological conditions.

SUMMARY OF THE INVENTION

Now the Applicants have surprisingly found that cyclic peptides of formula (I) reported below possess antagonist activity and high specificity toward human Urotensin-II receptor, and are devoid of any residual agonist activity.

Thanks to these properties the novel peptides of formula (I) are superior in efficacy as compared to the previously reported Urotensin-II peptide inhibitors, because they show a very potent antagonist activity and are devoid of the above mentioned limitations, typical of the previously described peptides. Therefore, the present peptides of formula (I) can be successfully used for the treatment of pathological conditions associated with Urotensin-II imbalance in humans, such as hypertension, cardiac arrhythmia, heart stroke, angina, ischemia of myocardium and restenosis.

Subject of the present invention are therefore cyclic peptides of general formula (I)

X-ciclo[Pen-A-B-C-D-Cys]-Y (I)

wherein:

X is selected from the group consisting of H, Ac, H-Asp, Ac-Asp, H-Phe, H-D-Phe and H-Glu-Thr-Pro-Asp,

Y is selected from the group consisting of OH, NH_2, Val-OH, and Val-NH_2,

A and D, equal or different from each other, are selected from the group consisting of Phe, D-Phe, Tyr and D-Tyr,

B is selected from the group consisting of D-Trp, D-(α-Me)Trp, D-Trp(Me), D-Trp(CHO), D-Nal(1) and D-Nal(2);

C is selected from the group consisting of Lys, Asp, Glu, Orn, Cit, Dap and (p-amino)Phe;

or pharmaceutically acceptable salts thereof.

Further subjects of the invention are the pharmaceutical compositions comprising the above said cyclic peptides of formula (I) and/or their salts.

Further subject of the invention is the use of the cyclic peptides of formula (I) and/or of their salts as reagents for the pharmacological characterization of Urotensin-II receptors, and their use for the preparation of pharmaceutical compositions for the treatment of pathological conditions associated with unbalance of Urotensin-II.

Features and advantages of the present invention will be illustrated in details in the following description.

DETAILED DESCRIPTION OF THE INVENTION

Within the scope of the present invention natural amino acids are indicated using the common three-letters code, while not genetically coded amino acids were indicated using the following abbreviations:

Pen	Penicillamine;
Nal(1)	3-(1-Naphtyl)alanine;
Nal(2)	3-(2-Naphtyl)alanine;
Orn	Ornitine;
Cit	Citrulline;
Dap	2-amino-propionic acid.

With the abbreviation Ac, an acetyl group is meant.

Some of the peptides of formula (I) according to the present invention are included in the general formula already described in Grieco P. et al., *J. Med. Chem.*, 2002,

45:4391-4394, but they are not specifically described.

The present peptides contain a disulphide bridge between Pen and Cys residues and are characterized by the presence of an amino acid residue B of the D series and by a suitable combination of amino acid residues B and C as reported above.

In fact, the Applicants surprisingly found that whenever the two central residues B and C within the cyclic portion of the said peptides of general formula (I) are those mentioned above, and the B residue presents the inversion of configuration from L to D, the resulting peptides are endowed with potent and highly specific antagonist activity toward the human Urotensin-II receptor, and are devoid of any residual agonist activity toward the same receptor.

Preferred peptides of formula (I) according to the invention are those in which C is selected from the group consisting of Lys, Orn, and (p-amino)Phe.

Particularly notable results were observed when in the general formula (I) B is D-Trp and C is Orn.

According to a preferred embodiment of the present invention in the general formula (I) X is H-Asp, Y is Val-OH, B is D-Trp, and C is Orn.

Particularly preferred are the following peptides:

H-Asp-cyclo[Pen-Phe-DTrp-Orn-Tyr-Cys]-Val-OH (SEQ. ID. NO. 1)

Ac-cyclo[Pen-Phe-DTrp-Orn-Tyr-Cys]-NH_2 (SEQ. ID. NO. 2)

H-Glu-Thr-Pro-Asp-cyclo[Pen-Phe-DTrp-Orn-Tyr-Cys]-Val-OH (SEQ. ID. NO. 3)

H-Asp-cyclo[Pen-DPhe-DTrp-Orn-Tyr-Cys]-Val-OH (SEQ. ID. NO. 4)

H-Asp-cyclo[Pen-Phe-DTrp-Orn-DTyr-Cys]-Val-OH (SEQ. ID. NO. 5)

H-Asp-cyclo[Pen-Phe-DTrp-Lys-Tyr-Cys]-Val-OH (SEQ. ID. NO. 6)

H-Asp-cyclo[Pen-Phe-DNal(1)-Orn-Tyr-Cys]-Val-OH (SEQ. ID. NO. 7)

H-Asp-cyclo[Pen-Phe-DNal(2)-Orn-Tyr-Cys]-Val-OH (SEQ. ID. NO. 8)

H-Asp-cyclo[Pen-Phe-D-(α-Me)Trp-Orn-Tyr-Cys]-Val-OH (SEQ. ID. NO. 9)

H-Asp-cyclo[Pen-Phe-D-Trp(Me)-Orn-Tyr-Cys]-Val-OH (SEQ. ID. NO. 10)

H-Asp-cyclo[Pen-Phe-D-Trp(CHO)-Orn-Tyr-Cys]-Val-OH (SEQ. ID. NO. 11).

The amino acid residues included in said peptides of formula (I) belong to the L-series, unless otherwise specified.

The peptides according to the invention can be prepared by conventional solution and solid-phase peptide synthesis, known to any person skilled in the art. Thus, for

example, to prepare peptides with a free acid at C-terminal, the synthesis in solid-phase can be performed using a Wang resin. Instead, to obtain peptides as C-terminal amide the synthesis in solid phase can be performed using a resin like as a PAL resin [Tris(alkoxy)benzylamide].

The synthesis of the peptides object of this application can be performed by using orthogonal protection using Fluorenylmethoxycarbonyl (hereinafter referred to as "Fmoc") and t-Butyloxycarbonyl (hereinafter referred to as "Boc") as protecting groups at α-amino group of amino acids, and t-Butyl (hereinafter referred to as "t-Bu) and Benzyl (hereinafter referred to as "Bzl") as protecting groups at side-chain of amino acids, such as Asp, Glu (as t-butyl ester), Lys (Boc), Tyr, Thr (OtBu). The thiolic group of Cys and Pen can be protected by a Trityl group (hereinafter referred to as "Trt").

Regarding the strategy "Fmoc/t-Bu", the peptide synthesis consists of the following steps:

a) loading of first C-terminal residue onto the resin;

b) deprotection of α-amino group by a solution of piperidine 25% (v/v) in dimethylformamide (DMF);

c) coupling of the next amino acid, appropriately protected as above said, using a condensing or activating agent, such as N,N'-dicyclohexylcarbodiimide (DCC), O-(benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU), O-benzotriazole-1-yl-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU), 1-hydroxy-benzotriazole (HOBt), etc.;

d) repeating of steps a) and b) until the desired sequence is completed;

e) cleavage of the linear peptide from the resin and deprotection of amino acids side-chains by using trifluoroacetic acid in the presence of suitable "scavengers", such as triethylsilane (TES) and water (5% v/v, each);

f) formation of disulfide bridge by oxidation, for example with Ferricyanide, oxygen or dimethyl sulfoxide (DMSO);

g) purification of crude cyclic peptide by semipreparative HPLC, preferably by reverse-phase HPLC on C-18 column, using as eluents acetonitrile and water in the presence of 0.1% of trifluoroacetic acid (TFA);

h) lyophilization of final purified product;

i) characterization of final compound by analytical HPLC, Mass spectrometry (MS) and amino acids analysis (AAA).

The present peptides of formula (I), in free form or as pharmaceutically acceptable salts, can be used for the preparation of pharmaceutical compositions according to conventional methods of preparation, well-known in pharmaceutical field.

These pharmaceutical compositions can be conventionally formulated, and may further comprise one or more pharmaceutically acceptable excipients and/or diluents.

The administration of the present compositions is feasible by any conventional way, for example by parenteral injection in the form of injectable solutions or suspensions, or by oral, topic, nasal administration, etc.

The formulations of the present peptides include compresses, capsules, pills, solutions, dispersions, creams and ointments, emulsions, aerosol, and can also be used to accomplish a controlled or delayed release of the active compound.

The present pharmaceutical compositions may comprise the peptides of formula (I) according to the invention as sole active component, or may comprise the present peptides in combination with other active compounds or adjuvants, suitably chosen according to the pathological conditions to be treated.

The pharmaceutical compositions comprising the present peptides are useful for the pharmacological treatment of pathologies associated with an alteration of Urotensin-II balance, such as hypertension, heart arrhythmia, heart stroke, angina, ischemia of myocardium and restenosis.

The present peptides of general formula (I) can also be used as reagents in biotechnological and pharmaceutical research, for example as reagents in characterisation of human Urotensin-II receptor.

All peptides according to the invention were synthesised by the methodologies described above and illustrated in details in Example 1.

The following examples are reported for illustrative but not limitative purposes of present invention.

EXAMPLE 1

Preparation of H-Asp-cyclo[Pen-Phe-D-Trp-Orn-Tyr-Cys]-Val-OH (SEQ. ID. NO. 1)

The compound was synthesised by standard solid-phase methodology, starting

from 0.5 g of Wang resin (0.7 mmol/g) using N^{α}-Fmoc chemistry and an orthogonal side chain protection strategy. The first amino acid, N^{α}-Fmoc-Val-OH, was linked to the resin using as coupling reagents a 3-fold excess of HBTU/HOBt in the presence of N,N'-diisopropylethylamine (DIEA). The following amino acids were then added stepwise to the growing peptide: N^{α}-Fmoc-Cys(Trt)-OH, N^{α}-Fmoc-Tyr(OtBu)-OH, N^{α}-Fmoc-Orn(N^{ε}-Boc)-OH, N^{α}-Fmoc-D-Trp(N^{in}-Boc)-OH, N^{α}-Fmoc-Phe-OH, N^{α}-Fmoc-Pen(Trt)-OH and N^{α}-Fmoc-Asp(OtBu)-OH using standard solid phase methods. Each coupling reaction was achieved using a 3-fold excess of amino acid and of HBTU/HOBt in presence of DIEA. The N^{α}-Fmoc protecting group was removed by treating the protected peptide resin with 25% piperidine solution in DMF (1 x 50 mL, 5 min, 1 x 50 mL, 20 min). The peptide resin was washed with DMF (3 x 50 mL), DCM (3 x 50 mL) and again with DMF.

Upon complete formation of the protected linear peptide, the compound was cleaved from the resin and the other side chain protecting groups removed using the following mixture: TFA/TES/H_2O (9:0.5:0.5) for 3 h. All procedures were done under an Argon atmosphere. The resin was removed from solution by filtration and the crude peptide was recovered by precipitation with cold anhydrous ethyl ether giving a white powder that was purified by preparative HPLC on a C18-bonded silica gel column (Vydac 218TP1010, 1.0 x 25 cm) eluted with a linear gradient of acetonitrile in aqueous 0.1% of TFA (v/v). The purification was monitored at 280 nm, and the fraction corresponding to the major peak were collected, combined, and lyophilised to give the final compound as a pure (>98%) white powder. The linear peptide was characterised by analytical HPLC and FAB-MS (m/e 1073.282 [M^+]). The final cyclic peptide, containing the disulfide bridge, was achieved by oxidation with an aqueous solution of potassium ferricyanide at pH = 8.5 (ammonium buffer). This step was monitored by analytical HPLC to evaluate the grade of conversion. Final cyclic peptide was purified by reverse-phase HPLC using the condition above described.

EXAMPLES 2 - 9

Following the same synthetic methodology reported above and using appropriate reagents and amino acids, the following peptides 2-9 were also synthesised:

Example	Peptide	MS (m/e)
2	Ac-cyclo[Pen-Phe-DTrp-Orn-Tyr-Cys]-NH_2 (SEQ. ID. NO. 2)	900.112
3	H-Glu-Thr-Pro-Asp-cyclo[Pen-Phe-DTrp-Orn-Tyr-Cys]-Val-OH (SEQ. ID. NO. 3)	1400.622
4	H-Asp-cyclo[Pen-DPhe-DTrp-Orn-Tyr-Cys]-Val-OH (SEQ. ID. NO. 4)	1073.282
5	H-Asp-cyclo[Pen-Phe-DTrp-Orn-DTyr-Cys]-Val-OH (SEQ. ID. NO. 5)	1073.282
6	H-Asp-cyclo[Pen-Phe-DTrp-Lys-Tyr-Cys]-Val-OH (SEQ. ID. NO. 6)	1087.309
7	H-Asp-cyclo[Pen-Phe-DNal(1)-Orn-Tyr-Cys]-Val-OH (SEQ. ID. NO. 7)	1083.298
8	H-Asp-cyclo[Pen-Phe-DNal(2)-Orn-Tyr-Cys]-Val-OH (SEQ. ID. NO. 8)	1083.298
9	H-Asp-cyclo[Pen-Phe-D(α-Me)Trp-Orn-Tyr-Cys]-Val-OH (SEQ. ID. NO. 9)	1087.282
10	H-Asp-cyclo[Pen-Phe-DTrp(Me)-Orn-Tyr-Cys]-Val-OH (SEQ. ID. NO. 10)	1087.282
11	H-Asp-cyclo[Pen-Phe-DTrp(CHO)-Orn-Tyr-Cys]-Val-OH (SEQ. ID. NO. 11)	1101.298

BIOLOGICAL ACTIVITY

The cyclic peptides of the invention were tested in binding and functional assays as reported below.

Binding Assays

All experiments were performed on membranes obtained from stable CHO-K1 cells expressing the recombinant human UT receptor. The radioligand used for competition experiments was [^{125}I]Urotensin II. Nonspecific binding was determined in the presence of 1 mM of unlabelled hU-II. In this binding assay human Urotensin-II showed an affinity of K_i = 1.8 nM (nanomolar), while the compound achieved as in Example 1 and tested in same conditions described above, showed an affinity value expressed as pKi = 8.3.

Functional Assay

The biological activity of the said peptides of formula (I) was evaluated using the rat isolated thoracic aorta assay (Camarda, V. et al. *Naunyn-Schmiedeberg's Arch. Pharmacol.* (2002) *365*, 141). The thoracic aorta was excised from male albino rats (Wistar) and cleared of surrounding tissue; from each vessel, a helically cut strip was prepared, and then it was cut into two parallel strips. The endothelium was removed and the preparations were placed in 5 ml organ baths filled with oxygenated normal Krebs–Henseleit solution. Motor activity of the strips was recorded isotonically (load 5 mN). A cumulative concentration–response curve to hU-II was constructed on one of the two strips, which served as control. The other strip received the antagonist peptide under examination and, after a 30-min incubation period, hU-II was administered cumulatively. Antagonist activity was expressed in terms of pKB (negative logarithm of the antagonist dissociation constant; Kenankin, T.P. Pharmacologic analysis of drugreceptor interaction, *third ed.* Lippincott-Raven, Philadelphia, PA, 1997).

The peptide of formula (I), prepared as described in Example 1, and tested in these conditions, showed to be a potent antagonist at human Urotensin-II receptor, with a pKb value of 8.3. This value is almost 70 fold higher as compared to other antagonist compounds at Urotensin-II receptor described to date in literature.

CLAIMS

1. Cyclic peptides of general formula (I):

X-ciclo[Pen-A-B-C-D-Cys]-Y (I)

Wherein:

X is selected from the group consisting of H, Ac, H-Asp, Ac-Asp, H-Phe, H-D-Phe and H-Glu-Thr-Pro-Asp,

Y is selected from the group consisting of OH, NH_2, Val-OH, and Val-NH_2,

A and D, equal or different from each other, are selected from the group consisting of Phe, D-Phe, Tyr and D-Tyr,

B is selected from the group consisting of D-Trp, D-(α-Me)Trp, D-Trp(Me), D-Trp(CHO), D-Nal(1) and D-Nal(2);

C is selected from the group consisting of Lys, Asp, Glu, Orn, Cit, Dap and (p-amino)Phe;

or pharmaceutically acceptable salts thereof.

2. Cyclic peptides of formula (I) according to claim 1, wherein C is selected from the group consisting of Lys, Orn, and (p-ammino)Phe.

3. Cyclic peptides of formula (I) according to claim 1, wherein B is D-Trp and C is Orn.

4. Cyclic peptides of formula (I) according to claim 1, wherein X is H-Asp, Y is Val-OH, B is D-Trp, and C is Orn.

5. Cyclic peptides of formula (I) according to claim 1, selected from the following compounds:

H-Asp-cyclo[Pen-Phe-DTrp-Orn-Tyr-Cys]-Val-OH (SEQ. ID. NO. 1)

Ac-cyclo[Pen-Phe-DTrp-Orn-Tyr-Cys]-NH_2 (SEQ. ID. NO. 2)

H-Glu-Thr-Pro-Asp-cyclo[Pen-Phe-DTrp-Orn-Tyr-Cys]-Val-OH (SEQ. ID. NO. 3)

H-Asp-cyclo[Pen-DPhe-DTrp-Orn-Tyr-Cys]-Val-OH (SEQ. ID. NO. 4)

H-Asp-cyclo[Pen-Phe-DTrp-Orn-DTyr-Cys]-Val-OH (SEQ. ID. NO. 5)

H-Asp-cyclo[Pen-Phe-DTrp-Lys-Tyr-Cys]-Val-OH (SEQ. ID. NO. 6)

H-Asp-cyclo[Pen-Phe-DNal(1)-Orn-Tyr-Cys]-Val-OH (SEQ. ID. NO. 7)

H-Asp-cyclo[Pen-Phe-DNal(2)-Orn-Tyr-Cys]-Val-OH (SEQ. ID. NO. 8)

H-Asp-cyclo[Pen-Phe-D-(α-Me)Trp-Orn-Tyr-Cys]-Val-OH (SEQ. ID. NO. 9)

H-Asp-cyclo[Pen-Phe-D-Trp(Me)-Orn-Tyr-Cys]-Val-OH (SEQ. ID. NO. 10)

H-Asp-cyclo[Pen-Phe-D-Trp(CHO)-Orn-Tyr-Cys]-Val-OH (SEQ. ID. NO. 11).

6. A reagent for the pharmacological characterisation of human Urotensin-II receptor comprising at least a cyclic peptide of general formula (I) as described in claims 1-5, or a pharmaceutically acceptable salt thereof.

7. A pharmaceutical composition comprising as active compound at least a cyclic peptide of general formula (I) as described in claims 1-5, or a pharmaceutically acceptable salt thereof, optionally further comprising pharmaceutically acceptable excipients and/or diluents.

8. Use of cyclic peptides of general formula (I) as described in claims 1-5, for the preparation of pharmaceutical compositions useful for the treatment of pathological conditions associated with unbalance of Urotensin-II.

9. Use of cyclic peptides of formula (I) according to claim 8, wherein said pathological conditions are selected from the group consisting of hypertension, cardiac arrhythmia, heart stroke, angina, ischemia of myocardium and restenosis.

10. Use of cyclic peptides of general formula (I) as described in claims 1-5, as reagents for the pharmacological characterization of human Urotensin-II receptor.

SEQUENCE LISTING

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Grieco, Paolo
Rovero, Paolo

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