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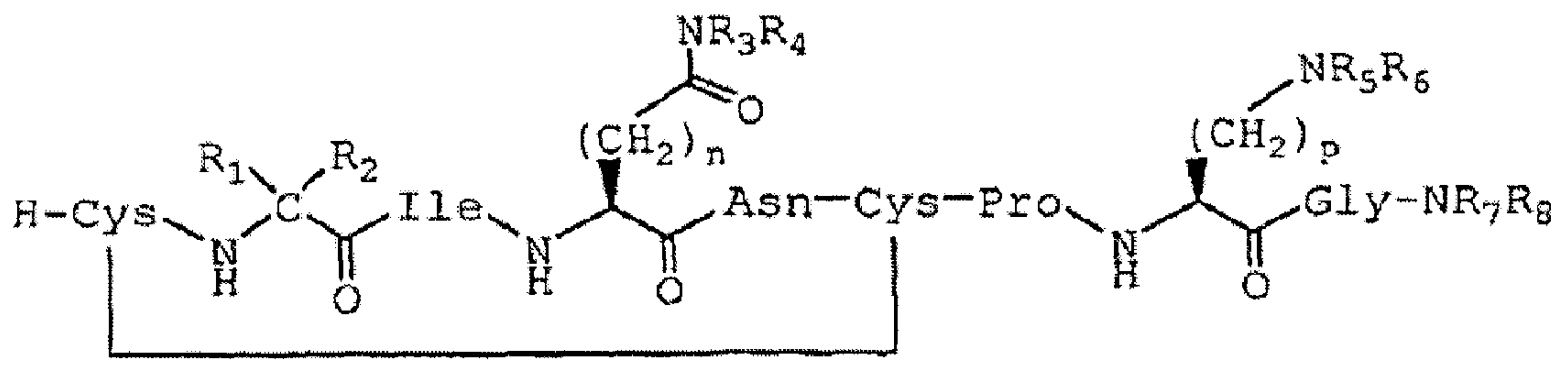

(I)

(57) Abrégé/Abstract:
The present invention relates to novel compounds, pharmaceutical compositions comprising the same, use of said compounds for the manufacture of a medicament for treatment of inter alia shock conditions as well as to a method for treatment of said conditions, wherein said compounds are administered. The compounds are represented by the general formula (I), as further defined in the specification.

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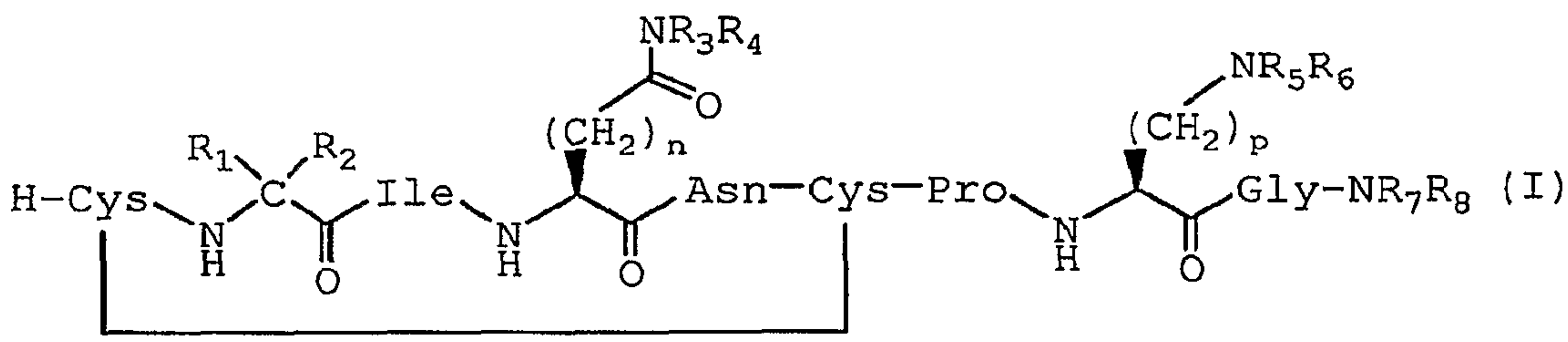

(57) Abstract: The present invention relates to novel compounds, pharmaceutical compositions comprising the same, use of said compounds for the manufacture of a medicament for treatment of *inter alia* shock conditions as well as to a method for treatment of said conditions, wherein said compounds are administered. The compounds are represented by the general formula (I), as further defined in the specification.

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NOVEL COMPOUNDS

Field of the Invention

The present invention relates to novel compounds, pharmaceutical compositions comprising the same, use of said compounds for the manufacture of a medicament for treatment of *inter alia* shock conditions as well as to a method for treatment of said conditions, wherein said compounds are administered.

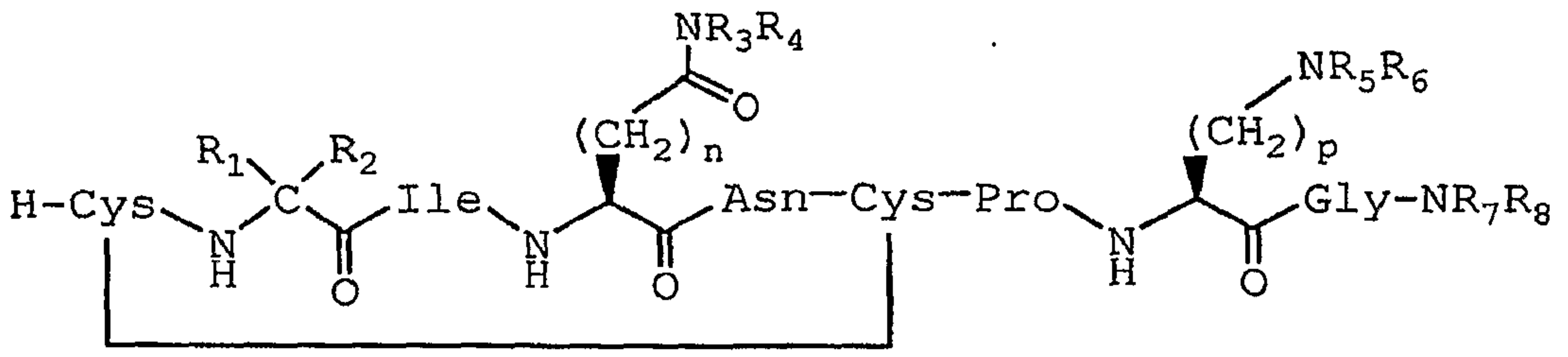
Background

Peptidic vasopressin V1a receptor agonists, such as terlipressin, have recently (see *e.g.* O'Brian *et al.*, Lancet 359 (9313):1209-10, June 4th, 2002) received increased attention for clinical use in treatment of critical care diseases and conditions, including shock of hypovolemic (*e.g.* hemorrhagic) or vasodilatory (*e.g.* septic) origin, bleeding esophageal varices (BEV), hepatorenal syndrome (HRS), cardiopulmonary resuscitation and anesthesia-induced hypotension. They have also been shown to have clinical use in the treatment of orthostatic hypotension, paracentesis-induced circulatory dysfunction, intra-operative blood loss and blood loss associated with burn débridement and epistaxis, and for treatment of various ocular diseases by increasing lacrimation/tear formation.

It is an objective of the present invention to provide efficacious compounds, especially at the human V1a (hV1a) receptor, that may provide alternatives, *e.g.*, to terlipressin in the treatment of critical care conditions.

Disclosure of the Invention

The present invention relates to compounds represented by the general formula (I):



(I)

wherein:

R_1 is selected from H and part of an alicyclic structure that comprises from 3 to 8 carbon atoms;

R_2 is selected from $(CH_2)_m$-X and part of said alicyclic structure;

m is selected from 0, 1, 2 and 3;

n is selected from 0, 1, 2, 3 and 4;

p is selected from 2, 3 and 4;

when R_1 is H, R_2 is $(CH_2)_m$-X;

when R_1 is not H, R_1 and R_2 together with the α carbon atom to which they are attached form said alicyclic structure;

when m is 0, 2 or 3, X is selected from C_{3-8}-cycloalkyl, C_{5-8}-cycloalkenyl and C_{5-8}-cycloalkynyl;

when m is 1, X is selected from C_{3-8}-cycloalkyl, C_{5-8}-cycloalkenyl, C_{5-8}-cycloalkynyl, isopropyl and tert-butyl;

said alicyclic structure, C_{3-8}-cycloalkyl, C_{5-8}-cycloalkenyl and C_{5-8}-cycloalkynyl optionally have at least one alkyl, O-alkyl or hydroxyl substituent;

R_3, R_4, R_5, R_6, R_7 and R_8 are each independently selected from H, alkyl, OH, O-alkyl and OC(O)-alkyl;

alkyl is selected from C_{1-6} straight and C_{4-8} branched chain alkyl and optionally has at least one hydroxyl substituent; and

solvates and pharmaceutically acceptable salts thereof.

It deserves mentioning that *e.g.* also isopropyl and 2-*n*-butyl groups are encompassed by the expression C_{1-6} straight chain alkyl, as said expression is not related to the binding site of the straight chain in question.

C_{1-6} denotes having from one to six carbon atoms, including any number therebetween, and this nomenclature is used analogously herein.

The abbreviations used herein are:

AcBuc	1-aminocyclobutane-1-carboxylic acid
Ala(cPe)	cyclopentylalanine
Boc	*tert*-butoxycarbonyl
BOP	benzotriazol-1-yloxy trisdimethylamino-phosphonium hexafluorophosphate
Bu	butyl
Cha	cyclohexylalanine
Dbu	2,4-diaminobutyric acid
DCC	N,N'-dicyclohexylcarbodiimide
DCHA	dicyclohexylamine
DCM	dichloromethane
DIAD	diisopropyl diazodicarboxylate
DIC	*N,N'*-diisopropylcarbodiimide
DIEA	*N,N*-diisopropyl-*N*-ethylamine
DMF	*N,N*-dimethylformamide
Fm	9-fluorenylmethyl
Fmoc	9-fluorenylmethoxycarbonyl
HOBt	1-hydroxybenzotriazole
HPLC	high performance liquid chromatography
i	iso
Mmt	4-methoxytrityl
Mob	*p*-methoxybenzyl
MS	mass spectrometry
Orn	ornithine
Ph	phenyl
Pr	propyl

PyBOP	benzotriazol-1-yloxy trispyrrolidine-phosphonium hexafluorophosphate
o-NBS-Cl	2-nitrobenzenesulfonyl chloride
OT	oxytocin
Rt	retention time
t	tert
TFA	trifluoroacetic acid
TIS	triisopropylsilane
TMOF	trimethylorthoformate
TPP	triphenylphosphine
Trt	trityl
VT	vasotocin, [Ile^3]vasopressin
Z	benzyloxycarbonyl

Unless otherwise specified L-amino acids were used, and conventional amino acid terminology is adhered to.

Examples of pharmaceutically acceptable salts comprise acid addition salts, *e.g.* a salt formed by reaction with hydrohalogen acids, such as hydrochloric acid, and mineral acids, such as sulphuric acid, phosphoric acid and nitric acid, as well as aliphatic, alicyclic, aromatic or heterocyclic sulphonic or carboxylic acids, such as formic acid, acetic acid, propionic acid, succinic acid, glycolic acid, lactic acid, malic acid, tartaric acid, citric acid, ascorbic acid, maleic acid, hydroxymaleic acid, pyruvic acid, *p*-hydroxybenzoic acid, embonic acid, methanesulphonic acid, ethanesulphonic acid, hydroxyethanesulphonic acid, halobenzenesulphonic acid, toluenesulphonic acid and naphtalenesulphonic acid.

In preferred embodiments R_7 and R_8 are H. It is especially preferred that R_3 and R_4 are H.

It is also preferred that n is 1 or 2. Alkyl is typically selected from methyl, ethyl, *n*-propyl, *i*-propyl, *t*-butyl and *i*-amyl.

X is preferably selected from cyclopentyl and cyclohexyl.

Said alicyclic structure is preferably a cyclobutyl structure.

In the most preferred embodiment, said compound having the formula (I) is selected from a group consisting of:

H-Cys-Cha-Ile-Gln-Asn-Cys-Pro-Dbu-Gly-NH_2 (Cmpd. 1)

H-Cys-Ala(cPe)-Ile-Gln-Asn-Cys-Pro-Dbu-Gly-NH_2 (Cmpd. 2)

H-Cys-AcBuc-Ile-Gln-Asn-Cys-Pro-Dbu-Gly-NH_2 (Cmpd. 3)

and

H-Cys-Cha-Ile-Asn-Asn-Cys-Pro-Orn(*i*-Pr)-Gly-NH_2 (Cmpd. 4)

The number in parenthesis denotes the compound as referered to in the following.

Furthermore the present invention relates to a compound as set forth above for use as a pharmaceutical.

Accordingly, the present invention also relates to a pharmaceutical composition comprising a compound as set forth above as active ingredient in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

The pharmaceutical composition may be adapted for oral, intravenous, topical, intraperitoneal, nasal, buccal, sublingual or subcutaneous administration or for administration via the respiratory tract *e.g.* in the form of an aerosol or an air-suspended fine powder. The composition may thus for instance be in the form of tablets, capsules, powders, microparticles, granules, syrups, suspensions, solutions, transdermal patches or suppositories.

It should be noted that the composition according to the present invention may optionally include two or more of the above outlined compounds.

The present pharmaceutical composition may optionally comprise *e.g.* at least one further additive selected from a disintegrating agent, binder, lubricant, flavoring agent, preservative, colorant and any mixture thereof. Examples of such and other additives are found in "*Handbook of Pharmaceutical Excipients*"; Ed. A.H. Kibbe, 3rd Ed., American Pharmaceutical Association, USA and Pharmaceutical Press UK, 2000.

The present pharmaceutical composition is most preferably adapted for parenteral administration. It may comprise a sterile aqueous preparation of the compounds of the invention preferably isotonic with the blood of the recipient. This aqueous preparation may be formulated according to known methods, using suitable dispersing or wetting agents and suspending agents. Illustrative of a preparation produced in such conventional fashion is the aqueous formulation, Remestype® (terlipressin). The preparation also may be a sterile injectable solution or suspension in a diluent or solvent, for example, as a solution in 1,3-butane diol. Water, Ringer's solution, and isotonic sodium chloride solution are exemplary acceptable diluents. Sterile, fixed oils may be employed as a solvent or suspending medium. Bland fixed oils, including synthetic mono or di-glycerides, and fatty acids, such as oleic acid, may also be used.

In addition, the present invention relates to use of a compound as outlined above for the manufacture of a medicament for treatment of shock of hypovolemic or vasodilatory orgin, BEV, HRS, cardiopulmonary resuscitation, anesthesia-induced hypotension, orthostatic hypotension, paracentesis-induced circulatory dysfunction, intra-operative blood loss or blood loss associated with burn débridement and epistaxis, and for treatment of various ocular diseases by increasing lacrimination/tear formation.

In another embodiment the invention relates to a method for treatment of shock of hypovolemic or vasodilatory origin, BEV, HRS, cardiopulmonary resuscitation, anesthesia-induced hypotension, orthostatic hypotension, paracentesis-induced circulatory dysfunction, intra-operative blood loss or blood loss associated with burn débridement and epistaxis, and of various ocular diseases by increasing lacrimation/tear formation, wherein said method comprises administering to an animal, including human, patient of a therapeutically effective amount of a compound as outlined above.

In another embodiment, the invention relates to a use of a compound according to the present invention for treatment of shock of hypovolemic or vasodilatory origin, bleeding esophageal varices, hepatorenal syndrome, cardiopulmonary resuscitation, anesthesia-induced hypotension, orthostatic hypotension, paracentesis-induced circulatory dysfunction, intra-operative blood loss or blood loss associated with burn debridement and epistaxis, and for treatment of various ocular diseases by increasing lacrimation/tear formation.

The typical dosage of the compounds according to the present invention varies within a wide range and will depend on various factors such as the individual needs of each patient and the route of administration. The dosage administered by infusion is generally within the range of 0.01-200 μg/kg body weight per hour. A physician of ordinary skill in the art will be able to optimise the dosage to the situation at hand.

Experimental (synthesis)

Amino acid derivatives and resins were purchased from commercial providers (Novabiochem, Bachem, Peptide International and PepTech Corporation). Other chemicals and solvents were provided from Sigma-Aldrich, Fisher Scientific and VWR.

The compounds herein were synthesised by standard methods in solid phase peptide chemistry utilising both Fmoc and Boc methodology. Unless otherwise provided, all reactions were performed at room temperature. In addition to the references cited *supra*, the following standard reference literature provides further guidance on general experimental set up, as well as on the availability of required starting material and reagents:

Kates, S.A., Albericio, F., Eds., *Solid Phase Synthesis. A Practical Guide*, Marcel Dekker, New York, Basel, 2000;

Stewart, J.M., Young, J.D. *Solid Phase Synthesis*, Pierce Chemical Company, 1984;

Bisello, *et al.*, *J. Biol. Chem.* **1998**, 273, 22498-22505; and

Merrifield, *J. Am. Chem. Soc.* **1963**, 85, 2149-2154.

Purity of the synthesized peptide may be determined by analytical reversed phase HPLC. Structural integrity of the peptides may be confirmed using amino acid analysis and electrospray mass spectrometry.

The peptides synthesised by Fmoc methodology were cleaved with a TFA/TIS/H_2O 96/2/2 (v/v/v) solution, and cleavage in Boc methodology was accomplished with 90% HF/10% anisole (v/v) solution. Disulfide bridge (ring) formation was achieved by oxidation of linear peptides dissolved in 10% TFA (aq) with iodine. Peptides were purified by preparative HPLC in triethylammonium phosphate buffers (aq). The compounds were finally converted to acetate salts using conventional HPLC methodology. The fractions with a purity exceeding 97% were pooled and lyophilised.

Synthesis of peptides with alkylated side chain in position no. 8 (*e.g.* compound 4):

The peptides were assembled with Fmoc methodology. The diamino acid residue in position no. 8 was introduced with an acid labile (*i.e.* removable with a solution containing 1-2% TFA) protecting group, such as methoxytrityl (Mmt; see Barlos, K. *et al.* in *Peptides* 1992, Schneider, C.H., Eberle, A.N., Eds., ESCOM Science Publishers B.V., 1993, pp 283-284). Resin bound peptide was treated with a DCM/TIS/TFA 93/5/2 (v/v/v) solution for the Mmt group removal. Reductive alkylation with acetone/NaBH(OAc)$_3$ provided the *N*-isopropyl peptide.

To avoid undesirable *N,N*-dialkylation in reductive alkylation in the above procedure, which may occur when straight chain alkyl aldehydes are used, an alternative was developed, wherein after the Mmt removal the amino group was first derivatised with 2-nitrobenzenesulfonyl chloride (*o*-NBS-Cl; see Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, 36, 6373-6374). The resulting sulphonamide was then alkylated with an appropriate alcohol under conventional Mitsunobu reaction conditions, typically utilising TPP/DIAD in 1,2-dimethoxyethane (Mitsunobu, O. *Synthesis* **1981**, 1-28). The *o*-NBS-Cl group was subsequently removed with 5% potassium thiophenolate in DMF, after which the peptide was cleaved from the resin.

Synthesis of peptides with *N*-alkylated side chain in position no. 4:

The peptides were assembled with Boc methodology. The residue in position no. 4 was introduced in the sequence as Boc-Asp(OFm)-OH. After complete peptide assembly the side chain protection was removed with 30% piperidine in DMF. The resulting free carboxylic group was converted to the desired amide by coupling with an appropriate amine mediated by PyBOP or BOP/DIEA. The *N*-terminal Boc group was then removed, followed by HF cleavage, cyclisation and purification by HPLC.

Table 1 lists the compounds prepared by the above procedure together with the determined (*vide infra*) EC_{50} (median effective concentration) expressed in nanomol/L. R_3, R_4, R_5, R_6, R_7 and R_8 are H for all compounds except compound 4, where R_6 is isopropyl instead of H. For the listed compounds m is 1, except where R_1 and R_2 are part of an alicyclic structure (formed together with the α carbon of the amino acid in position no. 2) exemplified here as 1,1-cyclobutyl.

Table 1. Compounds prepared with the formula (I)

Substituent R_1	R_2	X	n	p	EC_{50}	Denoted
H	CH_2X	cyclohexyl	2	2	0.27	compound 1
H	CH_2X	cyclopentyl	2	2	0.80	compound 2
1,1-cyclobutyl		-	2	2	0.94	compound 3
H	CH_2X	*t*-butyl	2	2	10.7	compound 5
H	CH_2X	*i*-propyl	2	2	12.0	compound 6
1,1-cyclobutyl		-	1	3	7.93	compound 7
H	CH_2X	cyclopentyl	1	3	7.70	compound 8
H	CH_2X	cyclohexyl	1	3	0.75	compound 4
1,1-cyclobutyl		-	1	2	14.8	compound 9
H	CH_2X	cyclopentyl	1	2	17.8	compound 10
H	CH_2X	cyclohexyl	1	3	9.93	compound 11
H	CH_2X	cyclohexyl	1	2	2.28	compound 12
N/A					82.1	terli-pressin

The following detailed examples are provided to further illustrate the synthesis:

Compound 4; [Cha^2,Asn^4,Orn(*i*-Pr)^8]VT:

The amino acid derivatives used were Boc-Cys(Trt)-OH, Fmoc-Cha-OH, Fmoc-Ile-OH, Fmoc-Gln(Trt)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Cys(Trt)-OH, Fmoc-Pro-OH, Fmoc-Orn(Mmt)-OH and Fmoc-Gly-OH. Analytical HPLC was performed on a Waters 600 Liquid Chromatograph using a Vydac C18, 5μ 4.6 x 250 mm, column at a flow rate of 2 ml/min. Preparative HPLC was performed on a Waters 2000 Liquid Chromatograph using a Prepak 47 x 300 mm cartridge at a flow rate of 100 ml/min. Final compound analysis was performed on a 1100 Agilent Liquid Chromatograph using a Vydac C18, 5μ 2.1 x 250 mm, column at a flow rate of 0.3

ml/min. Mass spectra were recorded on a Finnigan MAT spectrometer.

The fully protected peptide resin was synthesised on an Applied Biosystems 9050 Peptide Synthesiser starting from 0.4 g (0.1 mmol) of Tentagel-S-RAM resin (Peptides International). DIC/HOBt mediated single couplings with a 4-fold excess of amino acid derivatives were performed. The Fmoc group was removed with 20% piperidine in DMF. Upon completion of the automated synthesis, the resin was transferred into a manual synthesis vessel and was treated with DCM/TIS/TFA 93/5/2 (v/v/v) solution (30 ml) for 2 x 1.5 hours for removal of the Mmt group. The resin was thoroughly washed with DCM and was subsequently suspended in 15 ml of 1,2-dichloroetehane/TMOF 1:1 (v/v). 0.2 ml of acetone was then added followed by 0.6 g of $NaBH(OAc)_3$. The suspension was shaken overnight and the resin was washed with methanol, DMF and DCM and dried *in vacuo*. The resin was then treated with 30 ml of the TFA/TIS/H_2O 96/2/2 (v/v/v) solution for 1.5 hours and filtered off. The filtrate was evaporated and the crude linear peptide was precipitated with diethyl ether. The precipitate was immediately dissolved in 500 ml of 10% TFA (aq), and the peptide was oxidised by adding 0.1 M I_2 in methanol to the magnetically stirred solution until yellow color persisted. Excess of iodine was reduced with ascorbic acid. The reaction mixture was then cooled with crushed ice and pH was adjusted to about 5 by adding concentrated ammonia (aq). The mixture was loaded onto an HPLC column and purified using a triethylammonium phosphate buffer with pH 5.2. The compound was eluted with a gradient of acetonitrile. The fractions with a purity exceeding 97% were pooled, and the resulting solution was diluted with 2 volumes of water. The solution was reloaded onto the column which was then washed with 2 l of 0.1 M ammonium acetate (aq) and equilibrated with 2% acetic acid (aq). The compound was eluted with a fast (3%/min) gradient of acetonitrile. The fractions containing the desired product were pooled and lyophilised. 20.7 mg (20% yield) of white amorphous powder was obtained. HPLC: Rt=8.2 min, gradient: 30→50% B over 20 min, flow: 0.3 ml/min, t=40°C, solvent A 0.01% TFA (aq), solvent B 70% CH_3CN, 0.01% TFA (aq); Purity: 100%; MS $(M+H^+)$: expected 1026.5, observed 1026.5.

Compound 3; [AcBuc^2,Dbu^8]VT :

The amino acid derivatives used were Boc-Cys(Mob)-OH, Boc-AcBuc-OH, Boc-Ile-OH, Boc-Gln-OH, Boc-Asn-OH, Boc-Pro-OH, Boc-Dbu(Z)-OH DCHA salt and Boc-Gly-OH, all purchased from Novabiochem and Bachem. HPLC and MS operations were performed as in the synthesis of compound 4.

The fully protected peptide resin was manually synthesised starting from 0.6 g (0.4 mmol) of 4-methyl-benzhydrylamine resin (Novabiochem). DCC, PyBOP or DIC/HOBt mediated single couplings with 2.5-fold excess of amino acid derivatives were employed. The Boc group was removed with 50% TFA in DCM containing 1% of *m*-cresol. The finished resin was washed with methanol, DMF and DCM and dried *in vacuo*. The peptide was cleaved from the resin by using 30 ml of anhydrous HF containing 3 ml of anisole at 0°C for 90 minutes. The HF was evaporated off, and the crude linear peptide was washed with diethyl ether. The peptide was immediately dissolved in 200 ml of 25% acetonitrile/10% TFA (aq) and oxidised as described *supra*. The resulting mixture was loaded directly onto an HPLC column and purified using triethylammonium phosphate buffer at pH 2.3. Unless otherwise provided the subsequent steps were identical to the procedure for compound 4. 80.6 mg (22% yield) of white amorphous powder was obtained. HPLC: Rt=7.3 min, gradient: 20→40% B over 20 min, flow: 0.3 ml/min, t=40°C, solvent A 0.01% TFA (aq), solvent B 70% CH_3CN, 0.01% TFA (aq); Purity: 99.6%; MS $(M+H^+)$: expected 928.4, observed 928.3.

The other compounds were prepared by analogous variation of these synthetic procedures.

Experimental (biological testing)

In vitro receptor assay:

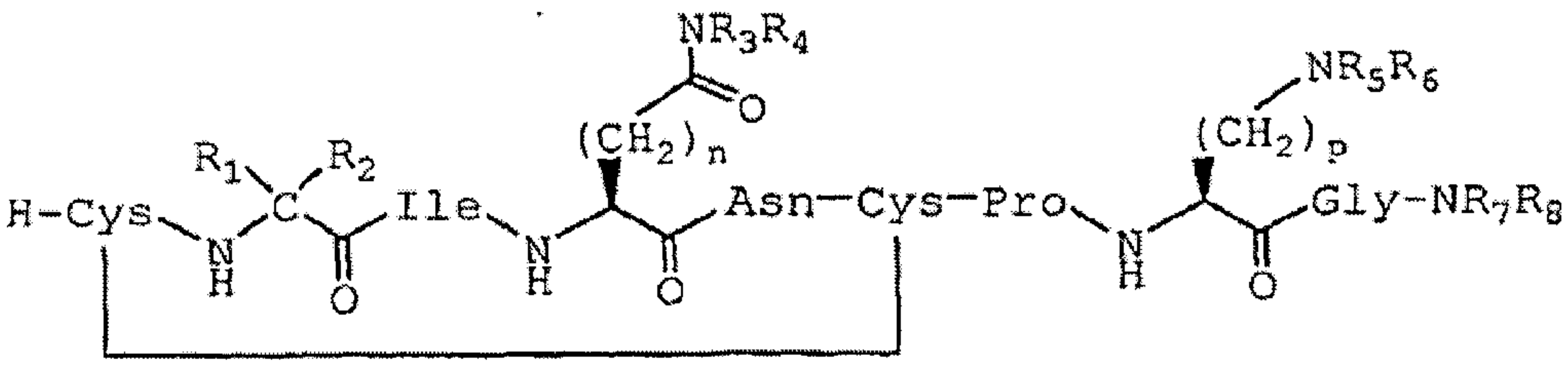
Agonist activity of compounds on the hV1a receptor was determined in a transcriptional reporter assay by transiently transfecting a hV1a receptor expression DNA into HEK-293 cells in concert with a reporter DNA containing intracellular calcium responsive promoter elements regulating expression of firefly luciferase. See Boss, V., Talpade, D.J., Murphy, T.J. *J. Biol. Chem.* **1996**, May 3; 271(18), 10429-10432 for further guidance on this assay. Cells were exposed to serial dilutions of compounds diluted 10-fold per dose for 5 hours, followed by lysis of cells, determination of luciferace activity, and determination of compound efficacies and EC_{50} values through non-linear regression. Arginine-vasopressin (AVP) was used as an internal control in each experiment (EC_{50} = 0.21 nM), and compounds were tested in at least three independent experiments.

The results of the *in vitro* assays are depicted in table 1 *supra*, including results for terlipressin. The EC_{50} value given is the geometric mean expressed in nanomol/L (nM).

All references listed are to be regarded as an integral part of the present writ.

CLAIMS:

1. A compound having the formula (I):



(I)

wherein:

R_1 is H; and

R_2 is $(CH_2)_m$-X;

or R_1 and R_2 in combination with the carbon atom to which they are attached together form an acyclic structure that comprises from 3 to 8 carbon atoms;

m is selected from 0, 1, 2 and 3;

n is selected from 0, 1, 2, 3 and 4;

p is selected from 2, 3 and 4;

when m is 0, 2 or 3, X is selected from C_{3-8}-cycloalkyl and C_{5-8}-cycloalkenyl;

when m is 1, X is selected from C_{3-8}-cycloalkyl, C_{5-8}-cycloalkenyl, isopropyl and tert-butyl; said alicyclic structure, C_{3-8}-cycloalkyl, and C_{5-8}-cyclo-alkenyl optionally have at least one alkyl, O-alkyl or hydroxyl substituent;

R_3, R_4, R_5, R_6, R_7 and R_8 are each independently selected from H, alkyl, OH, O-alkyl and OC(O)-alkyl;

alkyl is selected from C_{1-6} straight and C_{4-8} branched chain alkyl and optionally has at least one hydroxyl substituent; and

solvates and pharmaceutically acceptable salts thereof.

2. A compound according to claim 1, wherein R_7 and R_8 are H.

3. A compound according to any one of claims 1-2, wherein R_3 and R_4 are H.

4. A compound according to any one of claims 1-3, wherein n is 1 or 2.

5. A compound according to any one of claims 1-4, wherein alkyl is selected from methyl, ethyl, *n*-propyl, *i*-propyl, *t*-butyl and *i*-amyl.

6. A compound according to any one of claims 1-5, wherein X is cyclopentyl or cyclohexyl.

7. A compound according to any one of claims 1-5, wherein said alicyclic structure is a cyclobutyl structure.

8. A compound according to claim 1, wherein the compound is selected from the group consisting of:

H-Cys-Cha-Ile-Gln-Asn-Cys-Pro-Dbu-Gly-NH_2

H-Cys-Ala(cPe)-Ile-Gln-Asn-Cys-Pro-Dbu-Gly-NH_2

H-Cys-AcBuc-Ile-Gln-Asn-Cys-Pro-Dbu-Gly-NH_2

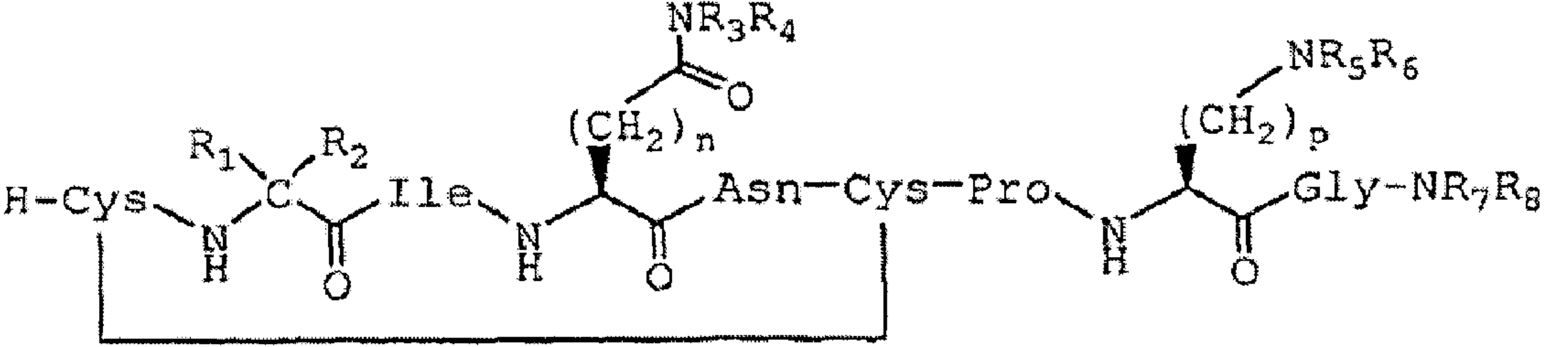
and

H-Cys-Cha-Ile-Asn-Asn-Cys-Pro-Orn(*i*-Pr)-Gly-NH_2.

9. A pharmaceutical composition comprising a compound according to any one of claims 1-8 as active ingredient in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

10. Use of a compound according to any one of claims 1-8 for the manufacture of a medicament for treatment of shock of hypovolemic or vasodilatory origin, bleeding esophageal varices, hepatorenal syndrome, cardiopulmonary resuscitation, anesthesia-induced hypotension, orthostatic hypotension paracentesis-induced circulatory dysfunction, intra-operative blood loss or blood loss associated with burn débridement and epistaxis, and for treatment of ocular diseases by increasing lacrimation/tear formation.

11. Use of a compound according to any one of claims 1-8 for treatment of shock of hypovolemic or vasodilatory origin, bleeding esophageal varices, hepatorenal syndrome, cardiopulmonary resuscitation, anesthesia-induced hypotension, orthostatic hypotension, paracentesis-induced circulatory dysfunction, intra-operative blood loss or blood loss associated with burn débridement and epistaxis, or for increasing lacrimation/tear formation.



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