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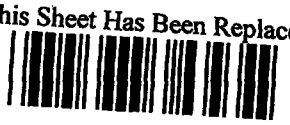

Description

Agents acting at central cholecystokinin (CCK) receptors induce satiety (Schick, Yaksh and Go, Regulatory Peptides 14:277-291, 1986. They are also expected to act as analgesics (Hill, Hughes and Pittaway, Neuropharmacology 26:289-300, 1987, and as anticonvulsants (MacVicar, Kerrin and Davison, Brain Research, 406:130-135, 1987.

Reduced levels of CCK-peptides have been found in the brains of schizophrenic patients compared with controls (Roberts, Ferrier, Lee, Crow, Johnstone, Owens, Bacarese-Hamilton, McGregor, O'Shaughnessey, Polak and Bloom. Brain Research 288, 199-211, 1983). It has been proposed that changes in the activity of CCK neurones projecting to the nucleus accumbens may play a role in schizophrenic processes by influencing dopaminergic function (Totterdell and Smith, Neuroscience 19, 181-192, 1986). This is consistent with numerous reports that CCK peptides modulate dopaminergic function in the basal ganglia and particularly the nucleus accumbens (Weiss, Tanzer, and Ettenberg, Pharmacology, Biochemistry and Behaviour 30, 309-317, 1988; Schneider, Allpert and Iversen, Peptides 4, 749-753, 1983). It may therefore be expected that agents modifying CCK receptor activity may have therapeutic value in conditions associated with disturbed function of central dopaminergic function such as schizophrenia and Parkinson's disease.

CCK and gastrin peptides share a common carboxy terminal pentapeptide sequence and CCK peptides can bind to the gastrin receptor of the stomach mucosa and elicit acid secretion in many species including human (Konturek, Gastrointestinal Hormones, Ch. 23, pp 529-564, 1980, ed. G.B.J. Glass, Raven Press, NY). Antagonists of the CCK-8 receptor would also be expected to be antagonists at the stomach gastrin receptor and thus be of value for conditions involving excessive acid secretion.

CCK and gastrin peptides have trophic effects on the pancreas and various tissues of the gastrointestinal tract (Johnson, ibid., pp 507-527), actions which are associated with increased DNA and RNA synthesis. Moreover, gastrin secreting cells are associated with certain gastrointestinal tumors as in the Zollinger-Ellison syndrome (Stadil, ibid., pp 279-739), and some colorectal tumors may also be gastrin/CCK dependent (Singh, Walker, Townsend and Thompson, Cancer Research, 46, 1612 (1986), and Smith, J.P., Gastroenterology, 95:1541 (1988)). Antagonists of CCK/gastrin receptors could therefore be of therapeutic value as antitumor agents.

The cholecystokinin peptides are widely distributed in various organs of the body including the gastrointestinal tract, endocrine glands, and the nerves of the peripheral and central nervous systems. Various biologically active forms have been identified including a 33-amino acid hormone and various carboxyl-terminus fragments of this peptide (e.g., the octapeptide CCK26-33 and the tetrapeptide CCK30-33). (G.J. Dockray, Br. Med. Bull., 38 (No. 3):253-258, 1982).

The various CCK peptides are thought to be involved in the control of smooth muscle contractility, exocrine and endocrine gland secretion, sensory nerve transmission, and numerous brain functions. Administration of the native peptides cause gall bladder contraction, amylase secretion, excitation of central neurons, inhibition of feeding, anticonvulsive actions and other behavioral effects. ("Cholecystokinin: Isolation, Structure and Functions," G.B.J. Glass, Ed., Raven Press, New York, 1980, pp 169-221; J.E. Morley, Life Sciences 27:355-368, 1980; "Cholecystokinin in the Nervous System," J. de Belleroche and G.J. Dockray, Ed., Ellis Horwood, Chichester, England, 1984, pp 110-127).

The high concentrations of CCK peptides in many brain areas also indicate major brain functions for these peptides (G.J. Dockray, Br. Med. Bull., 38 (No. 3):253-258, 1982). The most abundant form of brain CCK found is CCK26-33, although small quantities of CCK30-33 exist (Rehfeld and Gotterman, J. Neurochem., 32:1339-1341, 1979). The role of central nervous system CCK is not known with certainty, but it has been implicated in the control of feeding (Della-Fera and Baile, Science 206:471-473, 1979).

CCK is known to be present in some cortical interneurones which also contain gamma-aminobutyric acid (GABA) (H. Demeulemeester, et al, J Neuroscience 8:988-1000, 1988). Agents that modify GABA action may have utility as anxiolytic or hypnotic agents (S.C. Harvey, The Pharmacological Basis of Therapeutics (7th ed.) 1985, pp 339-371, MacMillan). Thus, agents which modify CCK action may have parallel anxiolytic or hypnotic activities.

It has now been found that CCK-B ligands are useful as antianxiety agents.

This includes all CCK-B ligands. CCK-B antagonists have now been shown to be agents useful in the treatment of withdrawal from drugs and alcohol. Although some ligands are CCK-A selective they do have some CCK-B activity as well and therefore are included also. Mixed CCK A/B ligands are also included.

The present invention is related to the use of CCK-ligands and pharmaceutically acceptable salts thereof in the treatment of anxiety and the withdrawal response caused by chronic treatment or abuse followed by withdrawal of drugs or alcohol. The compounds and methods of preparing them are found in

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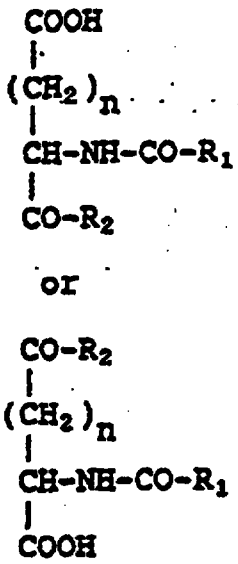
United States Patents 4,791,215 and 4,820,834 and European Application 167,919.

The uses disclosed are gastric acid secretion disorders, gastrointestinal motility, pancreatic secretions, dopaminergic functions, analgesics, psychic disturbances, anorexia, weight increases in farm animals, and pathological cellular growth such as tumors.

The present invention relates to the use of pharmaceutically active derivatives of D,L-glutamic acid and D,L-aspartic acid of formula:



I

IA

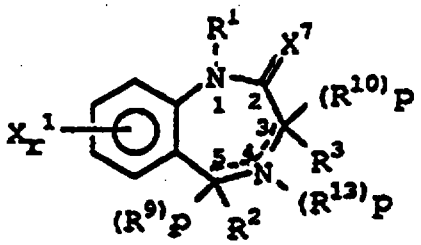
wherein

n is 1 or 2;

R_1 is a phenyl group mono-, di, or tri-substituted with linear or branched C_1-C_4 alkyl groups, which may be the same or different, or with halogens, with a cyano group or with a trifluoromethyl group; and

R_2 is selected from the group consisting of morpholino, piperidino and amino with one or two linear, branched or cyclic alkyl group substituents containing from 1 to 8 carbon atoms which may be the same or different;

or



II

wherein

R^1 is H, C_1-C_6 linear or branched alkyl, C_{1-5} alkenyl, C_{1-5} alkynyl, $-X^{12}COOR^5$, $-X^{11}$cyclo(C_{3-7})alkyl, $-X^{12}NR^4R^5$, $X^{12}CONR^4R^5$, $-X^{12}CN$, or $-X^{11}CX_3{}^{10}$;

R^2 is H, C_{1-7} alkyl, substituted or unsubstituted phenyl (wherein the substituents may be 1 or 2 of halo, C_{1-7} alkyl, C_{1-7} alkoxy, C_{1-7} alkylthio, carboxyl, carboxy(C_{1-7})alkyl, nitro, $-CF_3$, or hydroxy), 2-, 3-, 4-pyridyl,

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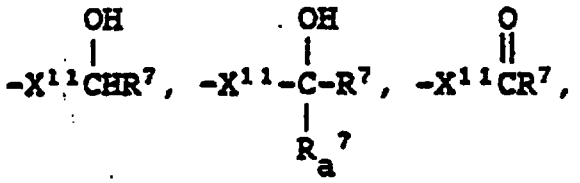
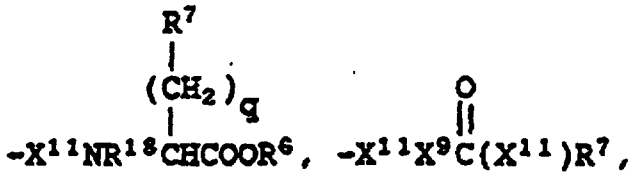
$-X^{12}SCH_3$, $-X^{12}SOCH_3$ $-X^{12}SO_2CH_3$, or $-X^{12}COOR^6$;

R^3 is $-X^{11}R^7$,

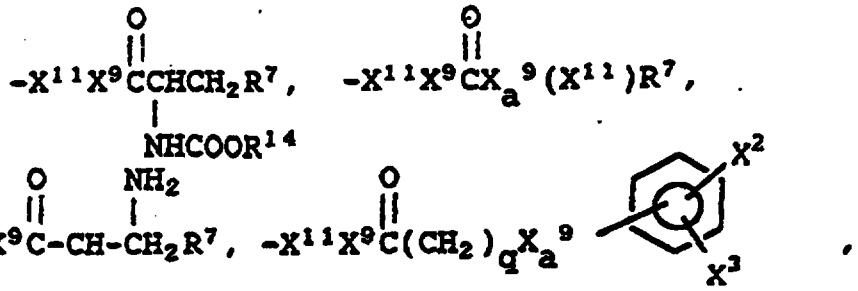


$-X^{11}NR^{18}(CH_2)_qR^7$,





$-NH(CH_2)_{2-3}NHR^7$, $-NH(CH_2)_{2-3}NHCOR^7$,



$-X^{11}NR^{18}SO_2(CH_2)_qR^7$ or



wherein

R_4 and R_5 are independently R^6 or in combination the N of the NR^4R^5 group form an unsubstituted or mono or disubstituted, saturated or unsaturated, 4-7 membered heterocyclic ring or benzofused 4-7 membered heterocyclic ring, or said heterocyclic ring or said benzofused heterocyclic ring which further comprises a second heteroatom selected from O and NCH_3 and the substituents(s) is/are independently selected from C_{1-4} alkyl;

R^6 is H, C_{1-7} alkyl, cyclo(C_{3-7})alkyl, substituted or unsubstituted phenyl, or substituted or

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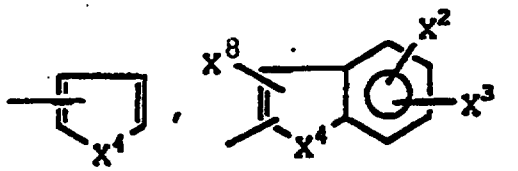
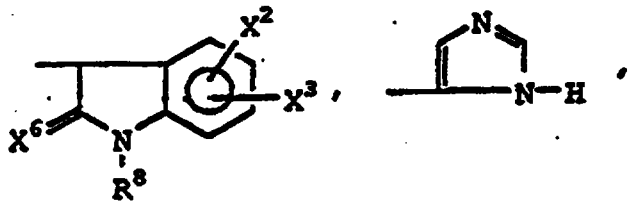
unsubstituted phenyl(C_{1-7})alkyl wherein the phenyl or phenyl(C_{1-7})alkyl substituents may be 1 or 2 of halo, C_{1-7} alkyl, C_{1-7} alkoxy, nitro, or CF_3;

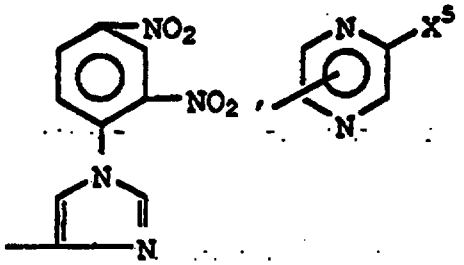
R_7 and R_a^7 are independently α- or β-naphthyl, substituted or unsubstituted phenyl (wherein the substituents may be 1 or 2 of halo $-NO_2$, -OH, $-X^{11}NR_4R_5$, C_{1-7} alkyl, CF_3, CN, SCF_3, C≡CH, CH_2SCF_3,

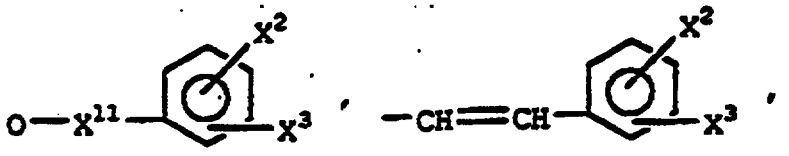


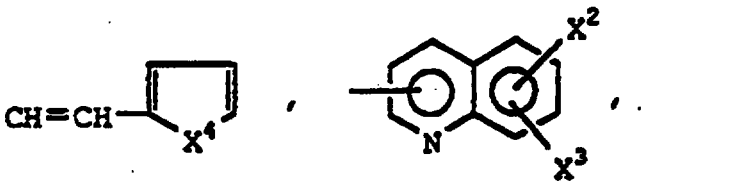
$OCHF_2$, SH, SPh, PO_3H-(C_{1-7})alkoxy, or C_{1-7} alkylthio, COOH), 2-, 3-, 4- pyridyl,

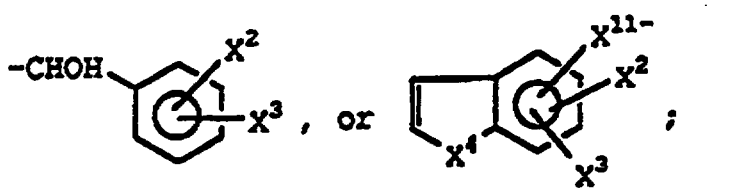












R^8 is H, C_{1-7} alkyl, cyclo(C_{3-7})alkyl, $-X^{12}CONH_2$, $-X^{12}COOR^6$, $-X^{12}$-cyclo(C_{3-7})alkyl, $-X^{12}NR^4R^5$,

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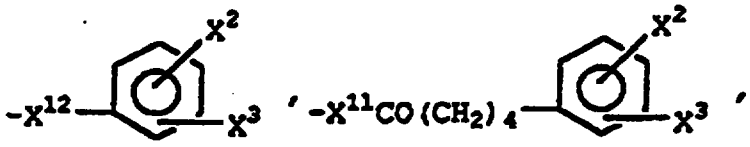
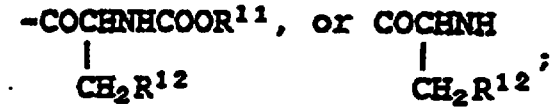
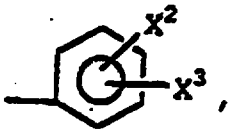


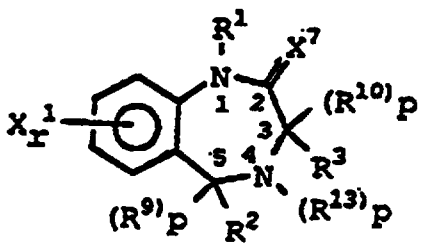


	R^9 and R^{10}	are independently H, -OH, or $-CH_3$;
	R^{11} and R^{12}	are independently C_{1-7} alkyl or cyclo(C_{3-7})alkyl;
	R^{13} is	H, C_{1-7} alkyl, acyl, O, or cyclo(C_{3-7})alkyl;
	R^{14} is	C_{1-7} alkyl or phenylloweralkyl;
	R^{15} is	H, C_{1-7} alkyl,



		or $-NH_2$;
	R^{18} is	H, (C_{1-7})alkyl, or acyl;
	p is	0 when its adjacent = = is unsaturated and 1 when its adjacent = = is saturated except that when R^{13} is O, p = 1 and = = is unsaturated;
	q is	0-4;
	r is	1 or 2;
	X^1 is	H, $-NO_2$, CF_3, CN, OH, C_{1-7} alkyl, halo, C_{1-7} alkylthio, C_{1-7} alkoxy, $-X^{11}COOR^6$, or $-X^{11}NR^4R^5-$;
	X^2 and X^3	are independently H, -OH, $-NO^2$, halo, C_{1-7} alkylthio, C_{1-7} alkyl, or C_{1-7} alkoxy;
	X^4 is	S, O, CH_2, or NR^{18} or NR^8;
	X^5 is	H, CF_3, CN, $-COOR^6$, NO_2, or halo;
	X^6 is	O or HH;
	X^7 is	O, S, HH, or NR^{15};
	X^8 is	H, C_{1-7} alkyl;
	X^9 and X_a^9	are independently NR^{18} or O;
	X^{10} is	F, Cl, or Br;
	X^{11} is	absent or C_{1-4} linear or branched alkylidene; X^{12} is C_{1-4} linear or branched alkylidene;
	--is	a saturated or unsaturated bond;

or



III

wherein R^1, R^2, R^4, R^5, R^5, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, p, q, r, X^1, X^2, X^3, X^5, X^6, X^7, X^8, X^9, X^{10}, X^{11} and X^{12} are as defined above,

R^3 is $-X^{11}NR^{18}(CH_2)_q R^{16}$,

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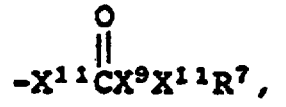
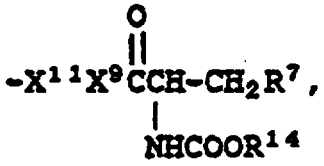
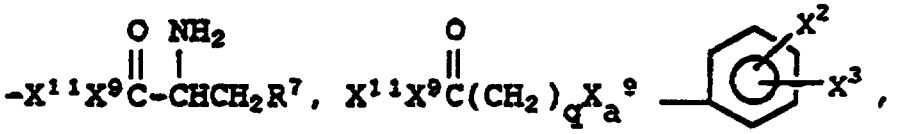
-NH(CH$_2$)$_{2-3}$NHR^7, -NH(CH$_2$)$_{2-3}$NHCOR^7,

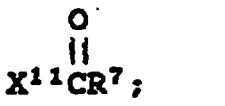




X^{11}NR^{18}CX$_a$ ^{9}X^{11}R^7,



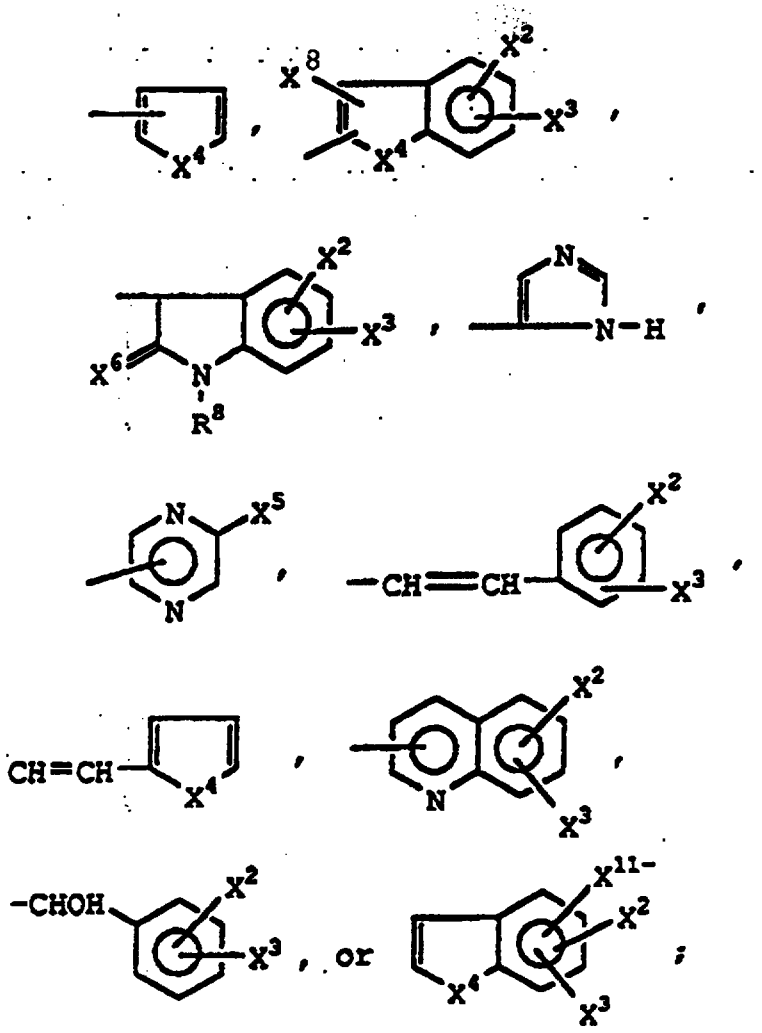
X^{11}NR^{18}SO$_2$(CH$_2$)$_q$R^7 or



R^7 is α- or β-naphthyl, substituted or unsubstituted phenyl (wherein the substituents may be 1 to 2 of halo, -NO$_2$, -OH,-X^{11}NR^{4}R^5, C$_{1-7}$ alkyl, CF$_3$, CN, SCF$_3$, C≡CH, CH$_2$SCF$_3$,



OCHF$_2$, SH, SPh, PO$_3$H, C$_{1-7}$ alkoxy, C$_{1-7}$ alkylthio or COOH), 2-, 3-, 4- pyridyl,



R^{16} is alpha or beta naphthyl or 2-indolyl;

R^{18} is H or C_{1-7} alkyl; and

= is a saturated or unsaturated bond;

or of a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment or the prevention of anxiety.

As used herein, the definition of each expression e.g. m, n, p, C_{1-7} alkyl, etc., when it occurs more than once in any structure, is intended to be independent of its definition elsewhere in the same structure.

As used herein, halo is F, Cl, Br or I; C_{1-7} alkyl is 1-7 carbon straight or branched chain alkyl and includes methyl, ethyl, propyl, isopropyl, butyl, isobutyl, and t-butyl, pentyl, hexyl, and heptyl; in C_{1-7} alkoxy and C_{1-7} alkylthio, the alkyl portion is C_{1-7} alkyl as previously defined; cyclo(C_{3-7})alkyl is cycloalkyl of 3-7 carbons; C_{1-5} alkenyl is 1-5 carbon straight or branched chain alkenyl; acyl is formyl, acetyl, propionyl, benzoyl or butyryl; C_{1-5} alkynyl is 1-5 carbon straight or branched chain alkynyl.

Preferred compounds of use in the instant invention are: lorglumide which is DL-4-(3,4-dichlorobenzoyl-amino)-5-(dipentylamino)-5-oxopentanoic acid, loxiglumide which is (±)-4-[(3,4-dichlorobenzoyl)amino]-5-[(3-methoxyproxyl)pentylamino]-5-oxo-pentanoic acid, L-364718 which is 3(S)-(-)-N-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-1H-indole-2-carboxamide, and L-365,260 which is (R)-N-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazapine-3-yl)-N'-(3-methylphenyl)urea.

The compounds of use in the instant invention may be administered in an amount of from 0.05 mg/kg to 50 mg/kg.

The compounds of use in the instant invention may be administered as a composition which is in oral dosage form.

The instant invention also relates to the use of a compound of formula I, IA, II or III as defined above for the manufacture of a medicament for treating anxiety in a mammal in need of such treatment.

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The instant invention also relates to the use of a compound of formula I, IA, II or III as defined above for the manufacture of a medicament for treating the withdrawal response produced by chronic treatment followed by withdrawal of diazepam, nicotine, alcohol or cocaine.

The compounds used in the invention may contain asymmetric carbon atoms. The invention includes the use of diastereomers, mixtures of diastereomers, or the use of mixed or the individual optical enantiomers. The invention includes all such forms of the compounds.

The compounds used in the instant invention include solvates, hydrates and pharmaceutically acceptable salts thereof.

The pharmaceutically acceptable salts of the compounds used in the present invention include conventional non-toxic salts or quarternary ammonium salts.

The usefulness of the compounds of the instant invention as agents for treating anxiety or withdrawal symptoms is demonstrated in the following pharmacological test procedure.

METHODS

The compounds of the instant invention are useful as anxiolytic agents as described and discussed below.

Figure I illustrates the effectiveness of orally administered compound L-365260. Anxiolytic activity was assessed in the light/dark exploration test in the mouse (B.J. Jones, et al, Br. J. Pharmacol. 93:985-993, 1988).

Generally the number of mice used was 5 and the pretreatment time was about 40 minutes. The compound was given p.o. in 1- and 10-mg/kg doses.

The apparatus was an open-topped box, 45 cm long, 27 cm wide, and 27 cm high, divided into a small (2/5) area and a large (3/5) area by a partition that extended 20 cm above the walls. There was a 7.5 x 7.5 cm opening in the partition at floor level. The small compartment was painted black and the large compartment white. The floor of each compartment was marked into 9 cm squares. The white compartment was illuminated by a 100-watt tungsten bulb 17 cm above the box and the black compartment by a similarly placed 60-watt red bulb. The laboratory was illuminated with red light.

All tests were performed between 13 hundred hours, 0 minutes and 18 hundred hours, 0 minutes. Each mouse was tested by placing it in the center of the white area and allowing it to explore the novel environment for five minutes. Its behavior was recorded on videotape and the behavioral analysis was performed subsequently from the recording. Five parameters were measured: the latency to entry into the dark compartment, the time spent in each area, the number of transitions between compartments, the number of lines crossed in each compartment, and the number of rears in each compartment.

In this test an increase in the time spent in the white area is a sensitive measure of the anxiolytic effects of several standard anxiolytic drugs. Drugs were dissolved in water or saline and administered either subcutaneously, intraperitoneally, or by mouth (PO) via a stomach needle.

Drugs such as alcohol, cocaine, diazepam and nicotine can also be used in the light/dark exploration test in the mouse. For example, alcohol can be given in the drinking water as an 8% W/V solution for fourteen days. After a twenty-four hour withdrawal period the withdrawal response may be blocked by a composition of the instant invention when administered 10 mg/kg i.p. twice daily.

The results obtained with L-365,260 are shown in Figure 1. Control mice, not treated with L-365,260, but subjected to the aversive stimulus, showed a high level of rearing and line crossing activity in the black compartment compared to the white compartment. Treatment with L-365,260 10 mg/kg orally reversed this response and the mice now showed higher rearing and line crossing activity in the white compartment than in the black compartment. Figure 1 also shows that L-365,260 reduced the total time spent by the mice in the black compartment and increased the time latency of the mice moving from the white side to the black side. These results show that L-365,260 possesses anxiolytic activity in this test.

For preparing pharmaceutical compositions from the compounds of use in the invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets, and suppositories.

A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, or tablet disintegrating agents; it can also be an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

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For preparing suppository preparations, a low-melting wax such as a mixture of fatty acid glycerides and cocoa butter is first melted and the active ingredient is dispersed therein by, for example, stirring. The molten homogeneous mixture is then poured into convenient sized molds and allowed to cool and solidify.

The powders and tablets preferably contain 5 to 70% of the active component. Suitable carriers are magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low-melting wax, cocoa butter, and the like.

The term "preparation" is intended to include the formulation of the active component with encapsulating material as a carrier providing a capsule in which the active component (with or without other carriers) is surrounded by a carrier which is thus in association with it. Similarly, cachets are included.

Tablets, powders, cachets, and capsules can be used as solid dosage forms suitable for oral administration.

Liquid form preparations include solutions, suspensions, and emulsions. Sterile water or water-propylene glycol solutions of the active compounds may be mentioned as an example of liquid preparations suitable for parenteral administration. Liquid preparations can also be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions for oral administration can be prepared by dissolving the active component in water and adding suitable colorants, flavoring agents, stabilizers, and thickening agents as desired. Aqueous suspensions for oral use can be made by dispersing the finely divided active component in water together with a viscous material such as natural synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other suspending agents known to the pharmaceutical formulation art.

Preferably the pharmaceutical preparation is in unit dosage form. In such form, the preparation is divided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of the preparation, for example, packeted tablets, capsules, and powders in vials or ampoules. The unit dosage form can also be a capsule, cachet, or tablet itself, or it can be the appropriate number of any of these packaged forms.

When a compound of formula I, IA, II, or III is used in the instant invention in a human subject, the daily dosage will normally be determined by the prescribing physician with the dosage generally varying according to the age, weight, and response of the individual patient, as well as the severity of that patient's symptoms. However, in most instances, an effective daily dosage will be in the range of from 0.05 mg/kg to 50 mg/kg of body weight, and preferably, of from 0.5 mg/kg to 20 mg/kg of body weight, administered in single or divided doses. In some cases, however, it may be necessary to use dosages outside these limits.

Examples of formulations of compounds or salts thereof of use in the instant invention are:

Example 1

Injectables

Lorglumide with water for injection USP q.s.

The hydrochloride salt of the compound is dissolved in water and passed through a 0.2-micron filter. Aliquots of the filtered solution are added to ampoules or vials, sealed and sterilized.

Example 2

Syrups

200 mg /5 ml syrup	
Compound	12.5 g
Purified Water USP	200 ml
Cherry Syrup qu	1000 ml

The compound is dissolved in water and to the resulting solution the syrup is added with mild stirring.

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Example 3

Capsules

50 mg, 100 mg, or 200 mg	
Compound 1	250 g
Lactose USP, Anhydrous q.s. or	250 g
Sterotex Powder HM	5 g

Combine the compound and the lactose in a tumble blend for two minutes, blend for one minute with the intensifier bar and then tumble blend again for one minute. A portion of the blend is then mixed with the Sterotex Powder, passed through a #30 screen and added back to the remainder of the blend. The mixed ingredients are then blended for one minute, blended with the intensifier bar for thirty seconds and tumble blended for an additional minute. The appropriately sized capsules are filled with 141 mg, 352.5 mg, or 705 mg of the blend, respectively, for the 50 mg, 125 mg, and 250 mg containing capsules.

Example 4

Tablets

50 mg, 100 mg, or 200 mg	
Corn Starch NF	200 g
Cellulose, Microcrystalline	46 g
Sterotex Powder HM	4 g
Purified Water q.s. or	300 ml

Combine the corn starch, the cellulose, and Compound 1 together in a planetary mixer and mix for two minutes. Add the water to this combination and mix for one minute. The resulting mix is spread on trays and dried in a hot air oven at 50°C until a moisture level of 1 to 2 percent is obtained. The dried mix is then milled with a Fitzmill through a #RH2B screen, and added back to the milled mixture and the total blended for five minutes by drum rolling. Compressed tablets of 150 mg, 375 mg, and 750 mg, respectively, of the total mix are formed with appropriate sized punches the 50 mg, 125 mg, or 500 mg containing tablets.

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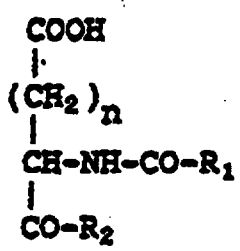
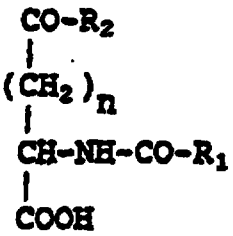
Claims

1. Use of pharmaceutically active derivatives of D,L-glutamic acid and D,L-aspartic acid of formula:



I

or



IA

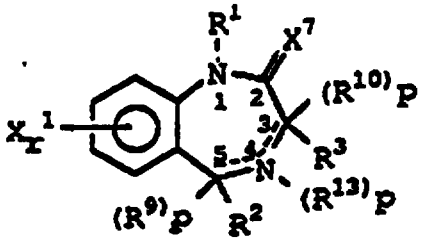
wherein

n is 1 or 2;

R_1 is a phenyl group mono-, di, or tri-substituted with linear or branched C_1-C_4 alkyl groups, which may be the same or different, or with halogens, with a cyano group or with a trifluoromethyl group; and

R_2 is selected from the group consisting of morpholino, piperidino and amino with one or two linear, branched or cyclic alkyl group substituents containing from 1 to 8 carbon atoms which may be the same or different;

or



II

wherein

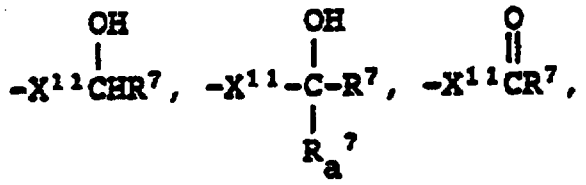
R^1 is H, C_1-C_6 linear or branched alkyl, C_{1-5} alkenyl, C_{1-5} alkynyl, $-X^{12}COOR^5$, $-X^{11}$cyclo(C_{3-7})-alkyl, $-X^{12}NR^4R^5$, $X^{12}CONR^4R^5$, $-X^{12}CN$, or $-X^{11}CX_3{}^{10}$;

R^2 is H, C_{1-7} alkyl, substituted or unsubstitinted phenyl (wherein the substituents may be 1 or 2 of halo, C_{1-7} alkyl, C_{1-7} alkoxy, C_{1-7} alkylthio, carboxyl, carboxy(C_{1-7})alkyl, nitro, $-CF_3$, or hydroxy), 2-, 3-, 4-pyridyl,

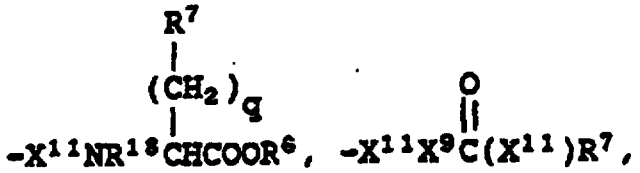


$-X^{12}SCH_3$, $-X^{12}SOCH_3$ $-X^{12}SO_2CH_3$, or $-X^{12}COOR^6$;

R^3 is $-X^{11}R^7$,

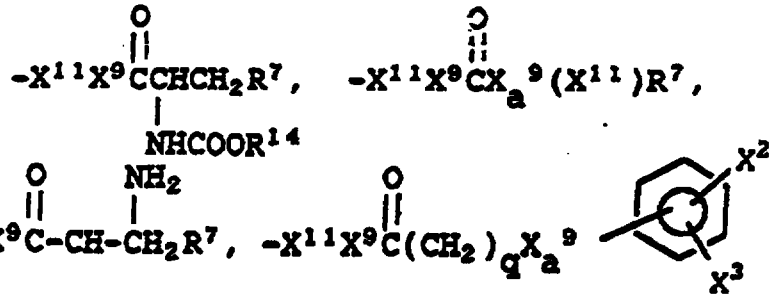


$-X^{11}NR^{18}(CH_2)_qR^7$,





$-NH(CH_2)_{2-3}NHR^7$, $-NH(CH_2)_{2-3}NHCOR^7$,

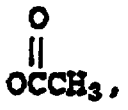


$-X^{11}NR^{18}SO_2(CH_2)_qR^7$ or

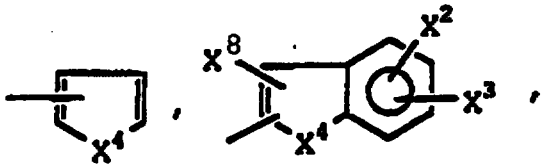


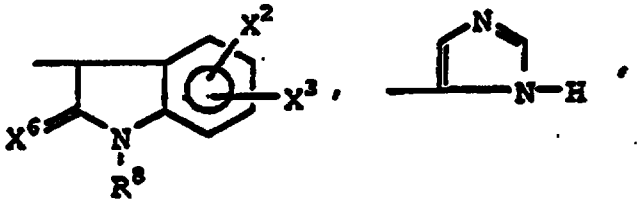
wherein

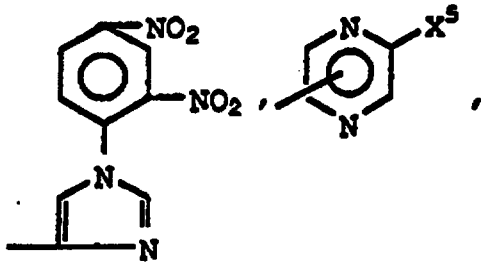
R_4 and R_5	are independently R^6 or in combination the N of the NR^4R^5 group form an unsubstituted or mono or disubstituted, saturated or unsaturated, 4-7 membered heterocyclic ring or benzofused 4-7 membered heterocyclic ring, or said heterocyclic ring or said benzofused heterocyclic ring which further comprises a second heteroatom selected from O and NCH_3 and the substituents(s) is/are independently selected from C_{1-4} alkyl;
R^6 is	H, C_{1-7} alkyl, cyclo(C_{3-7})alkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted phenyl(C_{1-7})alkyl wherein the phenyl or phenyl(C_{1-7})alkyl substituents may be 1 or 2 of halo, C_{1-7} alkyl, C_{1-7} alkoxy, nitro, or CF_3;
R_7 and R_a^7	are independently α- or β-naphthyl, substituted or unsubstituted phenyl (wherein the substituents may be 1 or 2 of halo $-NO_2$, -OH, $-X^{11}NR_4R_5$, C_{1-7} alkyl, CF_3, CN, SCF_3, C≡CH, CH_2SCF_3,

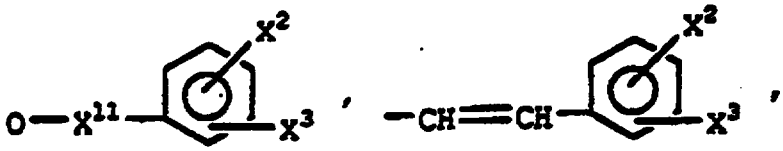


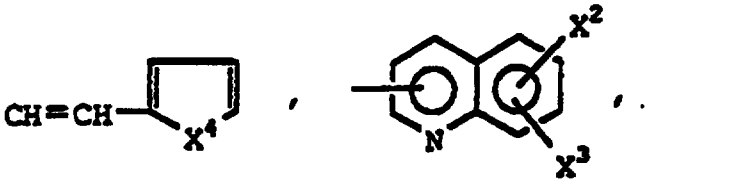
OCHF$_2$, SH, SPh, PO$_3$H-(C$_{1-7}$)alkoxy, or C$_{1-7}$ alkylthio, COOH), 2-, 3-, 4- pyridyl,

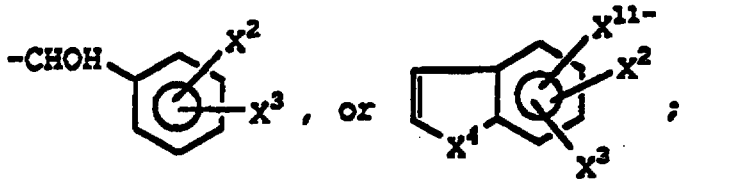


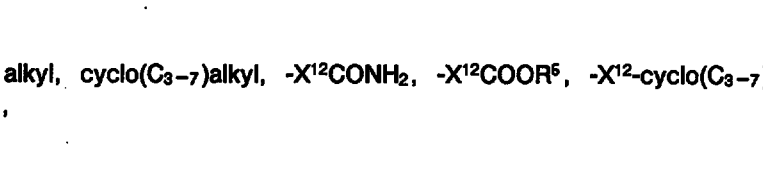




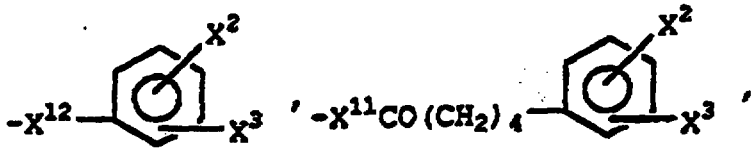






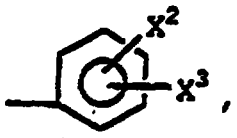


R^8 is H, C$_{1-7}$ alkyl, cyclo(C$_{3-7}$)alkyl, -X^{12}CONH$_2$, -X^{12}COOR^5, -X^{12}-cyclo(C$_{3-7}$)alkyl, -X^{12}NR^{4}R^5,



$-COCHNHCOOR^{11}$, or $-COCHNH$ (CH_2R^{12}; CH_2R^{12});

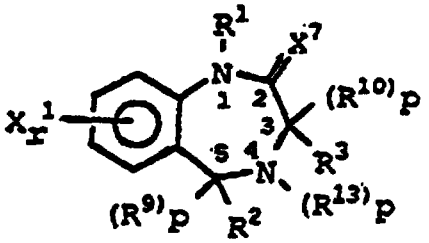
	R^9 and R^{10}	are independently H, -OH, or $-CH_3$;
	R^{11} and R^{12}	are independently C_{1-7} alkyl or cyclo(C_{3-7})alkyl;
	R^{13} is	H, C_{1-7} alkyl, acyl, O, or cyclo(C_{3-7})alkyl;
	R^{14} is	C_{1-7} alkyl or phenyl(C_{1-7})alkyl;
	R^{15} is	H, C_{1-7} alkyl,



or $-NH_2$;

	R^{18} is	H, C_{1-7} alkyl, or acyl;
	p is	0 when its adjacent = = is unsaturated and 1 when its adjacent = = is saturated except that when R^{13} is O, p = 1 and = = is unsaturated;
	q is	0-4;
	r is	1 or 2;
	X^1 is	H, $-NO_2$, CF_3, CN, OH, C_{1-7} alkyl, halo, C_{1-7} alkylthio, C_{1-7} alkoxy, $-X^{11}COOR^5$, or $-X^{11}NR^4R^5-$;
	X^2 and X^3	are independently H, -OH, $-NO^2$, halo, C_{1-7} alkylthio, C_{1-7} alkyl, or C_{1-7} alkoxy;
	X^4 is	S, O, CH_2, or NR^{18} or NR^8;
	X^5 is	H, CF_3, CN, $-COOR^6$, NO_2, or halo,
	X^6 is	O or HH;
	X^7 is	O, S, HH, or NR^{15};
	X^8 is	H, C_{1-7} alkyl;
	X^9 and X_a^9	are indepenaently NR^{18} or O;
	X^{10} is	F, Cl, or Br;
	X^{11} is	absent or C_{1-4} linear or branched alkylidene; X^{12} is C_{1-4} linear or branched alkylidene;
	--is	a saturated or unsaturated bond;

or



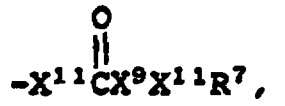
III

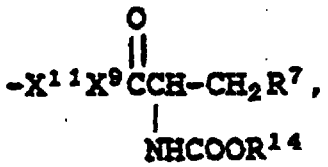
wherein R^1, R^2, R^4, R^5, R^6, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, p, q, r, X^1, X^2, X^3, X^5, X^6, X^7, X^8, X^9, X^{10}, X^{11} and X^{12} are as defined above,

R^3 is $-X^{11}NR^{18}(CH_2)_q R^{16}$,

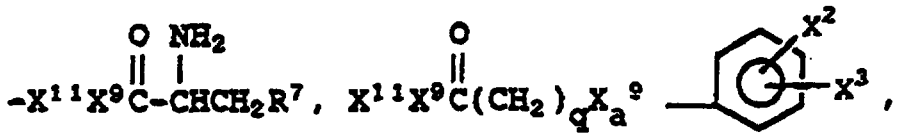


$-NH(CH_2)_{2-3}NHR^7$, $-NH(CH_2)_{2-3}NHCOR^7$,





$X^{11}NR^{18}CX_a{}^9X^{11}R^7$,



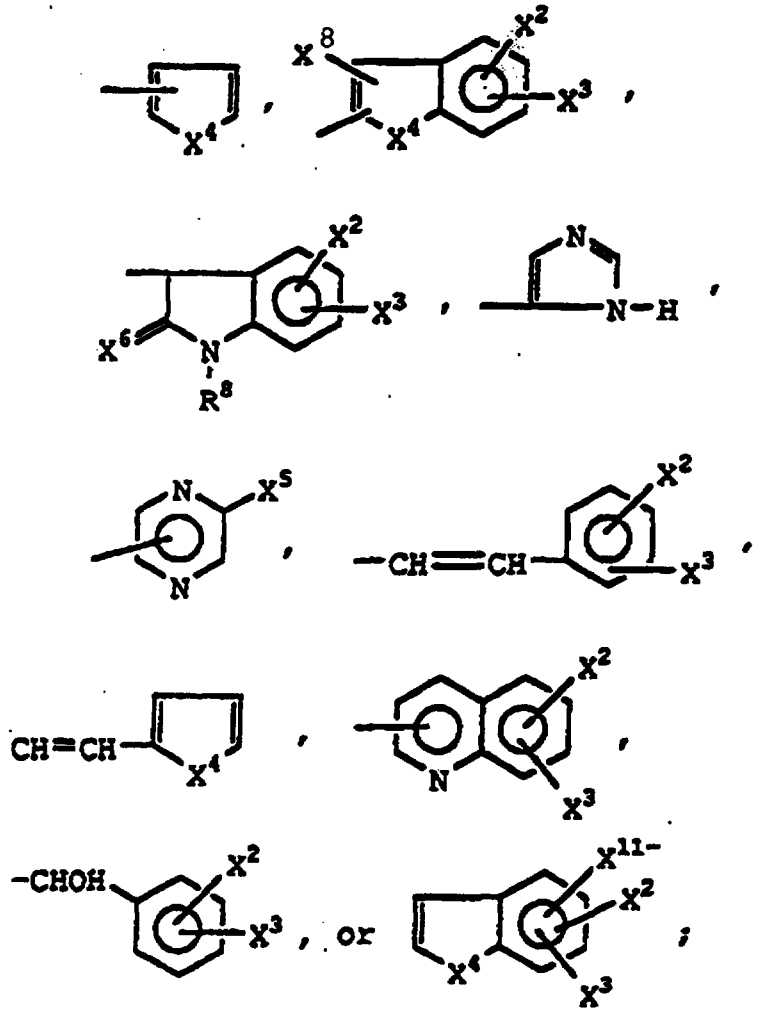
$X^{11}NR^{18}SO_2(CH_2)_qR^7$ or



R^7 is α- or β-naphthyl, substituted or unsubstituted phenyl (wherein the substituents may be 1 to 2 of halo, $-NO_2$, -OH,$-X^{11}NR^4R^5$, C_{1-7} alkyl, CF_3, CN, SCF_3, C≡CH, CH_2SCF_3,



$OCHF_2$, SH, SPh, PO_3H, C_{1-7} alkoxy, C_{1-7} alkylthio or COOH), 2-, 3-, 4- pyridyl,



R^{15} is alpha or beta naphthyl or 2-indolyl;
R^{18} is H or C_{1-7} alkyl; and
= is a saturated or unsaturated bond;

or of a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment or the prevention of anxiety.

2. Use according to Claim 1 wherein the derivative is DL-4-(3,4-dichlorobenzoyl-amino)-5-(dipentylamino)-5-oxopentanoic acid, (±)-4-[(3,4-dichlorobenzoyl)-amino]-5-[(3-methoxyproxyl)pentylamino]-5-oxo-pentanoic acid, 3(S)-(-)-N-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-1H-indole-2-carboxamide, (R)-N-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazapine-3-yl)-N'-(3-methylphenyl)urea or a pharmaceutically acceptable salt thereof.

3. Use of a derivative as defined in Claim 1 or Claim 2 for the manufacture of a medicament for treating or preventing the withdrawal response produced by withdrawal of chronic treatment with diazepam in a mammal.

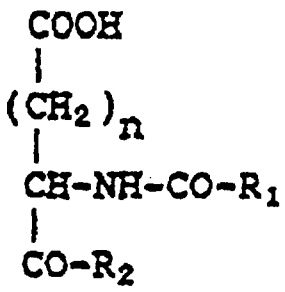
4. Use of a derivative as defined in Claim 1 or Claim 2 for the manufacture of a medicament for treating or preventing the withdrawal response produced by withdrawal from chronic use of cocaine in a mammal.

5. Use of a derivative as defined in Claim 1 or Claim 2 for the manufacture of a medicament for treating or preventing the withdrawal response produced by withdrawal from chronic use of alcohol in a mammal.

6. Use of a derivative as defined in Claim 1 or Claim 2 for the manufacture of a medicament for treating or preventing the withdrawal response produced by withdrawal from chronic use of nicotine in a mammal.

Patentansprüche

1. Verwendung von pharmazeutisch aktiven Derivaten von D,L-Glutaminsäure und D,L-Asparagin der Formel:



I

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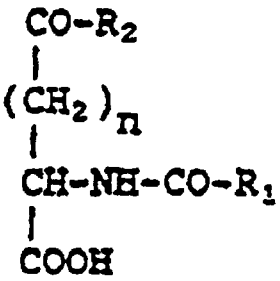


IA

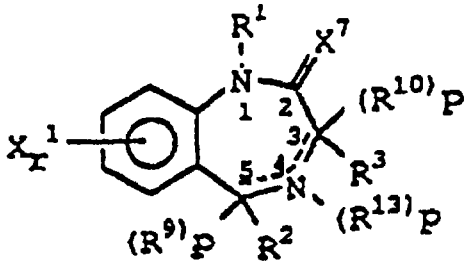
worin

n für 1 oder 2 steht;

R_1 für eine Phenylgruppe steht, die mono-, di- oder trisubstituiert ist mit linearen oder verzweigten C_1-C_4-Alkylgruppen, die gleich oder verschieden sein können, oder mit Halogenen einer Cyanogruppe oder mit einer Trifluormethylgruppe; und

R_2 ausgewählt ist aus der Gruppe, bestehend aus Morpholin; Piperidin und Amin mit einem oder zwei linearen, verzweigten oder cyclischen Alkylgruppen-Substituenten, die 1 bis 8 Kohlenstoffatome enthalten, die gleich oder verschieden Sein können;

oder von

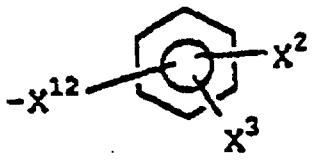


II

worin

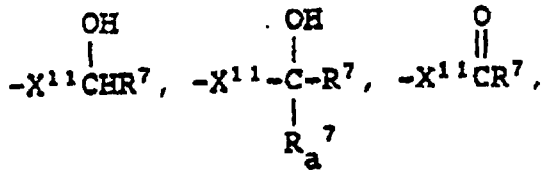
R^1 für H, lineares oder verzweigtes C_1-C_6-Alkyl, C_1-C_5-Alkenyl, C_{1-5}-Alkynyl, $-X^{12}COOR^6$, $-X^{11}$Cyclo(C_{3-7})-alkyl, $-X^{12}NR^4R^5$, $-X^{12}CONR^4R^5$, $-X^{12}CN$ oder $-X_{11}CX_3^{10}$ steht;

R^2 für H, C_{1-7}-Alkyl, substituiertes oder unsubstituiertes Phenyl (worin die Substituenten 1 oder 2 von Halogen, C_{1-7}-Alkyl, C_{1-7}-Alkoxy, C_{1-7}-Alkylthio, Carboxy, Carboxy-(C_{1-7})-alkyl, Nitro, $-CF_3$ oder Hydroxy sein können), 2-, 3-, 4-Pyridyl,

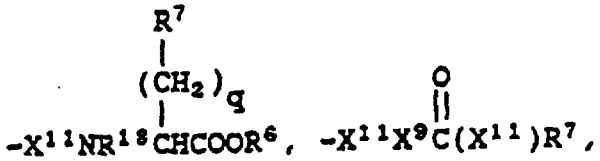


$-X^{12}SCH_3$, $-X^{12}SOCH_3$ $-X^{12}SO_2CH_3$, or $-X^{12}COOR^6$; steht;

R^3 für $-X^{11}R^7$,

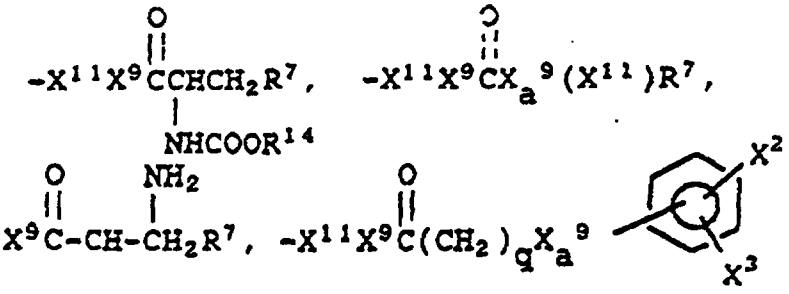


$-X^{11}NR^{18}(CH_2)_qR^7$,

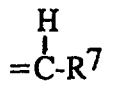




$-NH(CH_2)_{2-3}NHR^7$, $-NH(CH_2)_{2-3}NHCOR^7$,



$X^{11}NR^{18}SO_2(CH_2)_qR^7$ oder



steht:

worin

R_4 und R_5 unabhängig für R^6 stehen oder zusammen mit N der NR^4R^5-Gruppe einen unsubstituierten oder mono- oder disubstituierten gesättigten oder ungesättigten 4- bis 7-gliedrigen heterocyclischen Ring oder einen benzokondensierten 4- bis 7-gliedrigen heterocyclischen Ring bilden oder der genannte heterocyclische Ring oder der genannte benzokondensierte heterocyclische Ring, der außerdem ein zweites Hete-

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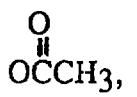
* C L M S *

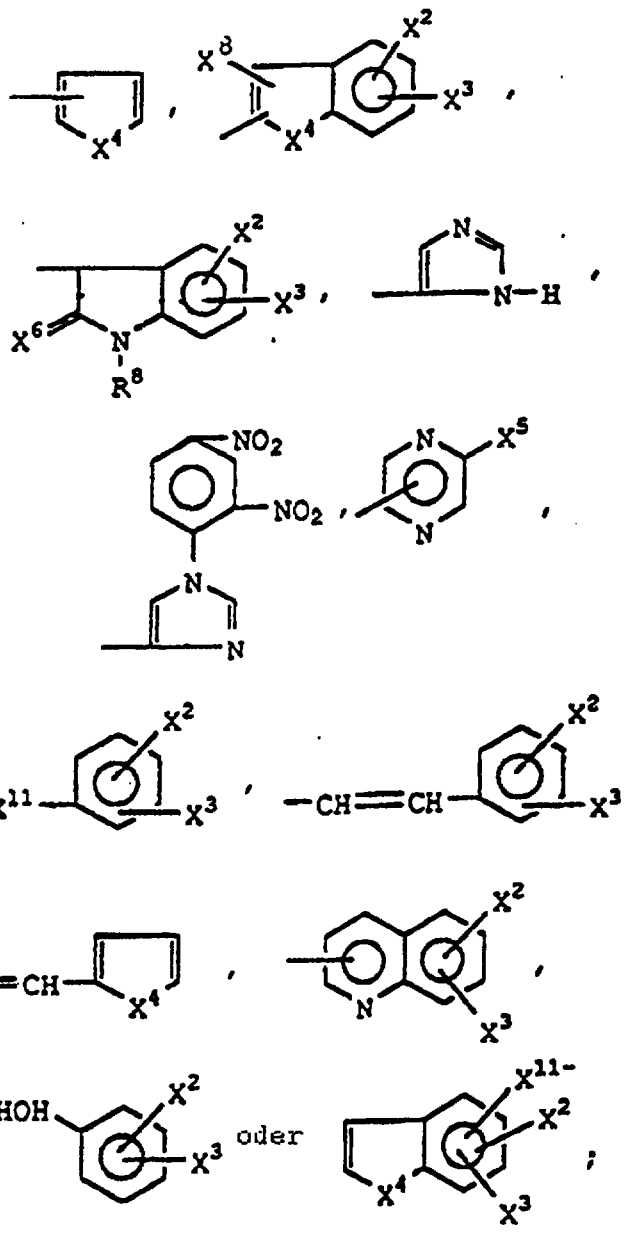
roatom, ausgewählt aus O und NCH_3, umfaßt, und der (die) Substituent(en) unabhängig ausgewählt werden aus C_{1-4}-Alkyl;

R^6 für H, C_{1-7}-Alkyl, Cyclo-(C_{3-7})-alkyl, substituiertes oder unsubstituiertes Phenyl oder substituiertes oder unsubstituiertes Phenyl, C_{1-7}-Alkyl steht, worin die Phenyl- oder Phenyl-(C_{1-7})-alkylsubstituenten 1 oder 2 von Halogen, C_{1-7}-Alkyl, C_{1-7}-Alkoxy, Nitro oder CF_3 sein können;

R_7 und R_a^7 unabhängig für α- oder β-Naphthyl, substituiertes oder unsubstituiertes Phenyl (worin die Substituenten 1 oder 2 vor) Halogen, $-NO_2$, -OH, $-X^{11}NR_4R_5$, C_{1-7}-Alkyl, CF_3, CN, SCF_3, C≡CH, CH_2SCF_3,



$OCHF_2$, SH, SPh, PO_3H-(C_{1-7})-Alkoxy oder C_{1-7}-Alkylthio, COOH bedeuten), 2-, 3-, 4-Pyridyl,



stehen;

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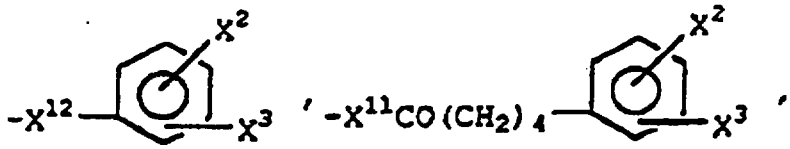
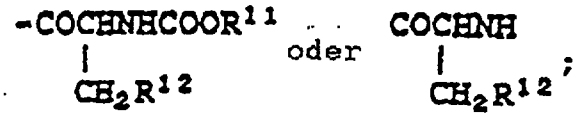
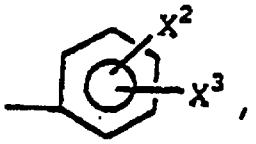
R^8	für H, C_{1-7}-Alkyl, Cyclo-(C_{3-7})-alkyl, $-X^{12}CONH_2$, $-X^{12}COOR^6$, $-X^{12}$-Cyclo-(C_{3-7})-alkyl, $-X^{12}NR^4R^5$,





steht;

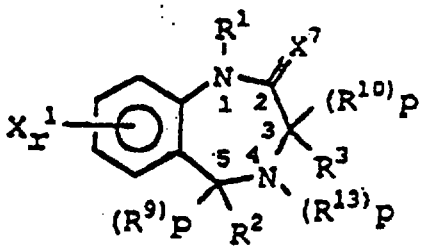
R^9 und R^{10}	unabhängig für H, -OH oder $-CH_3$ stehen;
R^{11} und R^{12}	unabhängig für C_{1-7}-Alkyl oder Cyclo-(C_3–C_7)-alkyl stehen;
R^{13}	für H, C_{1-7}-Alkyl, Acyl, O oder Cyclo-(C_{3-7})-alkyl steht;
R^{14}	für C_{1-7}-Alkyl oder Phenyl-(C_{1-7})-alkyl steht;
R^{15}	für H, C_{1-7}-Alkyl,



oder $-NH_2$ steht;

R^{18}	für H, C_{1-7}-Alkyl oder Acyl steht;
p	für 0 steht, wenn sein benachbartes = = ungesättigt ist und für 1 steht, wenn sein benachbartes = = gesättigt ist, außer daß p = 1 und = = ungesättigt ist, wenn R^{13} für O steht;
q	für 0-4 steht;
r	für 1 oder 2 steht;
X^1	für H, $-NO_2$, CF_3, CN, OH, C_{1-7}-Alkyl, Halogen, C_{1-7}-Alkylthio, C_{1-7}-Alkoxy, $-X^{11}COOR^6$ oder $-X^{11}NR^4R^5$- steht;
X^2 und X^3	unabhängig für H, -OH, $-NO_2$, Halogen, C_{1-7}-Alkylthio, C_{1-7}-Alkyl oder C_{1-7}-Alkoxy stehen;
X^4	für S, O, CH_2 oder NR^{18} oder NR^8 steht;
X^5	für H, CF_3, CN, $-COOR^6$, NO_2 oder Halogen steht,
X^6	für O oder HH steht;
X^7	für O, S, HH oder NR^{15} steht;
X^8	für H, C_{1-7}-Alkyl steht;
X^9 und X_a^9	unabhängig für NR^{18} oder O stehen;
X^{10}	für F, Cl oder Br stellt;
X^{11}	fehlt oder für lineares oder verzweigtes C_{1-4}-Alkyliden steht;
X^{12}	für lineares oder verzweigtes C_{1-4}-Alkyliden steht;
--	eine gesättigte oder ungesättigte Bindung bedeutet;

oder von



III

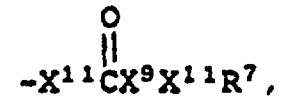
worin

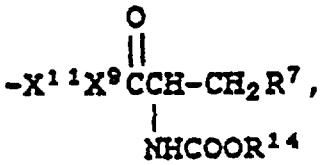
R^1, R^2, R^4, R^5, R^6, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, p, q, r, X^1, X^2, X^3, X^5, X^6, X^7, X^8, X^9, X^{10}, X^{11} und X^{12} die oben gegebenen Definitionen besitzen,

R^3 für $-X^{11}NR^{18}(CH_2)_q R^{16}$,

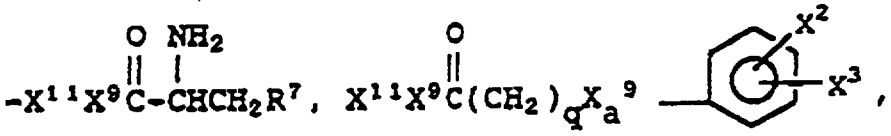


$-NH(CH_2)_{2-3}NHR^7$, $-NH(CH_2)_{2-3}NHCOR^7$,

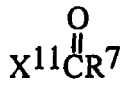




$X^{11}NR^{18}CX_a{}^9X^{11}R^7$,

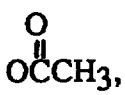


$X^{11}NR^{18}SO_2(CH_2)_qR^7$ oder



steht;

R^7 für α- oder β-Napthyl, substituiertes oder unsubstituiertes Phenyl (worin die Substituenten 1 bis 2 von Halogen, $-NO_2$, -OH, $-X^{11}NR^4R^5$, C_{1-7}-Alkyl, CF_3, CN, SCF_3, C≡CH, CH_2SCF_3,



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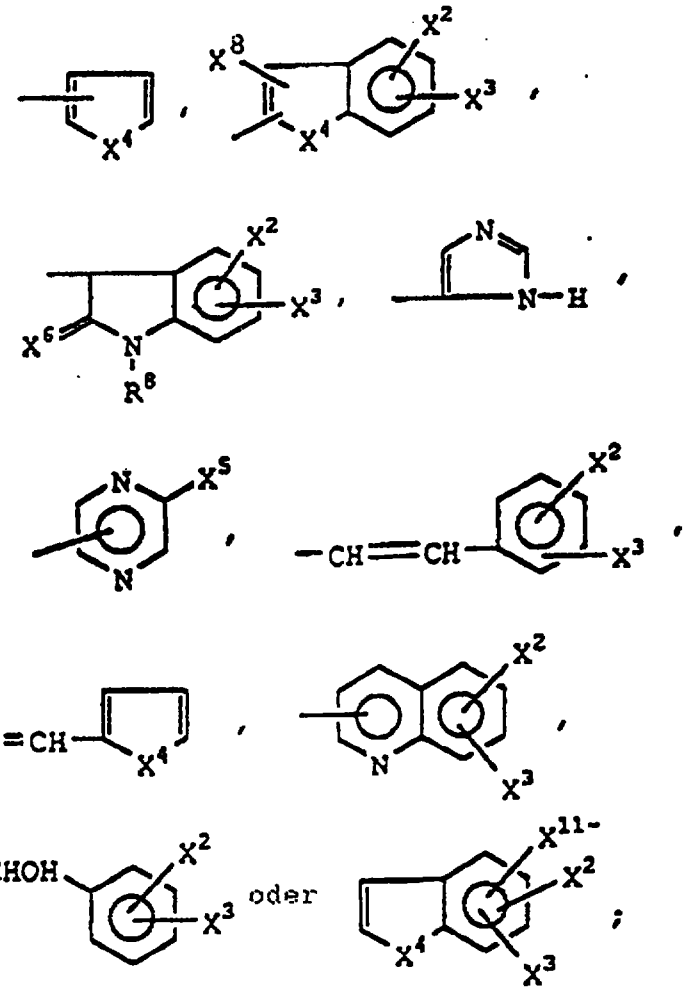
* C L M S *

$OCHF_2$, SH, SPh, PO_3H, C_{1-7}-Alkoxy, C_{1-7}-Alkylthio oder COOH bedeuten), 2-, 3-, 4-Pyridyl,



steht;

R^{16} für α- oder β-Napthyl oder 2-Indolyl steht;

R^{18} für H oder C_{1-7}-Alkyl steht; und

= eine gesättigte oder ungesättigte Bindung bedeutet;

oder ein pharmazeutisch verträgliches Salz davon zur Herstellung eines Medikaments zur Behandlung oder Prävention von Angst.

2. Verwendung nach Anspruch 1, worin das Derivat D,L-4-(3,4-Dichlorbenzoyl-amion)-5-(dipentylamino)-5-oxopentansäure, (±)-4-[(3,4-Dichlorbenzoy])-amino]-5-[(3-methoxyproxyl)-pentylamino]-5-oxo-pentansäure, 3(S)-(-)-N-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-1H-indol-2-carobxamid, (R)-N-(2,3-Dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N'-(3-methylphenyl)-harnstoff oder ein pharmazeutisch verträgliches Salz davon ist.

3. Verwendung eines Derivats nach Anspruch 1 oder Anspruch 2 zur Herstellung eines Medikaments zur Behandlung oder Prävention der Entzugsreaktion, die durch einen Entzug der chronischen Behandlung mit Diazepam bei einem Säuger hervorgerufen wird.

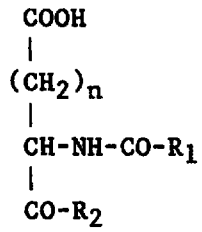
4. Verwendung eines Derivats nach Anspruch 1 oder Anspruch 2 zur Herstellung eines Medikaments zur Behandlung oder Prävention der Entzugsreaktion, die durch einen Entzug der chronischen Verwendung von Kokain bei einen, Säuger hervorgerufen wird.

5. Verwendung eines Derivats nach Anspruch 1 oder Anspruch 2 zur Herstellung eines Medikaments zur Behandlung oder Prävention der Entzugsreaktion, die durch einen Entzug der chronischen Verwendung von Alkohol bei einem Säuger hervorgerufen wird.

6. Verwendung eines Derivats nach Anspruch 1 oder Anspruch 2 zur Herstellung eines Medikaments zur Behandlung oder Prävention der Entzugsreaktion, die durch einen Entzug der chronischen Verwendung von Nikotin bei einem Säuger hervorgerufen wird.

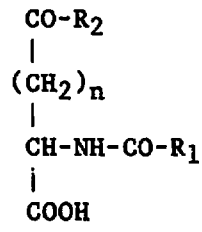
Revendications

1. Utilisation de dérivés pharmaceutiquement actifs de l'acide D,L-glutamique et de l'acide D,L-aspartique de formule :



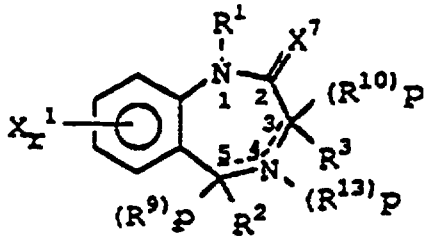
I

ou



IA

dans laquelle
n vaut 1 ou 2 ;
R_1 est un groupe phényle mono-, di-, ou tri-substitué par des groupes alkyle en C_{1-4} linéaires ou ramifiés, qui peuvent être identiques ou différents, ou par des atomes d'halogène, par un groupe cyano ou par un groupe trifluorométhyle, et
R_2 est choisi dans le groupe constitué des groupes morpholino, pipéridino et amino avec un ou deux groupes alkyle linéaires, ramifies ou cycliques substituants contenant de 1 à 8 atomes de carbone, qui peuvent être identiques ou différents ;
ou



II

dans laquelle
R_1 représente H, un groupe alkyle en C_{1-6} linéaire ou ramifié, alcényle en C_{1-5}, alcynyle en C_{1-5}, $-X^{12}COOR^5$, $-X^{11}$cyclo(alkyle en C_{3-7}), $-X^{12}NR^4R^5$, $-X^{12}CONR^4R^5$, $-X^{12}CN$ ou $-X^{11}CX_3^{10}$;
R^2 représente H ou un groupe alkyle en C_{1-7}, phényle substitué ou non substitué (dans lequel les substituants peuvent être un ou deux substituants parmi un groupe halogèno, alkyle en C_{1-7}, alcoxy en C_{1-7}, alkylthio en C_{1-7}, carboxyle, carboxy(alkyle en C_{1-7}), nitro, $-CF_3$ ou hydroxyle), 2-, 3-, 4-

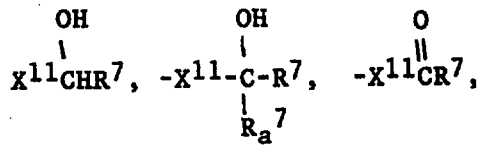
pyridyle,



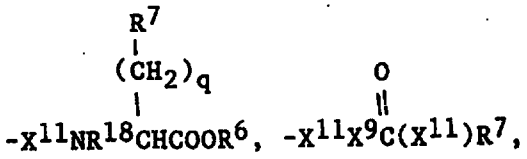
,

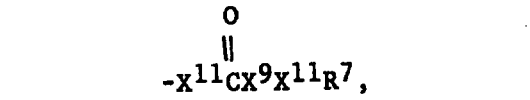
$-X^{12}SCH_3$, $-X^{12}SOCH_3$ $-X^{12}SO_2CH_3$, ou $-X^{12}COOR^6$;

R^3 représente $-X^{11}R^7$,

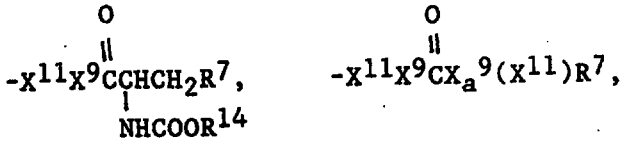


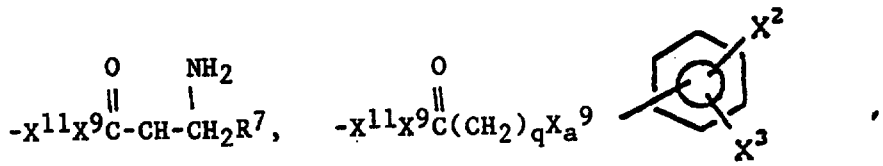
$-X^{11}NR^{18}(CH_2)_qR^7$,





$-NH(CH_2)_{2-3}NHR^7$, $-NH(CH_2)_{2-3}NHCOR^7$,





,

$-X^{11}NR^{18}SO_2(CH_2)_qR^7$ ou



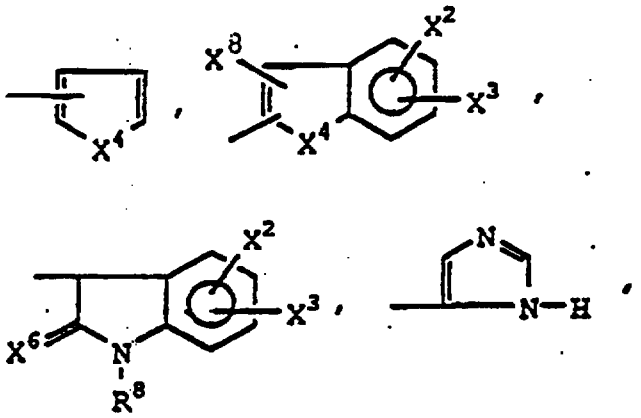
où

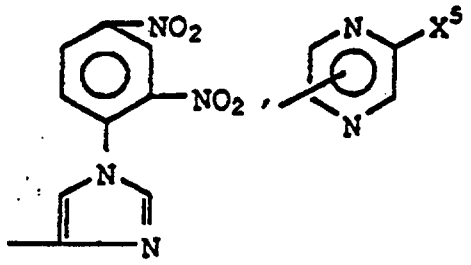
R_4 et R_5 sont indépendamment R^6 ou en combinaison avec le N du groupe NR^4R^5 forment un noyau hétérocyclique à 4-7 chaînons benzo-condensé ou un noyau hétérocyclique à 4-7 chaînons, saturé ou insaturé non substitué ou mono- ou di-substitué ou ledit noyau hétérocyclique ou ledit noyau hétérocylique benzo-condensé, qui comprend en outre un second hétéro-atome choisi parmi O et

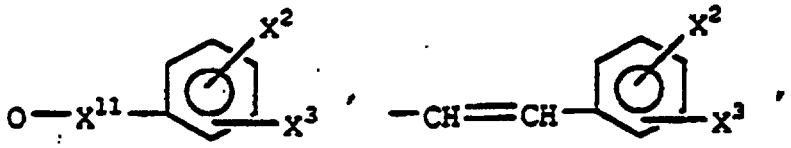
NCH_3, et le(s) substituant(s) est/sont indépendamment choisi(s) parmi les groupes alkyle en C_{1-4} ;
R^6 représente H ou un groupe alkyle en C_{1-7}, cycloalkyle en C_{3-7}, phényle substitué ou non substitué ou phényl(alkyle en C_{1-7}) substitué ou non substitué dans lequel les substituants du groupe phényle ou phényl(alkyle en C_{1-7}) peuvent être un ou deux atomes d'halogène ou groupes alkyle en C_{1-7}, alcoxy en C_{1-7}, nitro ou CF_3 ;
R_7 et R_a^7 sont indépendamment un groupe α- ou β-naphtyle, phényle substitué ou non substitué (dans lequel les substituants peuvent être 1 ou 2 atomes d'halogène ou groupes $-NO_2$, -OH, $-X^{11}NR_4R_5$, alkyle en C_{1-7}, CF_3, CN, SCF_3, C≡CH, CH_2SCF_3,

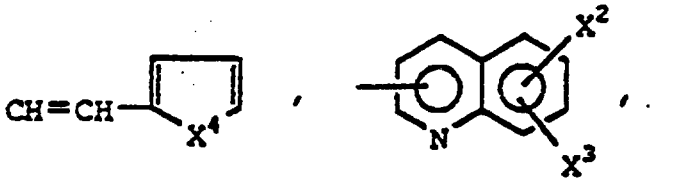


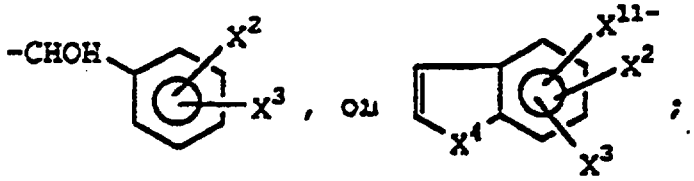
$OCHF_2$, SH, SPh, PO_3H(alcoxy en C_{1-7}) ou alkylthio en C_{1-7}, COOH), 2-, 3-, 4-pyridyle



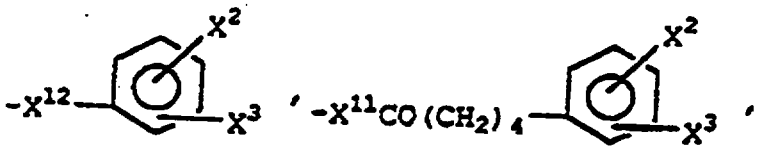




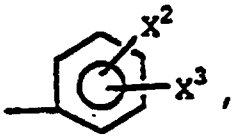




R^8 représente H ou un groupe alkyle en C_{1-7}, cycloalkyle en C_{3-7}, $-X^{12}CONH_2$, $-X^{12}COOR^6$, $-X^{12}$-cyclo(alkyle en C_{3-7}), $-X^{12}NR^4R^5$,

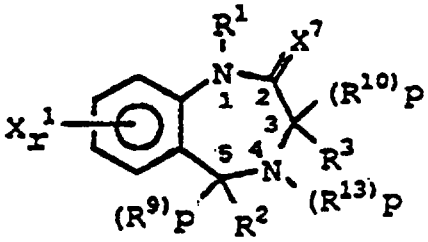


R^9 et R^{10} sont indépendamment H, -OH ou $-CH_3$;
R^{11} et R^{12} sont indépendamment un groupe alkyle en C_{1-7} ou cycloalkyle en C_{3-7} ;
R^{13} est H ou un groupe alkyle en C_{1-7}, acyle, O, ou cycloalkyle en C_{3-7} ;
R^{14} est un groupe alkyle en C_{1-7} ou phényl(alkyle inférieur) ;
R^{15} est H ou un groupe alkyle en C_{1-7}



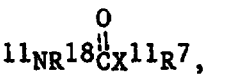
ou $-NH_2$;
R^{18} est H ou un groupe alkyle en C_{1-7} ou acyle ;

p vaut 0 lorsque sa = =adjacente est insaturée et 1 lorsque sa = =adjacente est saturée sauf lorsque R^{13} vaut 0, p=1 et = = est insaturée;
q vaut 0-4 ;
r vaut 1 ou 2 ;
X^1 est H, $-NO_2$, CF_3, CN, OH, ou un groupe alkyle en C_{1-7}, halogéno, alkylthio en C_{1-7}, alcoxy en C_{1-7}, $-X^{11}COOR^6$ ou $-X^{11}NR^4R^5$;
X^2 et X^3 sont indépendamment H, -OH, $-NO_2$ ou un groupe halogéno, alkylthio en C_{1-7}, alkyle en C_{1-7} ou alcoxy en C_{1-7} ;
X^4 est S, O, CH_2 ou NR^{18} ou NR^8 ;
X^5 est H, CF_3, CN, $-COOR^6$, NO_2 ou halogéno ;
X^6 est O ou HH ;
X^7 est O, S, HH ou NR^{15} ;
X^8 est H ou un groupe alkyle en C_{1-7} ;
X^9 et X_a^9 sont indépendamment NR^{18} ou O ;
X^{10} est F, Cl, ou Br ;
X^{11} est absent ou représente un groupe alkylidène ramifié ou linéaire en C_{1-4} ;
X^{12} est un groupe alkylidène linéaire ou ramifié en C_{1-4} ;
-- est une liaison saturée ou insaturée ;
ou

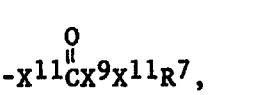


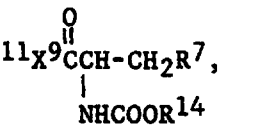
III

dans laquelle R^1, R^2, R^4, R^5, R^6, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, p, q, r, X^1, X^2, X^3, X^5, X^6, X^7, X^8, X^9, X^{10}, X^{11} et X^{12}, sont tels que définis ci-dessus ;
R^3 est $-X^{11}NR^{18}(CH_2)_qR^{15}$,

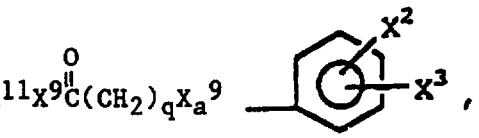


$-NH(CH_2)_{2-3}NHR^7$, $-NH(CH_2)_{2-3}NHCOR^7$,





$X^{11}NR^{18}CX_a^9X^{11}R^7$



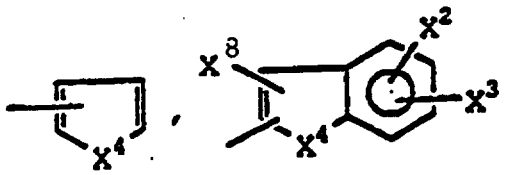
$X^{11}NR^{18}SO_2(CH_2)_qR^7$ ou

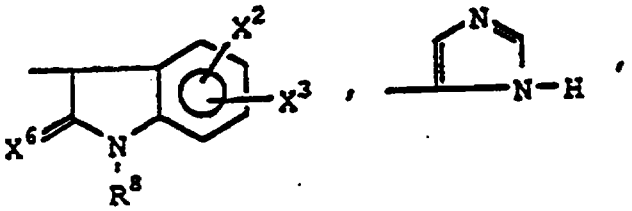
;

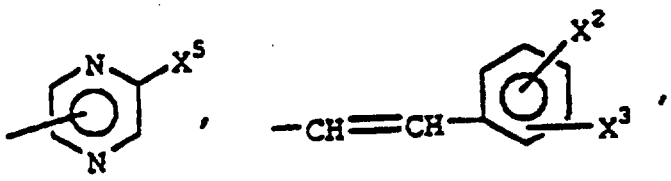
R^7 représente un groupe α- ou β-naphtyle, phényle substitué ou non substitué (dans lequel les substituants peuvent être un ou deux atomes d'halogène ou groupes $-NO_2$, -OH, $-X^{11}NR^4R^5$, alkyle en C_{1-7}, CF_3, CN, SCF_3, C≡CH, CH_2SCF_3 ,

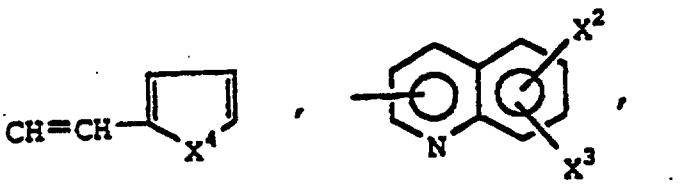


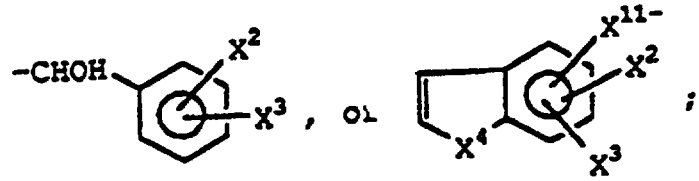
$OCHF_2$, SH, SPh, PO_3H, alcoxy en C_{1-7}, alkylthio en C_{1-7} ou COOH), 2-, 3,- 4-pyridyle,











R^{16} est un groupe alpha ou bêta-naphtyle ou 2-indolyle ;
R^{18} est H ou un groupe alkyle en C_{1-7} ; et
= est une liaison saturée ou insaturée ;
ou d'un de leurs sels pharmaceutiquement acceptables pour la préparation d'un médicament pour le traitement ou la prévention de l'anxiété.

2. Utilisation selon la revendication 1, dans laquelle le dérivé est l'acide DL-4-(3,4-dichlorobenzoylamino)-5-(dipentyl-amino)-5-oxopentanoïque, l'acide (±)-4-((3,4-dichlorobenzoyl)-amino)-3-((3-méthoxyproxyl)-pentylamino)-5-oxo-pentanoïque, le 3(S)-(-)-N-(2,3-dihydro-1-méthyl-2-oxo-5-phényl-1H-1-4-benzodiazépin-3-yl)-1H-indol-2-carboxamide, la (R)-N-(2,3-dihydro-1-méthyl-2-oxo-5-phényl-1H-1,4-benzodiazapine-3-yl)-N'-(3-méthylphényl)urée ou un de leurs sels pharmaceutiquement acceptables.

3. Utilisation d'un dérivé tel que défini dans la revendication 1 ou 2 pour la préparation d'un médicament pour traiter ou prévenir la réponse au retrait produite par la suppression du traitement chronique avec le diazépam chez un mammifère.

4. Utilisation d'un dérivé tel que défini dans la revendication 1 ou 2, pour la préparation d'un médicament pour traiter ou prévenir la réponse au retrait produite par la suppression de l'emploi chronique de cocaïne chez un mammifère.

5. Utilisation d'un dérivé tel que défini dans la revendication 1 ou 2 pour la préparation d'un médicament pour traiter ou prévenir la réponse au retrait produite par la suppression de l'emploi chronique d'alcool chez un mammifère.

6. Utilisation d'un dérivé tel que défini dans la revendication 1 ou 2 pour la préparation d'un médicament pour traiter ou prévenir la réponse au retrait produite par la suppression de l'emploi chronique de la nicotine chez un mammifère.