(12) STANDARD PATENT (11) Application No. **AU 2009233429 B2**
(19) AUSTRALIAN PATENT OFFICE

(54) Title
Oxytocin analogues

(51) International Patent Classification(s)
C07K 7/16 (2006.01)

(21) Application No: **2009233429** (22) Date of Filing: **2009.03.30**

(87) WIPO No: **WO09/122285**

(30) Priority Data

(31) Number	(32) Date	(33) Country
61/040,973	**2008.03.31**	**US**
08251739.2	**2008.05.19**	**EP**

(43) Publication Date: **2009.10.08**
(44) Accepted Journal Date: **2014.02.13**

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(56) Related Art
GRZONKA, Z. et al. J. Med. Chem. 1983), 26(4), 555-559

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

CORRECTED VERSION

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
8 October 2009 (08.10.2009)

PCT

(10) International Publication Number
WO 2009/122285 A8

(51) International Patent Classification:
C07K 7/16 (2006.01)

(21) International Application Number:
PCT/IB2009/005351

(22) International Filing Date:
30 March 2009 (30.03.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/040,973 31 March 2008 (31.03.2008) US
08251739.2 19 May 2008 (19.05.2008) EP

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

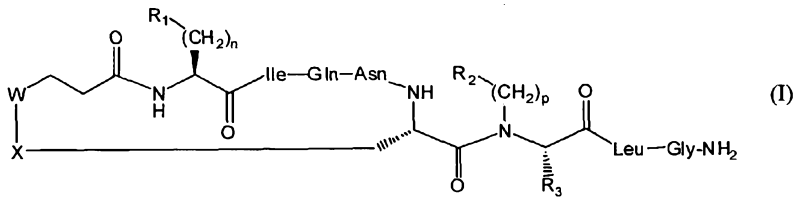
Published:

— *with international search report (Art. 21(3))*

(48) Date of publication of this corrected version:
10 December 2009

(15) Information about Correction:
see Notice of 10 December 2009

(54) Title: OXYTOCIN ANALOGUES



(I)

(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 compromised lactation 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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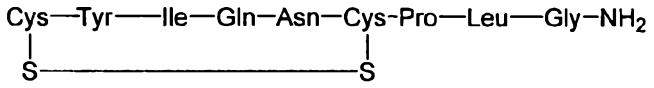
OXITOCIN ANALOGUES

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* compromised lactation conditions as well as to a method for treatment of said conditions, wherein said compounds are administered.

Background

Peptidic oxytocin receptor agonists include the natural hormone oxytocin, and carbetocin.



(oxytocin)

Oxytocin is a potent uterotonic agent, clinically used to induce labour, and has been shown to enhance the onset and maintenance of lactation, *Gimpl, G. et al., Physiol. Rev. 81 (2001) 629-683* and *Ruis H. et al., British Medical Journal 283 (1981) 340-342.* Carbetocin (1-deamino-1-carba-2-tyrosine(*O*-methyl)-oxytocin) is also a potent uterotonic agent clinically used for the control of uterine atony and excessive bleeding. Further research indicates that oxytocin agonists are useful for the treatment of inflammation and pain, including abdominal and back pain; sexual dysfunction, both male and female; irritable bowel syndrome (IBS), constipation and gastrointestinal obstruction; autism, stress, anxiety (including anxiety disorder) and depression *(Pitman R. et al., Psychiatry Research, 48:107-117; Kirsch P et al., The Journal of Neuroscience, 25(49):11489-11493);* surgical blood loss, the control of post-partum haemorrhage, wound healing and infection; mastitis and

placenta delivery; and osteoporosis. Additionally, oxytocin agonists may be useful for the diagnosis of both cancer and placental insufficiency.

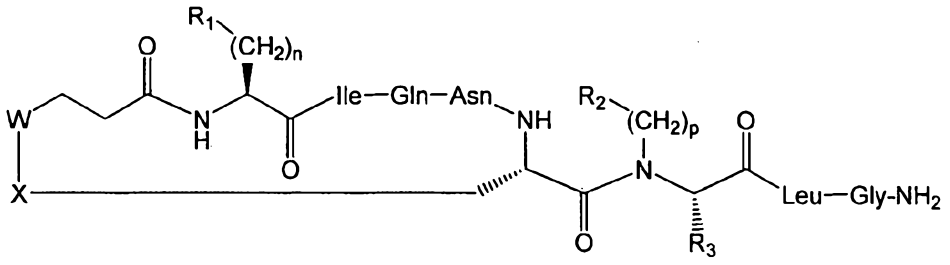
A disadvantage of both oxytocin and carbetocin are their lack of selectivity over the vasopressin receptors, especially the V_2 receptor. During administration of oxytocin this disadvantage is observed by such side effects as antidiuresis and hyponatremia.

In order to improve the pharmacological properties of oxytocin, analogues of oxytocin have been synthesised. Such analogues are described by Grozonka Z. *et al.* in *J. Med. Chem. 26 (1983) 555-559* and *J. Med. Chem. 26 (1983) 1786-1787*, and by Engstrøm T. *et al.* in *E. J. Pharmacol. 355 (1998) 203-210*. Additionally, oxytocin analogues with antagonist activity at the oxytocin receptor have been described by Fragiadaki M. *et al.* in *E. J. Med. Chem. (2007) 799-806*.

The present invention may provide selective, efficacious compounds, providing feasible alternatives and/or improvements e.g. in the treatment of compromised lactation conditions.

Disclosure of the Invention

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



(I)

wherein:

n is selected from 0, 1 and 2;

p is selected from 0, 1, 2, 3, 4, 5 and 6;

R_1 is selected from aryl optionally substituted with at least one OH, F, Cl, Br, alkyl or O-alkyl substituent;

R_2 is selected from R_4, H, alkyl, cycloalkyl, aryl and 5- and 6-membered heteroaromatic ring systems;

R_3 is selected from H and a covalent bond to R_2, when R_2 is R_4, to form a ring structure;

R_4 is C_{1-6} alkylene moiety substituted with at least one O-alkyl, S-alkyl or OH substituent;

W and X are each independently selected from CH_2 and S, but may not both be CH_2;

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

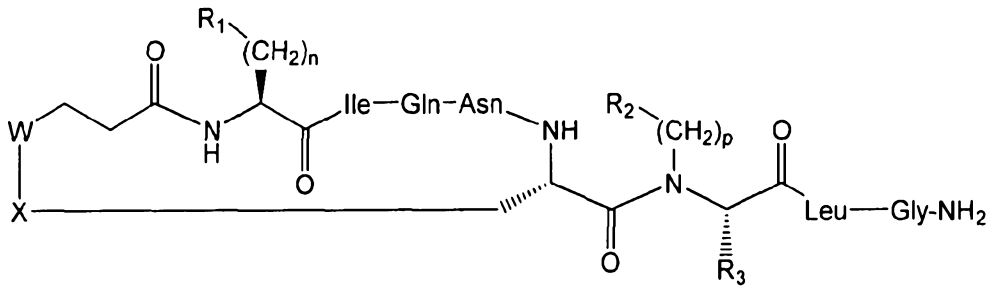
aryl is selected from phenyl and mono- or poly-substituted phenyl;

with the proviso that when R_2 is H, p is 0 or 1, R_3 is H or CH_3, n is 1 and W and X are both S, then R_1 is not 4-hydroxyphenyl; and

solvates and pharmaceutically acceptable salts thereof.

The present invention may further relate to compounds represented by formula (I) above with the further proviso that when R_2 is H, p is 0, R_3 is H, n is 1 and W and X are both S, R_1 is not 4-hydroxyphenyl. Thus, the present invention may relate to compounds of formula (I) above with the proviso that the compound is not [1-β-Mpa,7-Sar]OT and/or not {deamino [7-glycine] oxytocin}.

In one aspect, the present invention relates to a compound having the formula (I):



(I)

wherein:

n is selected from 0, 1 and 2;

p is selected from 1, 2, 3, 4, 5 and 6;

R_1 is selected from phenyl optionally substituted with at least one of the substituents selected from the group consisting of OH, F, Cl, Br, C_{1-6} straight or C_{4-8} branched chain alkyl optionally having at least one hydroxyl substituent or C_{1-6} straight or C_{4-8} branched chain alkoxy optionally having at least one hydroxyl substituent;

R_2 is selected from H, methoxy, C_{4-8} branched chain alkyl optionally having at least one hydroxyl substituent, C_{2-6} straight chain alkyl having at least one hydroxyl substituent, substituted or unsubstituted cycloalkyl, substituted or unsubstituted phenyl, and substituted or unsubstituted 5- and 6-membered heteroaromatic ring systems;

R_3 is H; and

W and X are each independently selected from CH_2 and S, provided that both W and X are not CH_2;

with the proviso that when R_2 is H, p is 1, n is 1 and W and X are both S, then R_1 is not 4-hydroxyphenyl;

and solvates and pharmaceutically acceptable salts thereof.

For the purposes of the present invention, the following terminology is used.

C_{1-6} straight chain alkyl denotes having from one to six carbon atoms, including any number therebetween.

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C_{4-8} branched chain alkyl denotes all branched alkyl groups containing four to eight carbon atoms, including

iso-, *sec*-, and *tert*-configurations, as said expression is not related to the binding site of the alkyl chain in question.

C_{3-6} cycloalkyl denotes a carbocyclic ring system containing from three to six carbon atoms, including any number therebetween. The ring system may contain unsaturated bonds between carbon atoms.

A five-membered heteroaromatic ring system is a monocyclic aromatic ring system having five ring atoms, wherein 1, 2, 3 or 4 ring atoms are independently selected from N, O and S. Preferred ring systems are selected from a group consisting of thienyl, furyl, imidazolyl, thiazolyl, thiadiazolyl and tetrazolyl.

A six-membered heteroaromatic ring system is a monocyclic aromatic ring system having six ring atoms, wherein 1, 2, 3 or 4 ring atoms are independently selected from N, O and S. Preferred ring systems are selected from a group consisting of pyridyl.

Aryl denotes an aromatic group selected from phenyl and mono- or polysubstituted phenyl.

Substituent moieties may be selected from fluorine (F), chlorine (Cl) and bromine (Br) atoms and alkyl, hydroxy (-OH), alkoxy (-O-alkyl) and alkylthio (-S-alkyl).

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, benzoic acid, ascorbic acid, maleic acid, hydroxymaleic acid,

pyruvic acid, *p*-hydroxybenzoic acid, embonic acid, methanesulphonic acid, ethanesulphonic acid, hydroxyethanesulphonic acid, halobenzenesulphonic acid, trifluoroacetic acid, trifluoromethanesulphonic acid, toluenesulphonic acid and naphthalenesulphonic acid.

In preferred embodiments n is 1.

In preferred embodiments p is selected from 1, 2, 3, 4 and 5.

In preferred embodiments R^1 is selected from phenyl, 4-hydroxyphenyl, 4-methoxyphenyl and 4-ethylphenyl.

In preferred embodiments R^2 is selected from ethyl, *n*-propyl, *n*-butyl, cyclopropyl, 2-hydroxyethyl, 2-methoxyethyl, 2-phenylethyl, phenyl, benzyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 4-methoxylphenyl, 4-fluorophenyl, 3,4-difluorophenyl, 2-thienyl, 2-tetrahydrofuryl, 2-furyl, 2-pyridyl and 4-pyridyl.

In preferred embodiments R^3 is H.

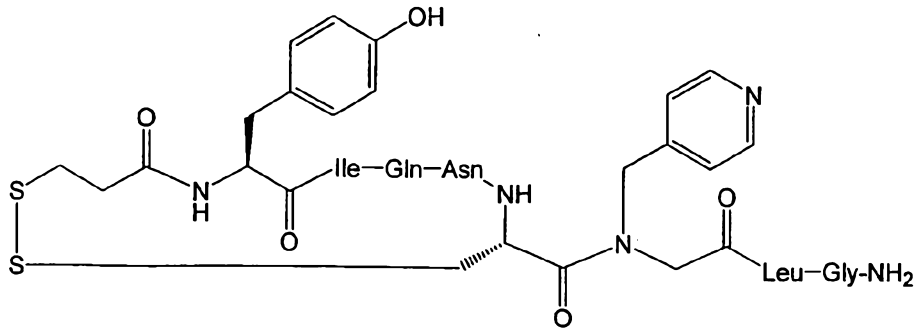
In preferred embodiments said ring structure is selected from (*R*)-4-methoxypyrrolidinyl, (*R*)-4-methylthiopyrrolidinyl and (*S*)-4-hydroxypyrrolidinyl.

In preferred embodiments W is CH_2 and X is S.

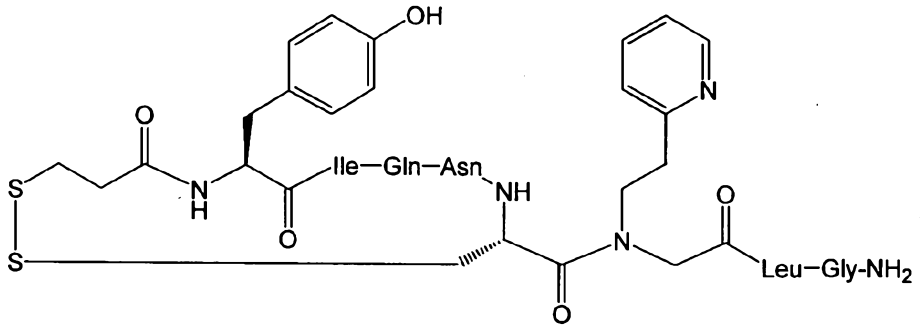
In preferred embodiments W is S and X is CH_2.

In preferred embodiments W and X are both S.

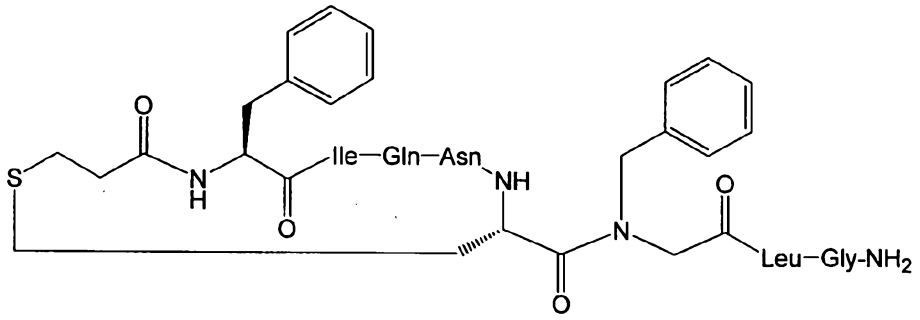
In the most preferred embodiment, the invention is a compound selected from a group consisting of:


OH
N
O
S
N
H
Ile—Gln—Asn
NH
O
S
O
N
Leu—Gly-NH2
O

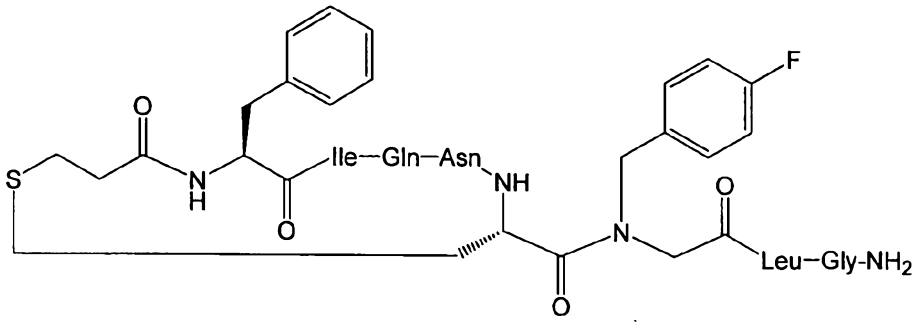
(10)


OH
N
O
S
N
H
Ile—Gln—Asn
NH
O
S
O
N
Leu—Gly-NH2
O

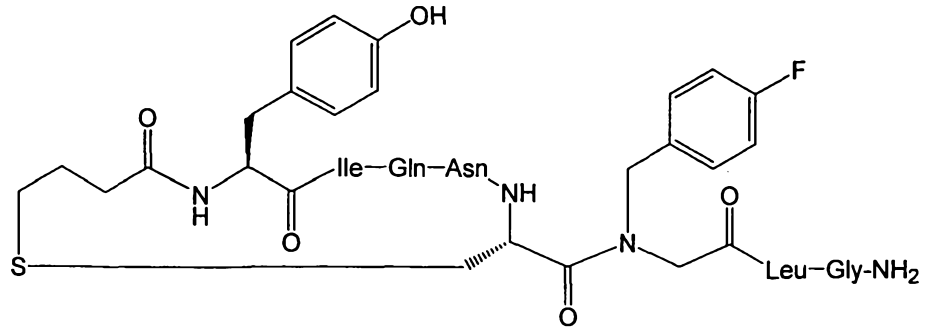
(18)


O
S
N
H
Ile—Gln—Asn
NH
O
O
N
Leu—Gly-NH2
O

(34)


F
O
S
N
H
Ile—Gln—Asn
NH
O
O
N
Leu—Gly-NH2
O

(47)



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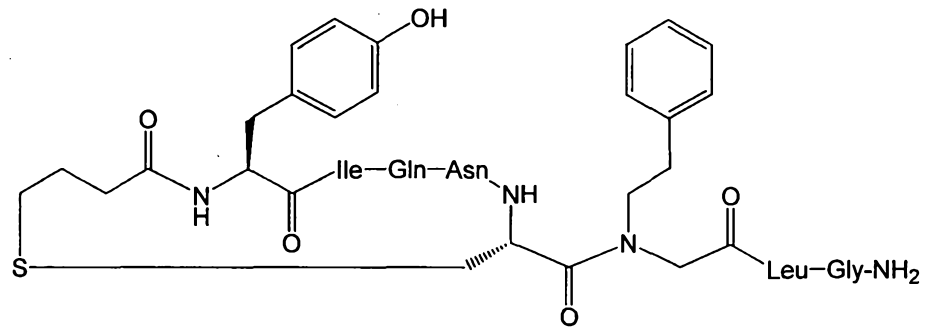

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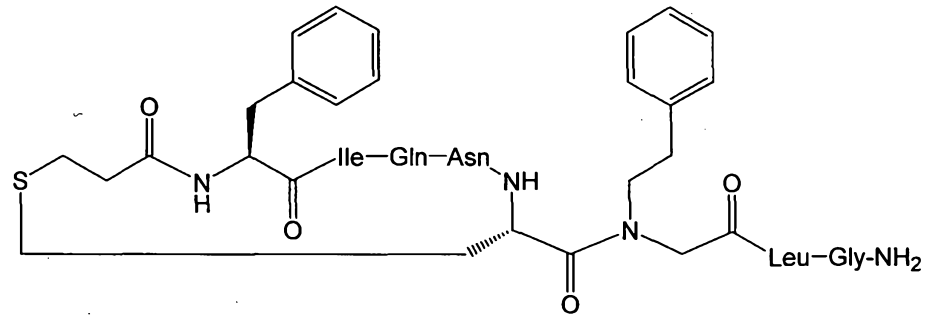


(52)

Furthermore the present invention relates to a compound as set forth above for the 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, interperitoneal, nasal, buccal, intraocular, intra-aural, 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, flavouring agent, preservative, colourant 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 may be adapted for nasal 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. The nasal spray formulation SYNTOCINON® (oxytocin) is exemplary of a suitable pharmaceutical formulation applicable also for the inventive compounds disclosed herein. Water, Ringer's solution, and isotonic sodium chloride solution are exemplary acceptable diluents. The preparation may also include excipients such as sodium phosphate, citric acid, sodium chloride, glycerine, sorbitol solution, methylparaben, propylparaben and chlorobutanol.

In addition, the present invention relates to use of a compound as outlined above for, or for the manufacture of a medicament for, treatment of one or more medical conditions such as compromised lactation conditions;

labour induction impairment; uterine atony conditions; excessive bleeding; inflammation and pain, including abdominal and back pain; sexual dysfunction, both male and female; irritable bowel syndrome (IBS), constipation and gastrointestinal obstruction; autism, stress, anxiety (including anxiety disorder) and depression; surgical blood loss, post-partum haemorrhage, wound healing and infection; mastitis and placenta delivery impairment; and osteoporosis; and for the diagnosis of cancer and placental insufficiency. Herein, the term anxiety includes anxiety disorder. Anxiety disorder includes the sub indications generalized anxiety disorder, panic disorder, agoraphobia, phobias, social anxiety disorder, obsessive-compulsive disorder, post-traumatic stress disorder, and separation anxiety.

In another embodiment the invention relates to a method for treatment of compromised lactation conditions; labour induction impairment; uterine atony conditions; excessive bleeding; inflammation and pain, including abdominal and back pain; sexual dysfunction, both male and female; irritable bowel syndrome (IBS), constipation and gastrointestinal obstruction; autism, stress, anxiety (including anxiety disorder) and depression; surgical blood loss, post-partum haemorrhage, wound healing and infection; mastitis and placenta delivery impairment; and osteoporosis; and for the diagnosis of cancer and placental insufficiency.

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. A physician of ordinary skill in the art will be able to optimise the dosage to the situation at hand.

For example, if the composition of the invention is for enhancing the onset and maintenance of lactation, (for example, for intranasal administration), a typical dose may be in the range of 0.05 to 1.0 µg/kg body weight for every breast pumping session. An intranasal dose may be divided into, for example, 1, 2, or 3 sub-doses (e.g. puffs), for example delivered to one or both nostrils as needed. The skilled person or physician may consider relevant variations to this dosage range and practical implementations to accommodate the situation at hand.

In a further example, the composition of the invention may be administered as an intravenous (iv) infusion, for example, for the treatment of postpartum haemorrhage or surgical blood loss. In this example it may be administered over a longer period. An example dosage for administration by intravenous infusion is 0.5 - 200 µg/kg body weight per hour.

In a further example, the composition of the invention may be for subcutaneous (sc), intranasal, or buccal administration, for example to treat anxiety disorder or depression. An example dosage for subcutaneous (sc), intranasal, or buccal administration is 0.5 - 1000 µg/kg body weight. The dosage may be, for example, for administration as many times a day as needed, for example, once or twice a day.

The abbreviations used are:

AcOH	acetic acid
Boc	*tert*-butoxycarbonyl
BOP	benzotriazol-1-yloxy trisdimethylaminophosphonium hexafluorophosphat
Bua	butyric acid

Bu	butyl - alkyl residues may be further denoted a *n* (normal, *i.e.* unbranched), *i* (iso), *s* (sec and *t* (tertiary)
CH_3CN	Acetonitrile
DCC	*N,N'*-dicyclohexylcarbodiimide
DCM	dichloromethane
DIC	*N,N'*-diisopropylcarbodiimide
DIPEA	*N,N*-diisopropylethylamine
DMF	*N,N*-dimethylformamide
4-FBzlGly	*N*-(4-fluorobenzyl)glycine
Fmoc	9-fluorenylmethoxycarbonyl
Fmoc-Cl	9-fluorenylmethoxycarbonyl chloride
Fmoc-OSu	*N*-(9-fluorenylmethoxycarbonyl) succinimide
h	hour(s)
HBTU	*O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate
Hcy	Homocysteine
HF	hydrogen fluoride
HOBt	1-hydroxybenzotriazole
HPLC	high performance liquid chromatography
IPA	isopropylalcohol
MeOH	Methanol
MBHA	4-methylbenzyhydrylamine
NMM	4-methylmorpholine
4-Pic	4-picolyl (4-pyridylmethyl)
PyBOP	benzotriazol-1-yloxy trispyrrolidinephosphoniu hexafluorophosphate
*t*Bu	*tert*-butyl
*t*BuOH	*tert*-butylalcohol
TEA	triethylamine
TFA	trifluoroacetic acid
TIS	triisopropylsilane
Trt	trityl [triphenylmethyl, $(C_6H_5)_3C$-]

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

Experimental (synthesis)

Amino acid derivatives and resins were purchased from commercial providers (Bachem, Novabiochem and Peptides International). *N*-Fmoc-*N*-($R_2(CH_2)_p$)glycine, Fmoc-Cys(*t*-butoxycarbonylpropyl)-OH and Fmoc-Hcy(*t*-butoxycarbonylethyl)-OH were synthesised according to literature [*Weber et al., J. Med. Chem., 46 1918 (2003), Prochazka et al. Collect. Czech. Chem. Commun., 57, 1335 (1992)* and Wisniewski et al. in WO 03/072597]. Other chemicals and solvents were provided from Sigma-Aldrich, Fluka and Acros Organics.

The compounds herein were synthesised by standard methods in solid phase peptide chemistry utilising both Fmoc and Boc methodology. All coupling of Fmoc-protected amino acids were mediated with DIC/HOBt/DMF and all coupling of Boc-protected amino acids were mediated with DIC or DCC in DCM. Removal of the Fmoc group was performed with 20% piperidine in DMF and removal of the Boc group was performed in 50% TFA/DCM with 1% *m*-cresol for 5 and 25 minutes. Requisite resin washings were performed with DCM, IPA, DMF, and MeOH. Neutralization, as necessary, was accomplished with 2 resin washes of 10% TEA/DCM for 5 minutes.

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

Fmoc and Boc methodologies were used to synthesise the resin bound 8 position (Leu) and 9 position(Gly) dipeptide.

The amino acid derivative in the 7 position of the amino acid residue was introduced via one of two routes: either bromoacetic acid was coupled to the resin bound dipeptide under DIC/HOBt/DMF conditions and the bromine atom was displaced with $(R_2(CH_2)_p)NH_2$ providing a resin-bound *N*-$(R_2(CH_2)_p)$glycine; or *N*-Fmoc-*N*-$(R_2(CH_2)_p)$glycine or an Fmoc-pro-OH derivative was coupled to the resin-bound dipeptide in accordance with Fmoc methodology. All subsequent amino acid couplings followed Fmoc methodology unless otherwise specified.

The amino acid derivative introduced in the 6 position was one of: Fmoc-Cys(Trt)-OH; Fmoc-Hcy(*t*-butoxycarbonylethyl)-OH or Fmoc-Cys(*t*-butoxycarbonylpropyl)-OH. Peptide analogues where position 6 was Fmoc-Cys(Trt)-OH required coupling of Mpa(Trt)-OH to the *N*-terminus of the resin-bound nonapeptide residue.

The peptides synthesised using a rink amide resin support were cleaved from the resin, together with any acid labile protecting groups such as Boc, trityl and *t*-butyl, with TFA/TIS/H_2O 95/2.5/2.5 (v/v/v) solution. Said peptides were cyclised after cleavage of the peptide from

the resin. The peptides synthesised using an MBHA resin support were cleaved from the resin with HF/anisole 14/1 (v/v) solution. Said peptides were cyclised prior to cleavage of the peptide from the resin.

Cyclisation of the linear nonapeptide through disulfide (ring) formation was achieved by oxidation of linear peptides dissolved in 10% TFA (aq) with iodine. Cyclisation of the linear nonapeptide through amide bond formation was achieved by mediation with HBTU/DIPEA/DMF or PyBOP/DIPEA/DMF at a high dilution.

Peptides were purified by preparative HPLC in triethylammonium phosphate buffers (aq) and desalted with acetic acid (aq)/acetonitrile buffer system. The fractions with a purity exceeding 97% were pooled and lyophilised.

Table 1 lists the compounds prepared by the above procedure. An asterisk '*' marks the most preferred embodiments.

Table 1: Compounds prepared with the formula (I)

Q	W	X	R_1	n	R_2	p	R_3
	CH_2	S	4-methoxyphenyl	1	CH_2-(*R*)-CH(OCH_3)-CH_2	-	bond
	CH_2	S	4-methoxyphenyl	1	CH_2-(*R*)-CH(SCH_3)-CH_2	-	bond
	CH_2	S	4-ethylphenyl	1	CH_2-(*R*)-CH(OCH_3)-CH_2	-	bond
	S	CH_2	4-ethylphenyl	1	CH_2-(*S*)-CH(OH)-CH_2	-	bond
	CH_2	S	4-methoxyphenyl	1	H	0	H
	CH_2	S	4-ethylphenyl	1	CH_2-(*S*)-CH(OH)-CH_2	-	bond
	S	S	4-hydroxyphenyl	1	H	4	H
	S	S	4-hydroxyphenyl	1	phenyl	2	H
	S	S	4-hydroxyphenyl	1	2-furyl	1	H

*	S	S	4-hydroxyphenyl	1	4-pyridyl	1	H
	S	S	4-hydroxyphenyl	1	3,4-difluorophenyl	1	H
	S	S	4-hydroxyphenyl	1	3-methylphenyl	1	H
	S	S	4-hydroxyphenyl	1	2-methylphenyl	1	H
	S	S	4-hydroxyphenyl	1	H	5	H
	S	S	4-hydroxyphenyl	1	4-methylphenyl	2	H
	S	S	4-hydroxyphenyl	1	2-thienyl	1	H
	S	S	4-hydroxyphenyl	1	4-pyridyl	2	H
*	S	S	4-hydroxyphenyl	1	2-pyridyl	2	H
	S	S	4-hydroxyphenyl	1	4-fluorophenyl	1	H
	S	S	4-hydroxyphenyl	1	methoxy	2	H
	S	S	4-hydroxyphenyl	1	cyclopropyl	1	H
	S	S	4-hydroxyphenyl	1	4-methoxyphenyl	1	H
	S	S	4-hydroxyphenyl	1	4-methylphenyl	1	H
	S	S	4-hydroxyphenyl	1	2-thienyl	2	H
	S	S	4-hydroxyphenyl	1	phenyl	3	H
	S	S	4-hydroxyphenyl	1	2-tetrahydrofuryl	1	H
	S	S	4-hydroxyphenyl	1	2-tetrahydrofuryl	1	H
	S	CH_2	phenyl	1	methoxy	2	H
	CH_2	S	phenyl	1	methoxy	2	H
	CH_2	S	4-hydroxyphenyl	1	methoxy	2	H
	S	CH_2	phenyl	1	2-thienyl	1	H
	S	CH_2	4-hydroxyphenyl	1	phenyl	1	H
	S	CH_2	4-hydroxyphenyl	1	phenyl	2	H
*	S	CH_2	phenyl	1	phenyl	1	H
	CH_2	S	4-hydroxyphenyl	1	H	4	H
	S	CH_2	phenyl	1	OH	3	H
	CH_2	S	phenyl	1	H	3	H
	S	CH_2	phenyl	1	H	3	H
	CH_2	S	phenyl	1	H	5	H
	S	CH_2	phenyl	1	H	5	H
	CH_2	S	phenyl	1	H	4	H
	S	CH_2	phenyl	1	H	4	H

3	CH_2	S	4-hydroxyphenyl	1	3,4-difluorophenyl	1	H
4	S	CH_2	4-hydroxyphenyl	1	3-methylphenyl	1	H
5	S	CH_2	4-hydroxyphenyl	1	4-fluorophenyl	1	H
6	CH_2	S	4-hydroxyphenyl	1	phenyl	1	H
7*	S	CH_2	phenyl	1	4-fluorophenyl	1	H
8	CH_2	S	4-hydroxyphenyl	1	2-thienyl	1	H
9*	CH_2	S	4-hydroxyphenyl	1	4-fluorophenyl	1	H
10	CH_2	S	4-hydroxyphenyl	1	3-methylphenyl	1	H
11*	CH_2	S	4-hydroxyphenyl	1	phenyl	2	H
12*	S	CH_2	phenyl	1	phenyl	2	H
13	S	CH_2	phenyl	1	3-methylphenyl	1	H
14	CH_2	S	4-hydroxyphenyl	1	OH	3	H

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

In all syntheses analytical HPLC was performed on a waters 600 Liquid Chromatograph using a Vydac C18, 5µm, 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, 5µm, 2.1 x 250 mm column at a flow rate of 0.3 ml/min. Mass spectra were recorded on a Finnigan MAT spectrometer.

Compound 49; carba-1-[4-FBzlGly^7]dOT:

The amino acid derivatives used were Fmoc-Gly-OH, Fmoc-Leu-OH, Fmoc-Cys(*t*-butoxycarbonylpropyl)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH and Boc-Tyr(*t*Bu)-OH (Peptides International). Fmoc-Cys(*t*-butoxycarbonylpropyl)-OH was synthesized as above.

The fully protected peptide resin was manually synthesised, starting from 1.45 g (0.87 mmol) of Rink Amide AM resin (200-400 mesh, Novabiochem). DIC/HOBt/DMF

mediated single couplings with a 3-fold excess of amino acid Gly and Leu derivatives were performed. The *N*-(4-fluorobenzyl)glycine residue was introduced with a 4-fold excess of $BrCH_2CO_2H$/DIC/HOBt in DMF and subsequent bromine substitution with a 10-fold excess of 4-fluorobenzyl amine in DMF. DIC/DCM mediated coupling with a 4-fold excess of Fmoc-Cys(*t*-butoxycarbonylpropyl)-OH was performed. Subsequent DIC/HOBt/DMF mediated single couplings with a 3-fold excess of amino acid Asn, Gln, Ile and Tyr derivatives were performed. The Fmoc groups were removed with 20% piperidine in DMF. Upon completion of the solid phase synthesis, the resin was treated with a TFA/TIS/H_2O 96/2.5/1.5 (v/v/v) solution (50 ml) for 1.5 h and filtered off. The filtrate was concentrated *in vacuo* and the crude linear peptide was precipitated with diethyl ether. The precipitate in DMF (300 ml) was added in 3 portions (3 x 100 ml) to a vigorously stirred solution of DIPEA (1 ml) in DMF (100 ml). HBTU (150 mg) in DMF (5 ml) was added to the reaction mixture after addition of each 100 ml portion of peptide solution; the pH of the reaction solution was maintained at pH 9 by addition of neat DIPEA, as required. The reaction was monitored by analytical HPLC. The reaction solution was concentrated *in vacuo* and the residue was dissolved in AcOH/CH_3CN/H_2O. 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, diluted with water (2 volumes), and loaded onto a column pre-equilibrated with 2% AcOH (aq). The desired compound was eluted with a fast (3%/min) gradient of CH_3CN. The fractions containing the desired product were pooled and lyophilised. 434 mg (~40% yield, based on the loading of the starting resin and assuming 85%

peptide content) of white amorphous powder was obtained. HPLC: Rt = 19.4 min, gradient: 5% B for 0.5 min., 5→30% B in 0.5 min, 30→50% B over 20 min and 100% B for 5 min., t = 40°C, solvent A 0.01% TFA (aq), solvent B 70% CH_3CN, 0.01% TFA (aq); Purity: 99.3%; MS ($M+H^+$): expected 1042.4, observed 1042.5.

The following is an exemplary large scale (i.e. scale-up) synthesis of Compound 49; carba-1-[4-FBzlGly^7]dOT:

The amino acid derivatives used were Fmoc-Gly-OH, Fmoc-Leu-OH, Fmoc-4-FBzlGly-OH, Fmoc-Cys(*t*-butoxycarbonylpropyl)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH and Boc-Tyr(*t*Bu)-OH (Peptides International). Fmoc-4-FBzlGly-OH and Fmoc-Cys(*t*-butoxycarbonylpropyl)-OH were synthesized as above. The peptide was synthesised by DIC/HOBt/DMF mediated single couplings with a 3-fold excess of amino acid derivative. The remaining synthesis and characterisation of compound 49 was followed as provided above. 434 mg (~40% yield, based on the loading of the starting resin and assuming 85% peptide content) of white amorphous powder was obtained.

Compound 10; [4-PicGly^7]dOT:

The amino acid derivatives used were Fmoc-Gly-OH, Fmoc-Leu-OH, Fmoc-Cys(Trt)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH, Fmoc-Tyr(*t*Bu)-OH and Mpa(Trt)-OH (Peptides International). The fully protected peptide resin was manually synthesized, starting from 1.33 g (0.65 mmol) of Rink AM resin (200-400 mesh, Novabiochem). DIC/HOBt/DMF mediated single couplings with a 3-fold excess of amino acid Gly and Leu derivatives were performed. The *N*-(4-picolyl)glycine residue was introduced with a 4-fold excess of $BrCH_2CO_2H$/DIC/HOBt in

DMF and subsequent bromine substitution with a 10-fold excess of 4-picolyl amine in DMF. DIC/DCM mediated coupling with a 4-fold excess of Fmoc-Cys(Trt)-OH and DIC/HOBt/DMF mediated single couplings with a 3-fold excess of amino acid Asn, Gln, Ile, Tyr and Mpa derivatives were performed. The Fmoc groups were removed with 20% piperidine in DMF. Upon completion of the solid phase synthesis, the resin was treated with TFA/TIS/H_2O 96/2/2 (v/v/v) solution (50 ml) for 1.5 h and filtered off. The filtrate was concentrated *in vacuo* and the crude linear peptide was precipitated with diethyl ether. The precipitate was dissolved in neat TFA (50 ml), poured onto a magnetically stirred 5% aqueous acetonitrile (600 ml) solution and the peptide was oxidised by adding 0.1 M I_2 in methanol until yellow colour persisted. Excess of iodine was reduced with solid ascorbic acid (Sigma-Aldrich) and the pH of the solution was adjusted to about 4 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, diluted with water (2 volumes), and loaded onto a column pre-equilibrated with 2% AcOH (aq). The desired compound was eluted with a fast (3%/min) gradient of acetonitrile. The fractions containing the desired product were pooled and lyophilised. 348.7 mg (~44% yield, based on the loading of the starting resin and assuming 85% peptide content) of white amorphous powder was obtained. HPLC: Rt = 21.7 min, gradient: 5% B for 0.5 min., 5→10% B in 0.5 min, 10→30% B over 20 min and 100% B for 5 min., t = 40°C, solvent A 0.01% TFA (aq), solvent B 70% CH_3CN, 0.01% TFA (aq); Purity: 99.9%; MS ($M+H^+$): expected 1043.4, observed 1043.4.

Compound 29; carba-6-[Phe^2,$MeOEtGly^7$]dOT:

The amino acid derivatives used were Boc-Gly-OH and Boc-Leu-OH (Bachem), Fmoc-Hcy(*t*-butoxycarbonylethyl)-OH, Fmoc-Asn(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Ile-OH and Boc-Phe-OH (Peptides International). Fmoc-Hcy(*t*-butoxycarbonylethyl)-OH was synthesized as above.

The fully protected peptide resin was manually synthesized starting from 1.33 g of MBHA resin (0.94 mmol, Novabiochem). The resin was neutralized with 10% TEA in DCM. DIC/DCM mediated single couplings with a 1.7-fold excess of amino acids Boc-Gly-OH and Boc-Leu-OH were performed. The *N*-(2-methoxyethyl)glycine residue was introduced with a 3.6-fold excess of $BrCH_2CO_2H$/DIC/HOBt in DMF and subsequent substitution of the bromine with a 7-fold excess of 2-methoxyethyl amine and a 4-fold excess of DIPEA in DMF (10 ml); the reaction was stirred for 5 h. DIC/DCM mediated single coupling with a 4-fold excess of Fmoc-Hcy(*t*-butoxycarbonylethyl)-OH and DIC/HOBt/DMF mediated single couplings with a 3-fold excess of amino acid Asn and Gln derivatives were performed. The two final single couplings with Fmoc-Ile-OH and Boc-Phe-OH were performed with DIC/DCM to provide the desired protected resin-bound linear peptide. The Fmoc groups were removed with 20% piperidine in DMF. The resin was treated with TFA/H_2O/TIS 95/3/2 (v/v/v) for 2 h to remove the trityl, Boc, and *t*-butyl groups. BOP (4 eq) and DIPEA (10 eq) were added to a stirred suspension of the resin in DMF (10 mL); after 2 h PyBOP (2 eq) and DIPEA (5 eq) were added. The peptide was cleaved from the resin by using 70 ml of anhydrous HF containing 5 ml of anisole at 0 °C for 90 mins. The HF was removed *in vacuo* and the crude linear peptide was washed with diethyl; ether (300 ml). The peptide was dissolved in AcOH/CH_3CN/H_2O 1/2/7 (v/v/v) (400 ml). The resulting mixture was loaded

directly onto an HPLC column and purified using triethylammonium phosphate buffer at pH 2.3. The compound was eluted with an acetonitrile gradient. The fractions with a purity exceeding 97% were pooled, diluted with water (2 volumes), and loaded onto a column pre-equilibrated with 2% acetic acid (aq). The desired compound was eluted with a 1% AcOH/CH_3CN gradient. The fractions containing the desired product were pooled and lyophilised.

292.7 mg (~27% yield, based on the loading of the starting resin and assuming 85% peptide content) of white amorphous powder was obtained. HPLC: Rt = 16.7 min, gradient: 5% B for 0.5 min., 5→30% B in 0.5 min, 30→50% B over 20 min and 100% B for 5 min., t = 40°C, solvent A 0.01% TFA (aq), solvent B 70% CH_3CN, 0.01% TFA (aq); Purity: 100.0%; MS ($M+H^+$): expected 976.5, observed 976.3.

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

Experimental (biological testing)

In vitro receptor assays:

Agonist activity of compounds on the hOT receptor was determined in a transcriptional reporter gene assay by transiently transfecting a hOT receptor expression DNA into a Chinese Hamster Ovary (CHO) cell line 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 h, followed by lysis of cells, determination of luciferase activity, and determination of compound efficacies and EC_{50} values through non-linear regression.

Oxytocin (OT) was used as an internal control in each experiment, and compounds were tested in at least three independent experiments. To determine selectivity, compounds were further tested in luciferase-based transcriptional reporter gene assays expressing the human vasopressin (hV_2) receptor.

For further comparative purposes carbetocin was also used as a reference compound.

The results of the in vivo assays are depicted in table 2 *infra*. The EC_{50} value given is the geometric mean expressed in nanomol/l (nM). Selectivity values are given as EC_{50} ratios.

Table 2: Results of biological testing

Compound Tested	EC_{50} hOT receptor	EC_{50} hV_2 receptor	Selectivity hV_2/hOT
1	0.980	688.22	702
2	0.817	671.12	822
3	0.207	446.76	2158
4	0.033	17.70	544
5	0.370	448.67	1211
6	0.064	39.95	629
7	0.062	34.78	558
8	0.116	65.55	565
9	0.114	61.79	544
10	0.464	384.04	828
11	0.026	58.54	2217
12	0.011	29.78	2607
13	0.121	67.81	562
14	0.005	77.11	15124
15	0.040	101.77	2533
16	0.009	57.29	6067

17	0.023	47.27	2014
18	0.115	180.32	1561
19	0.012	82.03	6607
20	0.030	80.29	2659
21	0.006	9.87	1729
22	0.063	77.83	1245
23	0.148	83.55	565
24	0.016	86.10	5469
25	0.058	159.44	2736
26	0.072	226.14	3160
27	0.189	238.02	1259
28	0.847	1264.33	1493
29	0.957	1100.45	1149
30	0.109	69.68	639
31	0.297	760.80	2564
32	0.051	35.83	705
33	0.046	100.71	2203
34	0.405	718.38	1774
35	0.122	72.66	597
36	0.859	2551.62	2970
37	0.228	441.72	1941
38	0.271	227.03	839
39	0.254	2058.97	8115
40	0.069	1024.67	14945
41	0.227	1999.84	8793
42	0.086	1192.93	13901
43	0.104	123.61	1187
44	0.023	55.14	2404
45	0.036	140.24	3914
46	0.039	140.36	3632
47	0.228	1415.28	6221
48	0.089	253.03	2854
49	0.08	328.57	4293

50	0.077	212.57	2761
51	0.045	161.91	3614
52	0.779	3005.36	3860
53	0.562	1613.76	2870
54	0.013	496.61	37735
oxytocin	2.34	7.33	3
carbetocin	0.70	171.98	244

The foregoing results indicate that the Example compounds are within the scope of the invention and may for instance be useful in the safe and efficacious treatment of human beings in order to induce labour, control uterine atony, promote and maintain lactation etc.

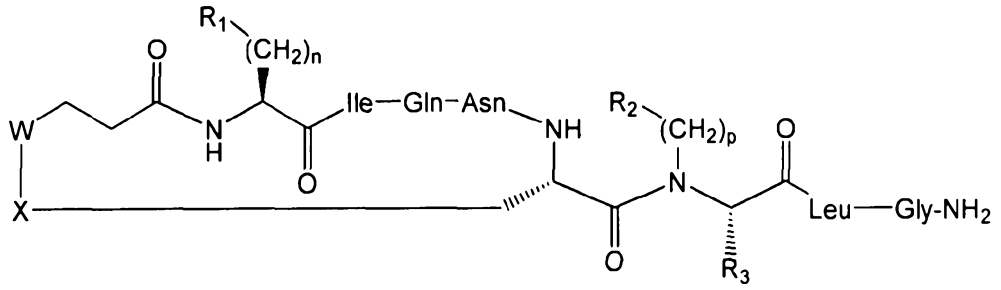
The scope of the present invention is further defined in the following claims.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A compound having the formula (I):



(I)

wherein:

n is selected from 0, 1 and 2;

p is selected from 1, 2, 3, 4, 5 and 6;

R_1 is selected from phenyl optionally substituted with at least one of the substituents selected from the group consisting of OH, F, Cl, Br, C_{1-6} straight or C_{4-8} branched chain alkyl optionally having at least one hydroxyl substituent or C_{1-6} straight or C_{4-8} branched chain alkoxy optionally having at least one hydroxyl substituent;

R_2 is selected from H, methoxy, C_{4-8} branched chain alkyl optionally having at least one hydroxyl substituent, C_{2-6} straight chain alkyl having at least one hydroxyl substituent, substituted or unsubstituted cycloalkyl, substituted or unsubstituted phenyl, and substituted or unsubstituted 5- and 6-membered heteroaromatic ring systems;

R_3 is H; and

W and X are each independently selected from CH_2 and S, provided that both W and X are not CH_2;

with the proviso that when R_2 is H, p is 1, n is 1 and W and X are both S, then R_1 is not 4-hydroxyphenyl;

and solvates and pharmaceutically acceptable salts thereof.

2. A compound according to claim 1, wherein the heteroaromatic ring systems are optionally substituted with at least one alkyl, O-alkyl, OH, F, Cl or Br substituent.

3. A compound according to claim 1 or 2, wherein n is 1.

4. A compound according to any one of claims 1-3, wherein p is selected from 1, 2, 3, 4 and 5.

5. A compound according to any one of claims 1-4, wherein R_1 is selected from the group consisting of phenyl, 4-hydroxyphenyl, 4-methoxyphenyl and 4-ethylphenyl.

6. A compound according to any one of claims 1-5, wherein R_2 is selected from the group consisting of cyclopropyl, 2-hydroxyethyl, methoxy, phenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 4-methoxyphenyl, 4-fluorophenyl, 3,4-difluorophenyl, 2-thienyl, 2-tetrahydrofuryl, 2-furyl, 2-pyridyl and 4-pyridyl.

7. A compound according to any one of claims 1-6, wherein W is CH_2 and X is S.

8. A compound according to any one of claims 1-6, wherein W is S and X is CH_2.

9. A compound according to any one of claims 1-6, wherein W and X are both S.

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

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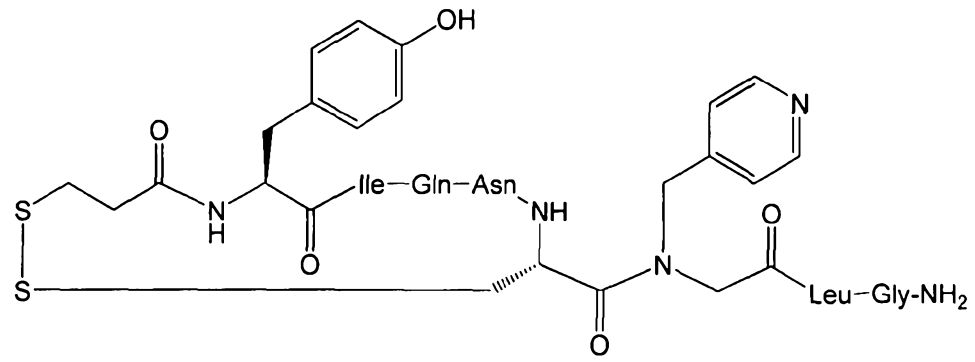

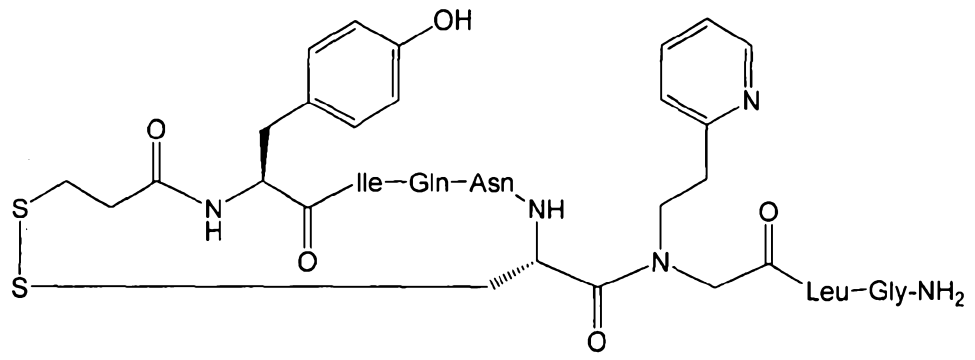

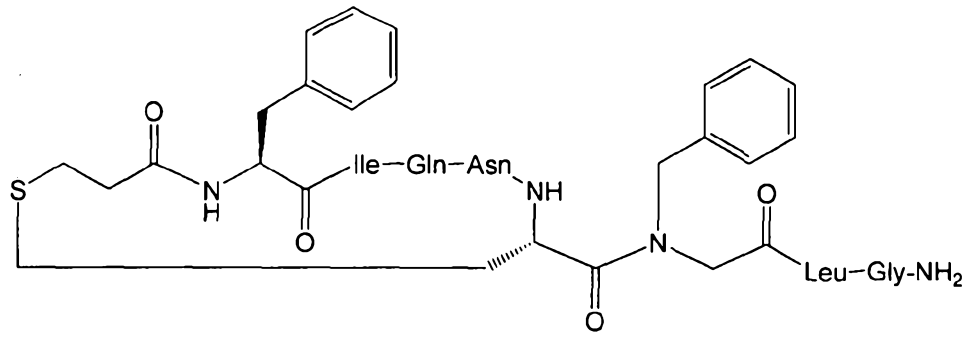

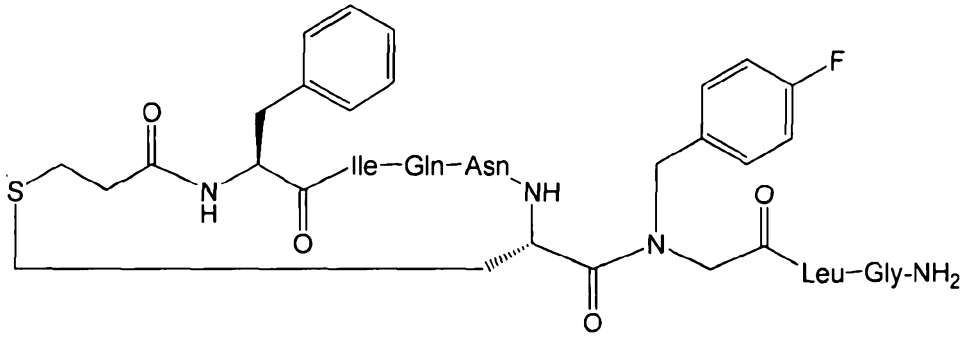

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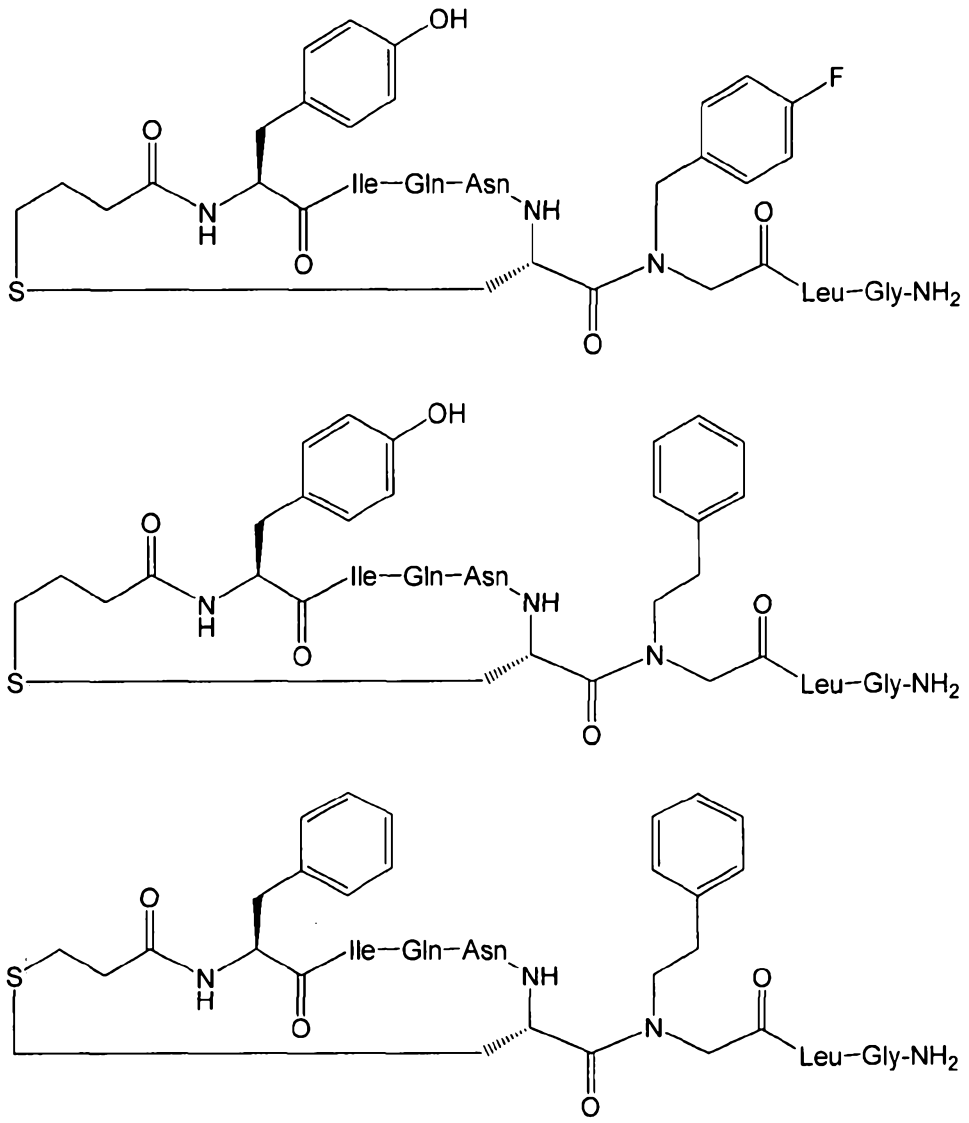

11. The compound of claim 1, wherein

n is selected from 1 and 2;

p is selected from 1, 2, 3, 4, 5 and 6;

R_1 is selected from phenyl optionally substituted with one of the substituents selected from the group consisting of OH, F, Cl, Br, C_{3-6} straight or C_{4-8} branched chain alkyl optionally having at least one hydroxyl substituent, or C_{3-6} straight or C_{4-8} branched chain alkoxy optionally having at least one hydroxyl substituent; and

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R_2 is selected from H, methoxy, C_{4-8} branched chain alkyl optionally having at least one hydroxyl substituent, C_{3-6} straight chain alkyl having at least one hydroxyl substituent, phenyl, 3-methylphenyl, 4-methylphenyl, 4-fluorophenyl, and 2-thienyl.

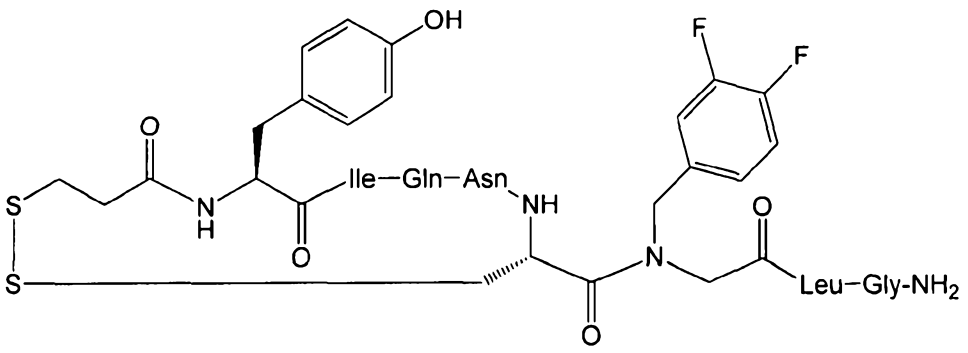
12. The compound of claim 11, wherein n is 1.

13. The compound of claim 11 or 12, wherein p is 1, 2, 3, 4, or 5.

14. The compound of any one of claims 11 to 13, wherein R_1 is phenyl or 4-hydroxyphenyl.

15. The compound of any one of claims 11 to 14, wherein R_2 is methoxy, 2-hydroxyethyl, phenyl, 3-methylphenyl, 4-methylphenyl, 4-fluorophenyl, or 2-thienyl.

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



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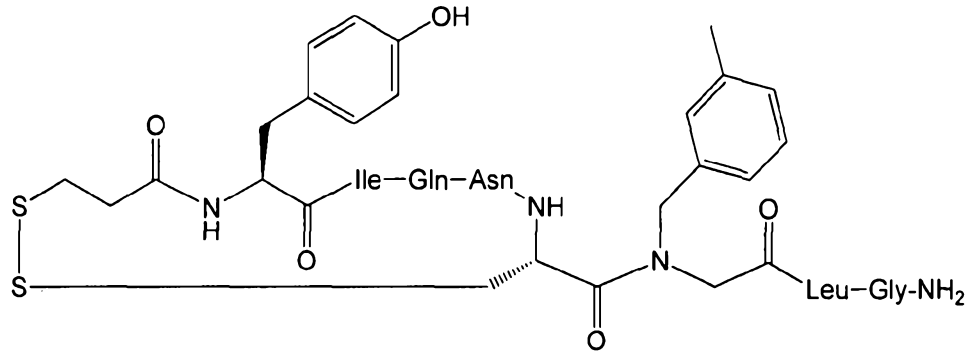

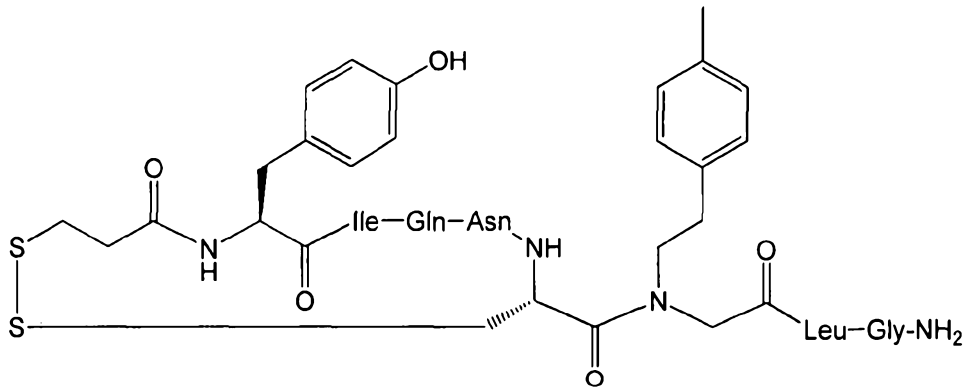

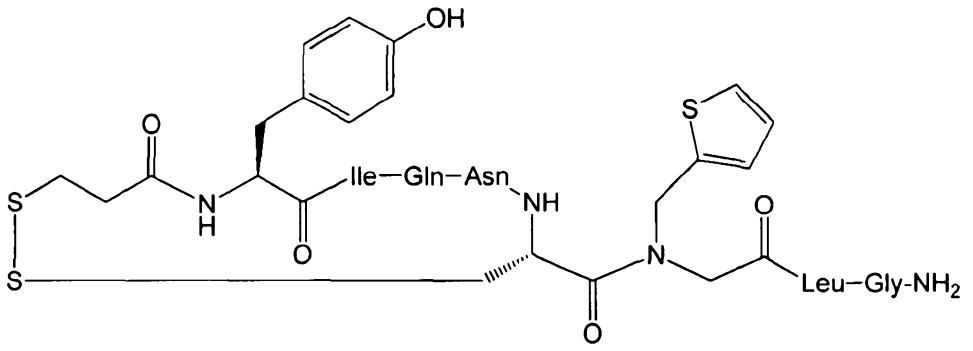

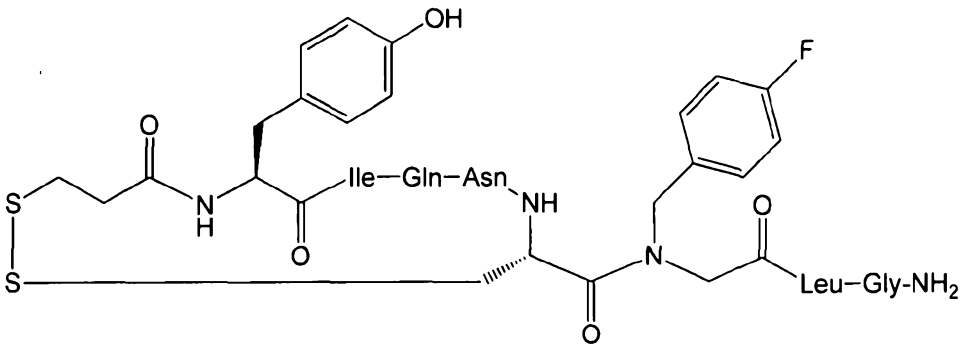

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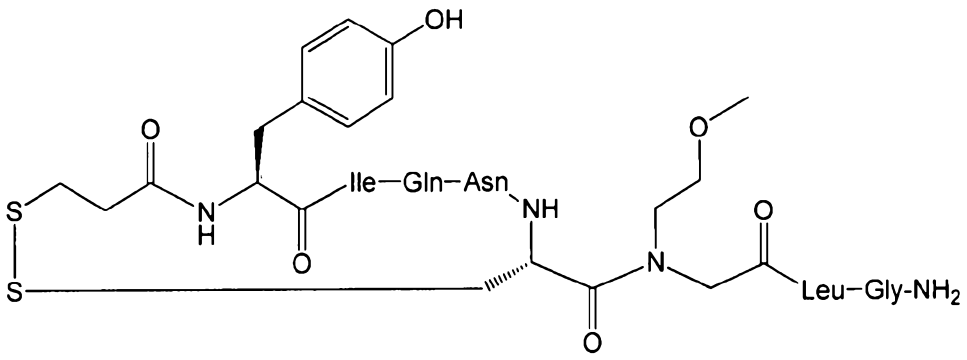

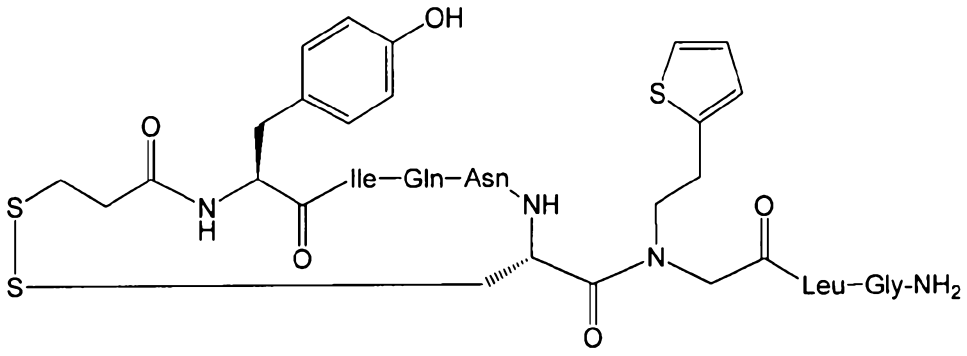

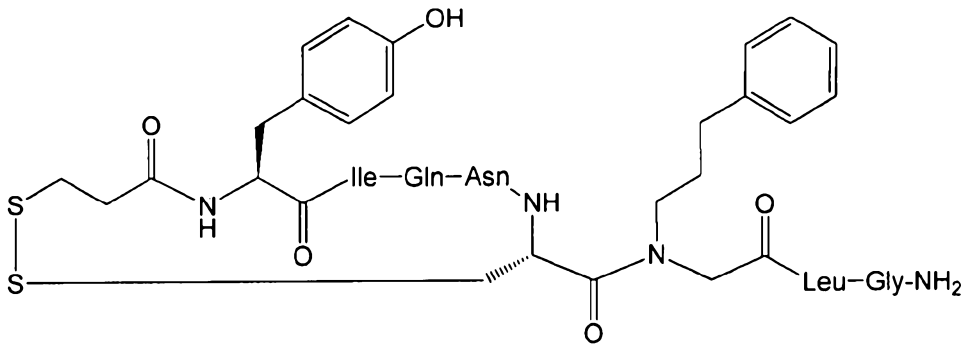

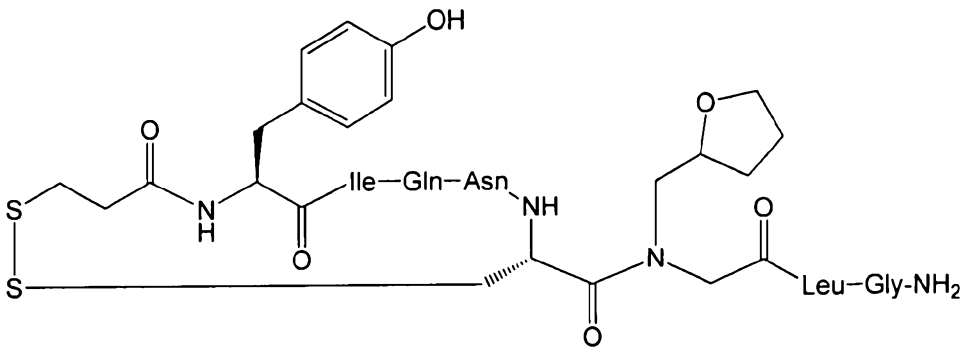

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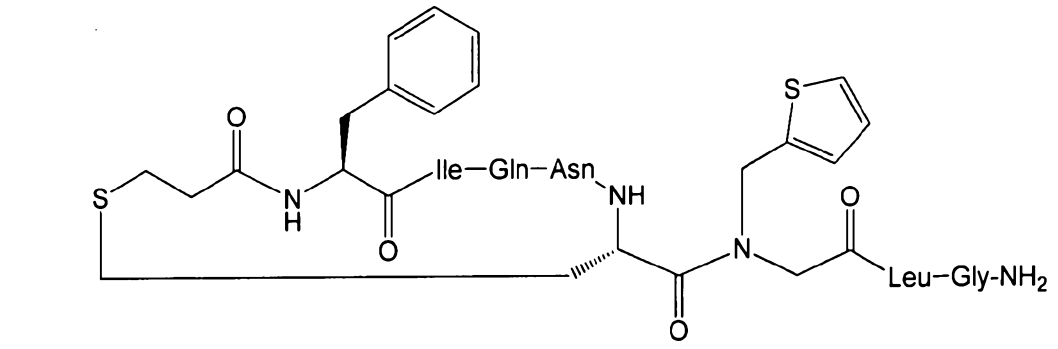

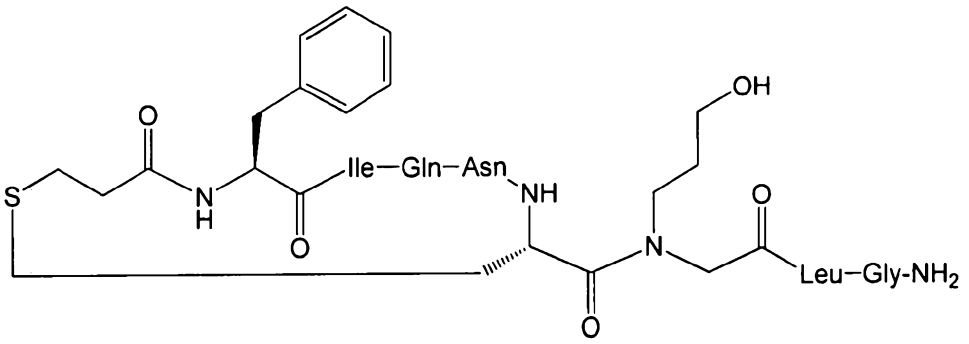

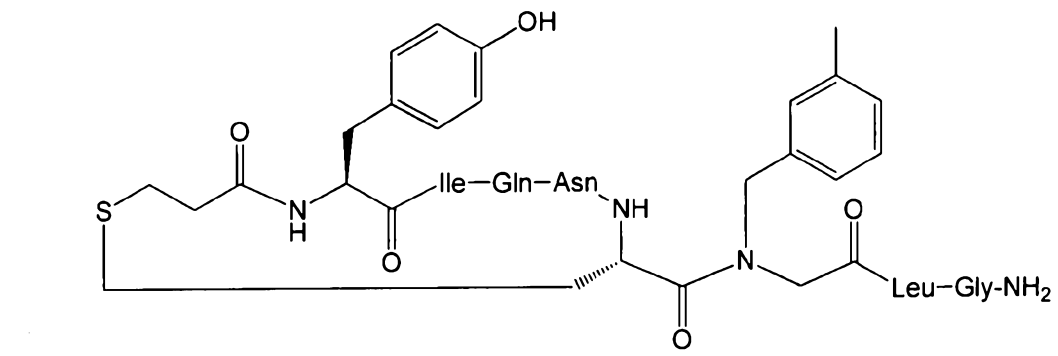

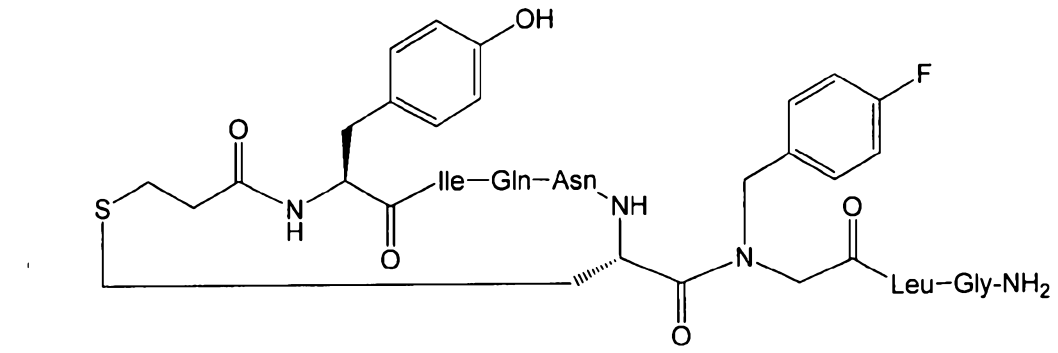

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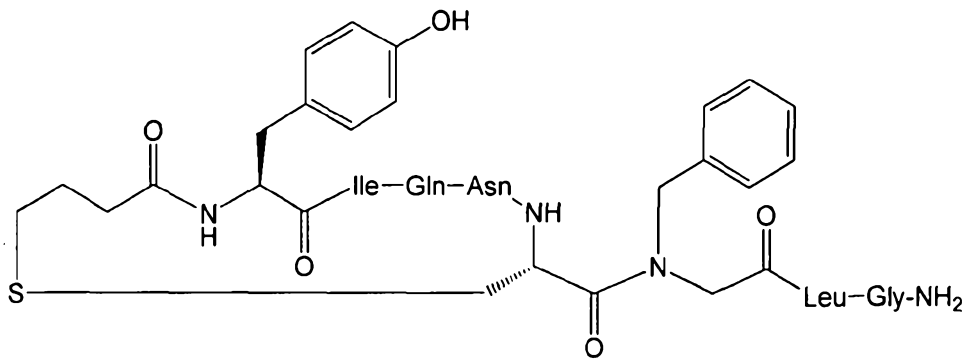

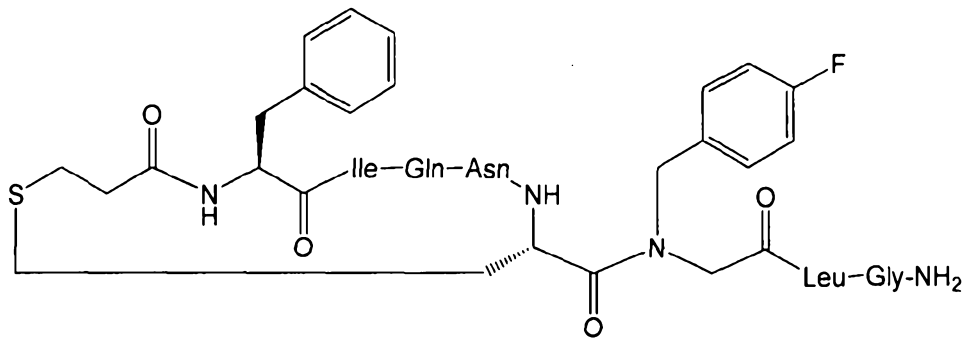

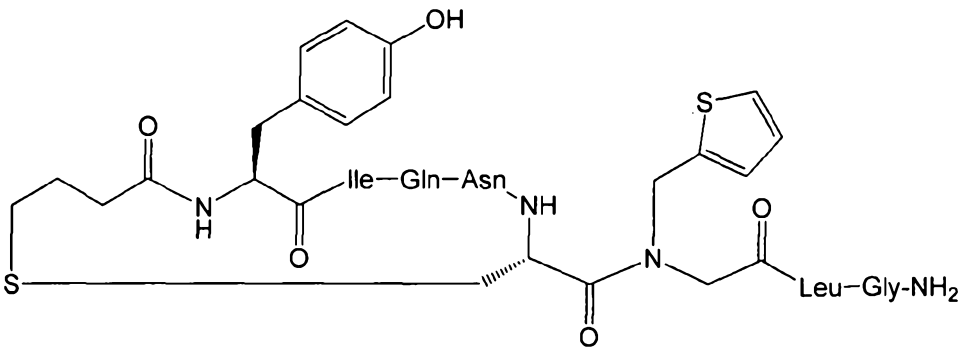

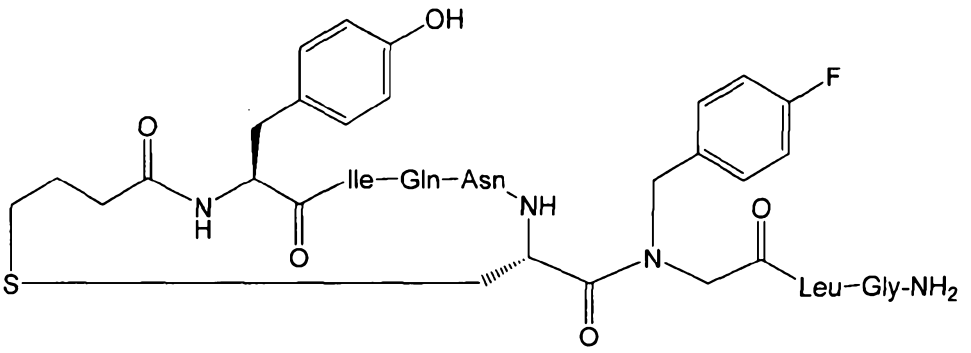

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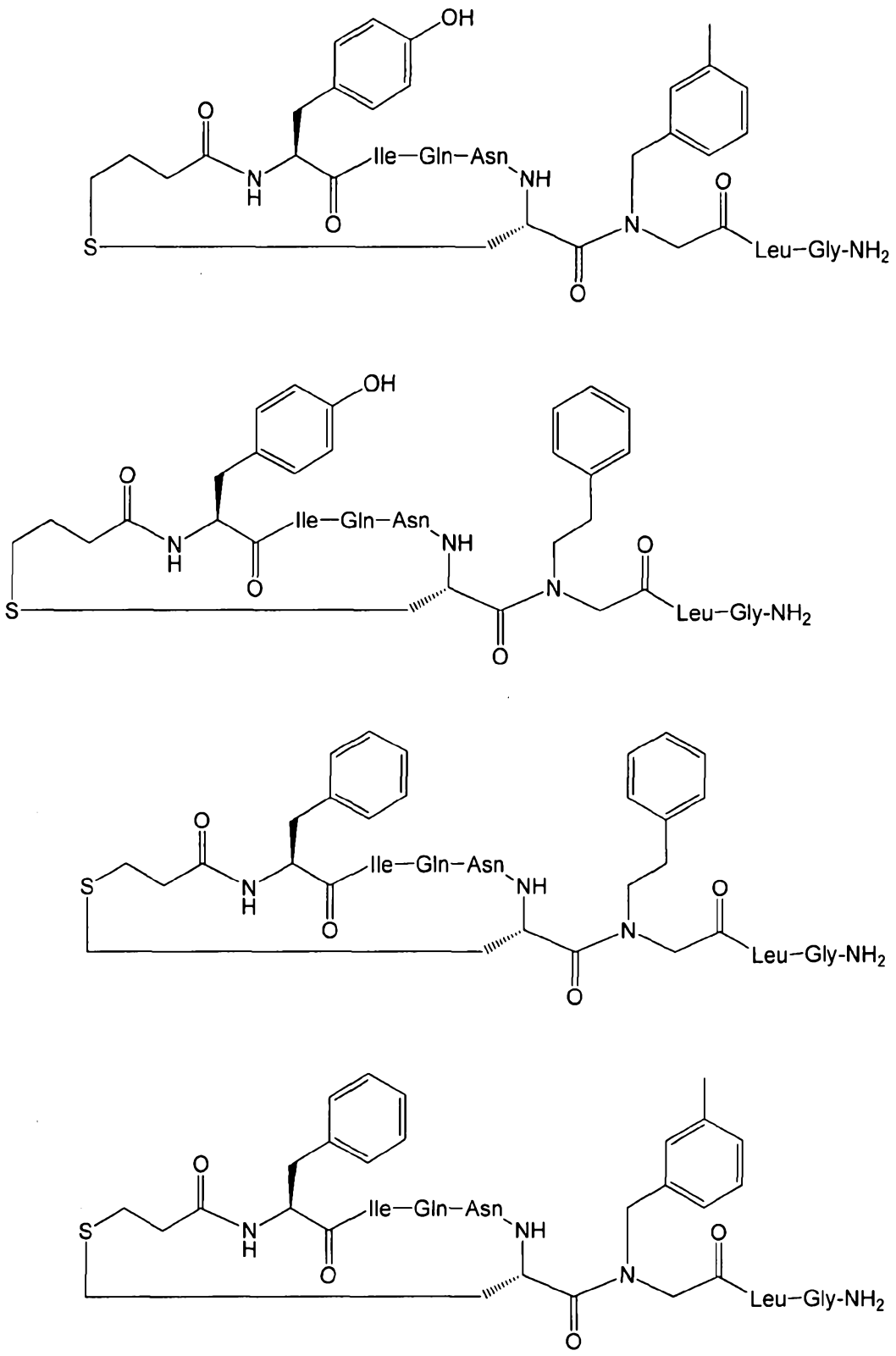
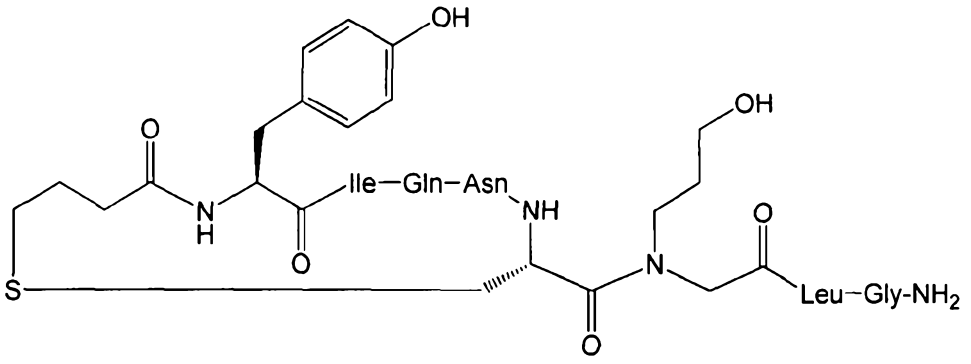
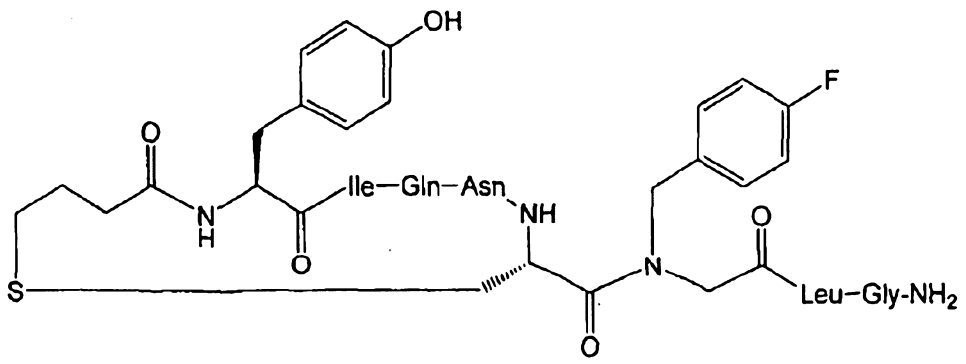
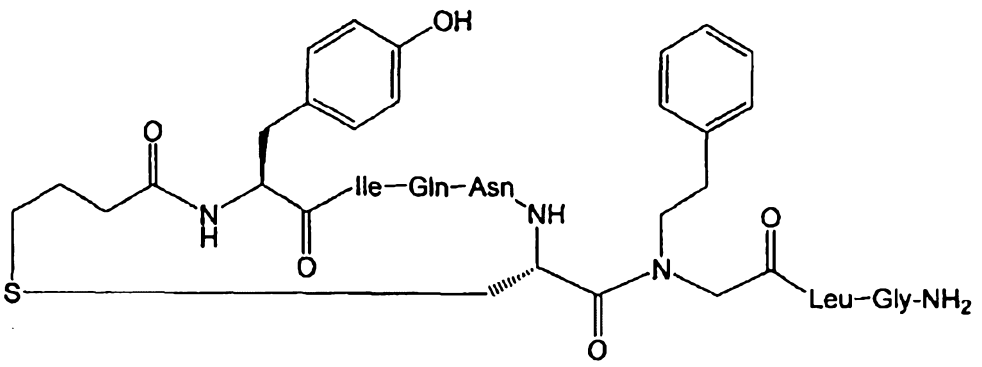
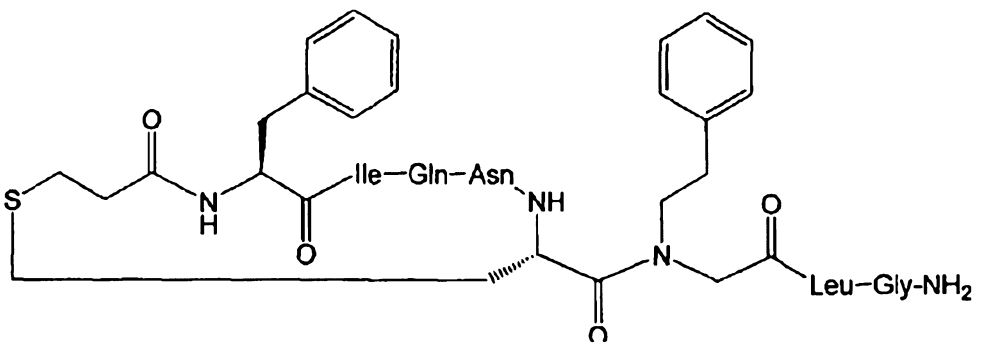




17. A compound according to claim 1, wherein the compound is:







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18. A pharmaceutical composition comprising a compound according to any one of claims 1-17 and a pharmaceutically acceptable adjuvant, diluent or carrier.

19. Use of a compound according to any one of claims 1-17 for the manufacture of a medicament for treatment of a condition selected from a compromised lactation condition, labour induction impairment, a uterine atony condition, inflammation, pain, abdominal pain, back pain, male and female sexual dysfunction, irritable bowel syndrome (IBS), constipation, gastrointestinal obstruction, autism, stress, anxiety, depression, anxiety disorder, surgical blood loss, post-partum haemorrhage, wound healing, infection, mastitis, placenta delivery impairment and osteoporosis.

20. A method for treatment of a condition selected from a compromised lactation condition, labour induction impairment, a uterine atony condition, inflammation, pain, abdominal pain, back pain, male and female sexual dysfunction, irritable bowel syndrome (IBS), constipation, gastrointestinal obstruction, autism, stress, anxiety, depression, anxiety disorder, surgical blood loss, post-partum haemorrhage, wound healing, infection, mastitis, placenta delivery impairment, osteoporosis, and for the diagnosis of cancer and placental insufficiency, wherein said method comprises administering to an animal a therapeutically effective amount of a compound according to any one of claims 1-17.

21. The method of claim 20 wherein the condition is abdominal pain or back pain.

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22. The method of claim 20 or claim 21 wherein the animal is a human.

23. A compound according to claim 1 substantially as hereinbefore described with reference to any one of the Examples.