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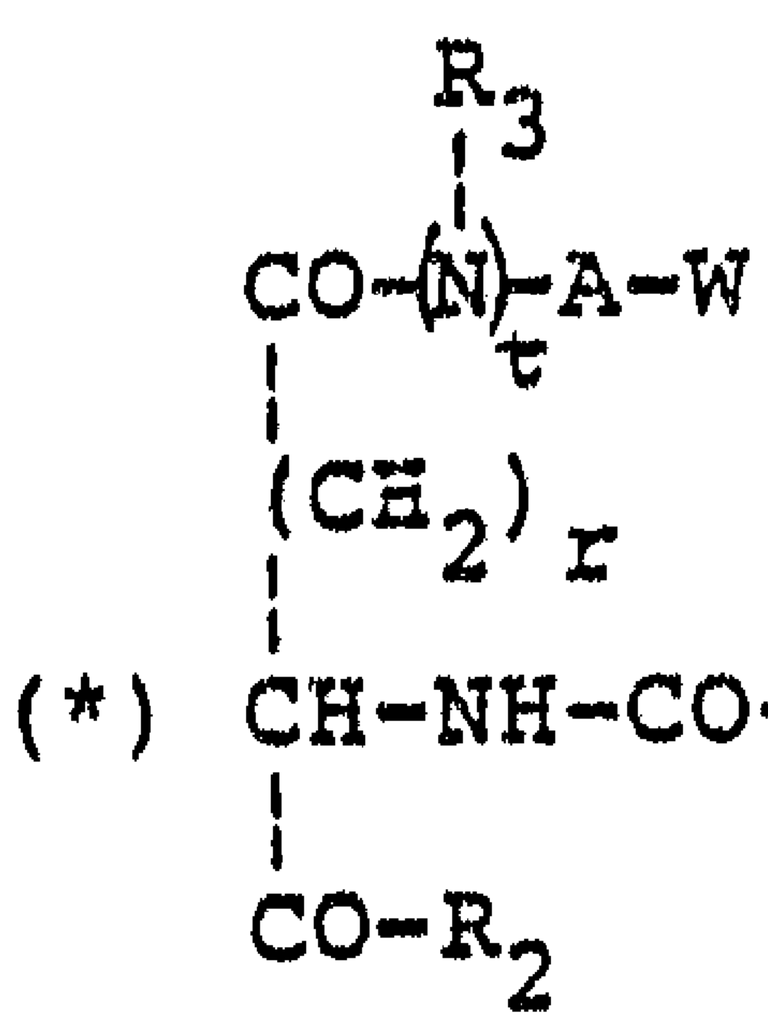
(54) Titre : DERIVES BASIQUES DE L'ACIDE GLUTAMIQUE ET DE L'ACIDE ASPARTIQUE, UTILISES COMME ANTAGONISTES DE LA GASTRINE OU DE LA CHOLECYSTOKININE

(54) Title: BASIC DERIVATIVES OF GLUTAMIC ACID AND ASPARTIC ACID AS GASTRIN OR CHOLECYSTOKININ ANTAGONISTS



(I)

(57) Abrégé/Abstract:
Compounds of general formula (I), in which r is 1 or 2, R_1 is selected independently from: unsubstituted, mono- or di-substituted phenyl groups, unsubstituted, mono- or di-substituted phenylamino groups, the 2(beta)-naphthyl group, and heterocyclic, monocyclic or dicyclic groups; R_2 is selected independently from: heterocyclic spiro groups, aminoalkyladamantyl groups, alkylamino groups, C_4-C_{10} cycloalkylamino groups, and dicyclic amino groups (condensed); R_3 is H, CH_3 or C_2H_5; A is a bond or a linear or branched alkylene group comprising from 1 to 4 carbon atoms; W is a tertiary amino group or a heterocyclic group.

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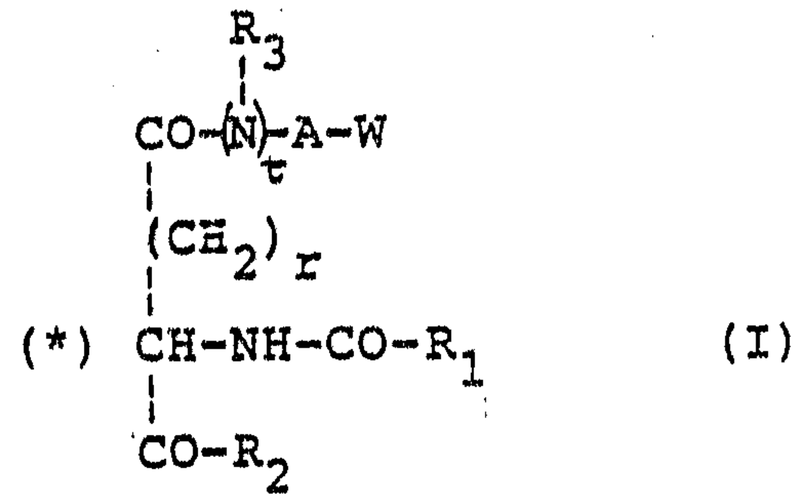


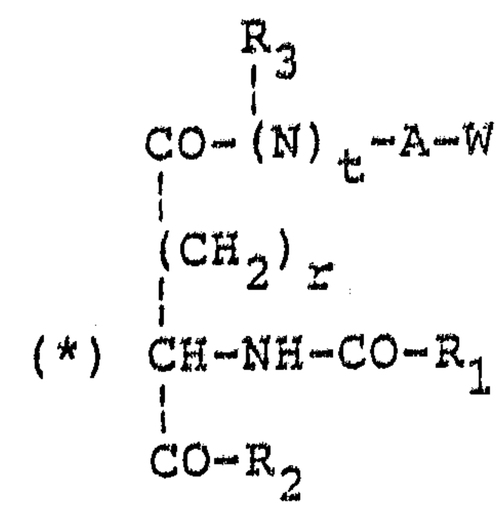
(I)

(57) Abstract

Compounds of general formula (I), in which r is 1 or 2, R_1 is selected independently from: unsubstituted, mono- or di-substituted phenyl groups, unsubstituted, mono- or di-substituted phenylamino groups, the 2(beta)-naphthyl group, and heterocyclic, monocyclic or dicyclic groups; R_2 is selected independently from: heterocyclic spiro groups, aminoalkyladamantyl groups, alkylamino groups, C_4-C_{10} cycloalkylamino groups, and dicyclic amino groups (condensed); R_3 is H, CH_3 or C_2H_5; A is a bond or a linear or branched alkylene group comprising from 1 to 4 carbon atoms; W is a tertiary amino group or a heterocyclic group.

BASIC DERIVATIVES OF GLUTAMIC ACID AND ASPARTIC ACID AS GASTRIN OR CHOLECYSTOKININ ANTAGONISTS

The subject of the present invention is basic derivatives of glutamic acid and aspartic acid which can be represented by the general formula indicated below:



(I)

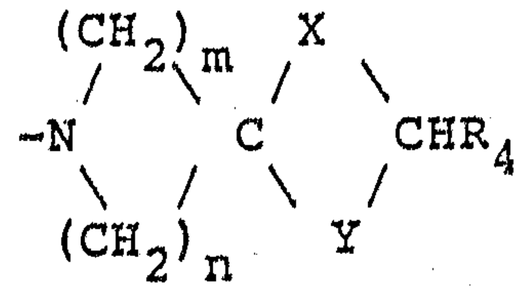
and in which r is 1 or 2;

R1 is selected independently from:

unsubstituted phenyl; mono- or di-substituted phenyl groups in which the substituents are selected from the halogens (chloro, fluoro, and bromo), linear or branched C_1-C_4 alkyl groups, and nitro, cyano, methoxy, and trifluoromethyl groups; an unsubstituted phenylamino group; phenylamino groups mono- or di-substituted as described above for the phenyl group; the 2(beta)-naphthyl group; heterocyclic, monocyclic or dicyclic groups selected from an unsubstituted pyridyl group, pyridyl groups mono- or di-substituted with methyl, chloro, furyl (2- or 3-yl), indolyl (2- or 3-yl), isoindolyl (3-yl), benzofuranyl (2- or 3-yl) quinolinyl (2- or 3-yl) or isoquinolinyl (3-yl);

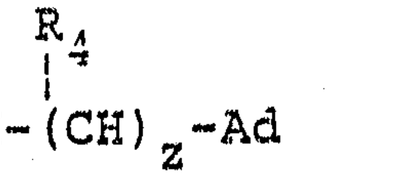
R_2 is selected independently from:

1) a heterocyclic spiro group represented by:



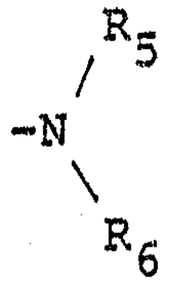
in which m and n are selected independently and may have values of between 1 and 3, provided that the ring formed consists of at least 5 atoms, X and Y are selected independently from $(CH\text{-}R_4)_z$, TCH_2 and CH_2T in which T is O or S, and in which R_4 is a group selected independently from H, linear and branched C_1-C_4 alkyl groups, OCH_3, and OH, and z may have values of from 0 to 3, provided that the ring formed consists of at least 3 atoms;

2) an aminoalkyladamantyl group represented by:



in which z and R_4 have the meanings given above and Ad is adamantyl (1- or 2-yl);

3) an alkylamino group represented by:



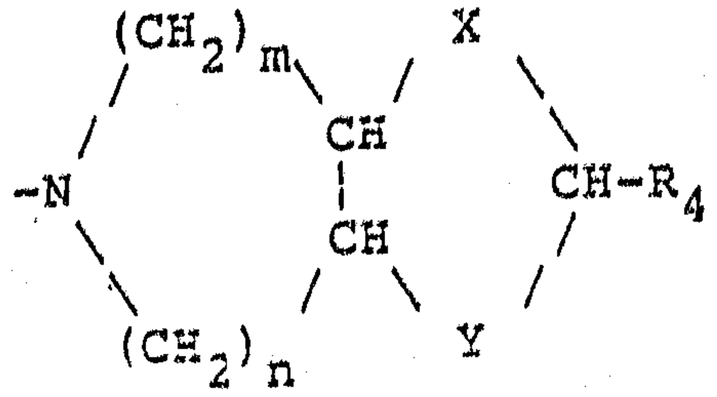
in which R_5 is a linear or branched alkyl chain containing from 4 to 10 carbon atoms or a C_5-C_{10} cycloaklyl group, or a linear or branched alkoxyalkyl group containing from 4 to 7 carbon atoms, and R_6 is selected independently from H, alkyl groups, linear and

3

branched alkoxyalkyl groups containing from 4 to 7 carbon atoms, and C_5-C_{10} cycloalkyl groups;

4) a C_4-C_{10} cycloalkylamine;

5) a dicyclic amino group (condensed) represented by:



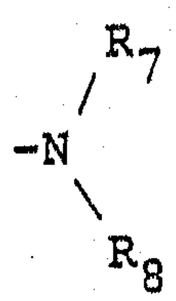
and in which m, n, X, Y, and R_4 have the meanings given above;

R3 is H, CH_3 or C_2H_5;

A is a bond or a linear or branched alkylene group comprising from 1 to 4 carbon atoms;

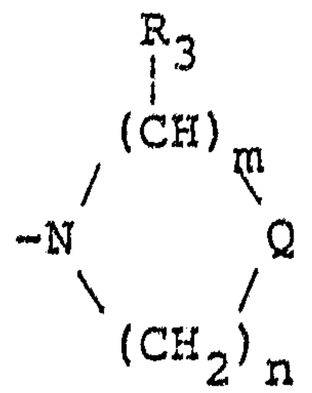
W may be:

1) a tertiary amino group represented by:



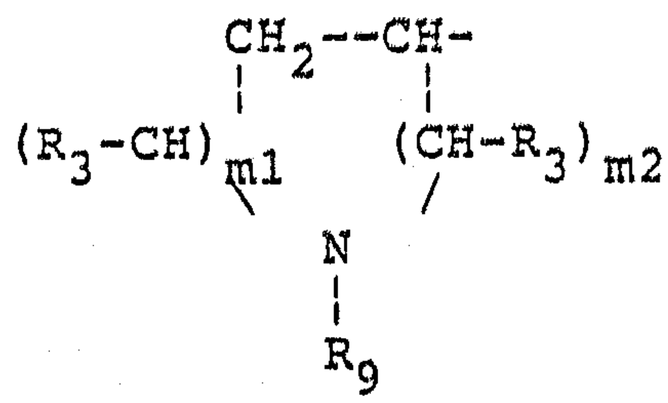
in which R_7 and R_8 are, independently, hydrogen or a linear or branched alkyl group comprising from 1 to 5 carbon atoms, provided that R_7 and R_8 are not both hydrogen;

2) a heterocyclic group represented by:



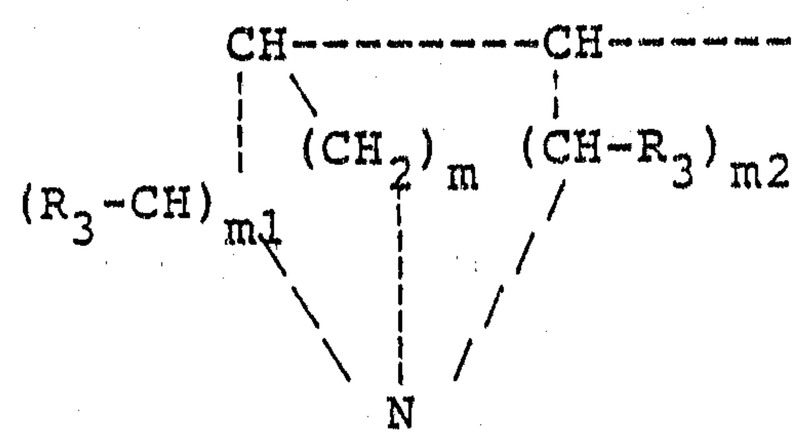
in which R_3, m and n have the meanings given above and Q may be a bond, CH_2, oxygen, sulphur or nitrogen, N-substituted with R_9, R_9 being a group selected independently from H, linear and branched C_1-C_4 alkyl groups, phenyl and benzyl groups, of which the aromatic groups may be unsubstituted or mono- or di-substituted as described for the phenyl group in R_1;

3) a heterocyclic group represented by:



in which m1 and m2 are selected independently and may have values of between 0 and 3 and R_3 and R_9 have the meanings given above;

4) a heterocyclic group represented by:



in which m, m1, m2 and R_3 have the meanings given above;

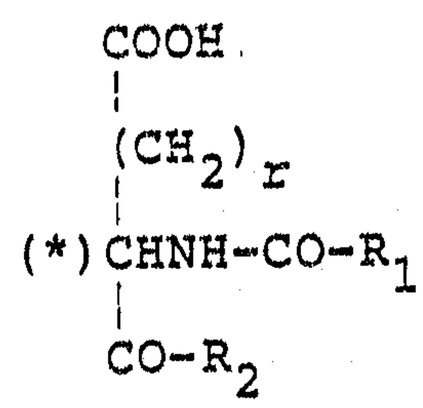
t is always 1; it may also have a value of 0, but only if W is a heterocyclic group selected from group 2, in which Q is $N-R_9$.

The stereochemistry of the compounds claimed at the chiral centre marked with an asterisk in formula (I) may be racemic (R, S), R (rectus), or S (sinister), r is preferably 2, and R_3 is preferably hydrogen.

According to the nature of the substitutents at R_1, R_2, A and W, the compounds of the present invention have been shown to have a potent antagonistic effect on gastrin (anti-CCK-B activity) and on cholecystokinin (anti-CCK-A activity) and can thus be used to advantage in the treatment of various diseases in man which are linked to imbalances in the physiological levels of gastrin, CCK, or other biologically active polypeptides related thereto, both at the level of the gastro-intestinal system and at the level of the central nervous system (CNS), or in other organs or systems in which these biologically active peptides play a physiological or pathological role. For example, it is possible to predict the advantageous use of these compounds, at the gastro-intestinal level, for the treatment of diseases linked to disturbances of motility and mucotrophism such as colitis, biliary dyskinesia, pancreatitis, gastritis, peptic ulcers and certain forms of intestinal tumours which are sustained by gastrin or polypeptide hormones related thereto, and at the level of the CNS, for the treatment of mental disorders such as, for example, anorexia, psychosis and anxiety states. Another use could be the treatment and prevention of some eye conditions such as, for example, myosis brought about in the course of the surgical treatment of cataracts or of chronic eye

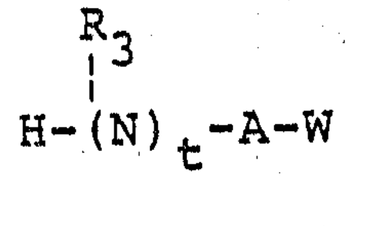
inflammation. As well as being active at the receptor level, many of the compounds of the invention also have an intrinsic antispastic effect on muscles, acting directly at the level of the smooth muscle cells. Thus, some of the compounds of the invention have very potent myorelaxant activity even on areas, such as the urino-genital area, which are not connected with the neurophysiological mediators mentioned above, that is, gastrin and CCK, but, inter alia, also linked to a potent anti-serotoninic action. As a result of this potent myorelaxant effect, it is also possible to predict their favourable use for the treatment of pathological conditions such as, for example, incontinence, other problems with urination or, more generally, spasms and dyskinesia of the ureteral, vesical and uterine musculature.

The method of preparing the derivatives of the invention consists of the amidation of acid derivatives of formula (II):



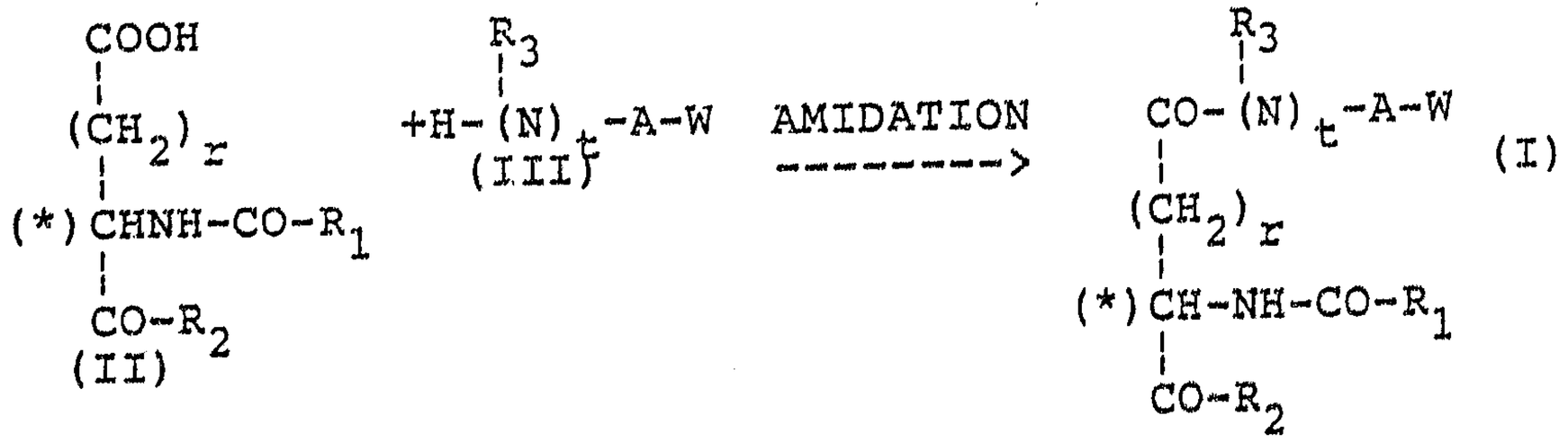
(II)

in which r, R_1 and R_2 have the meanings given above, with suitable amines of formula (III):



(III)

in which R_3, t, A and W have the meanings given above, to give the corresponding derivatives of formula (I) according to the following scheme:



where (*) indicates the chiral centre of the molecule.

The amidation process is preferably effected with the use of the mixed anhydride method, in an inert solvent, at a temperature of between -15° and +15° or by other suitable conventional methods.

The compounds of formula (I) may be isolated from the reaction mass as such, or in the form of salts by reacting them, in an inert solvent, with the appropriate quantities of inorganic acids such as, for example, hydrochloric acid, or organic acids such as, for example, oxalic acid or maleic acid.

The starting acid derivatives of formula (II) were prepared as described (Makovec et al, J. Med. Chem. 35 (1992), 28-38) and the amines of formula (III) are available commercially or were prepared by conventional methods described in the literature. The following example is given in order further to illustrate the invention:

Example 1

Preparation of: (RS) 1-[4'-(ethylenamino)morpholinyl]-1-oxo-4-[(3,4-dimethylbenzoyl)-amino]-5-(dipentylamino)-5-oxopentane, (compound 44).

60 g (0.1433 moles) of (R, S) 4-[(3,4-dimethylbenzoyl)

amino]-5-(dipentylamino)-5-oxopentanoic acid [tomoglumide, CAS Registry Number: 102742 - 69-8] and 20 ml of triethylamine (0.1435 moles) were dissolved in 600 ml of tetrahydrofuran and the mixture was cooled to -10°C. This temperature was maintained and 14 ml of ethyl chloroformate (0.1469 moles) were added. Upon completion of the addition, the mixture was left to react for 15 minutes, still at low temperature and then 20 ml of 4-(2-aminoethyl)morpholine (0.1535 moles) were added slowly and the temperature was kept below -5°C. Upon completion of the addition, the reaction mass was kept at low temperature for a further hour and then at ambient temperature for about 12 hours. The solvent was evaporated; the solid obtained was taken up with water and filtered. It was dried in an oven to give 57 g (0.1074 moles) of the product with a yield of 75%.

50 g (0.0942 moles) of the free base obtained was suspended in 250 ml of ethyl acetate and at 5°C a solution of HCl in acetone (10% excess) was quickly added dropwise. The product started to precipitate almost immediately and was filtered and washed with ethyl acetate and isopropyl ether. It was dried in air bath at 60°C to give 49 g of the crude product which was crystallised with ethyl acetate. After cooling, the precipitate was filtered and dried in an air bath at 60°C to give 46 g (0.0811 moles) of the product with an overall yield of 70.5%.

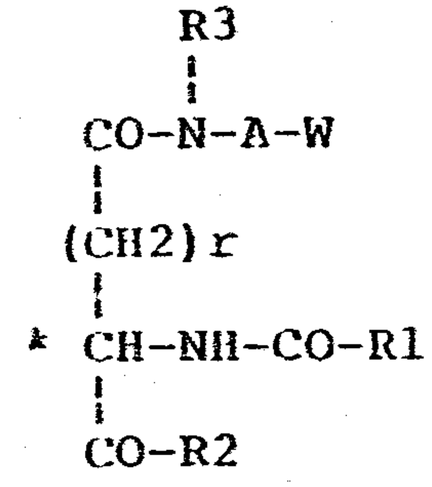
M.P. 150-53°C.

TLC ($nBuOH/AcOH/H_2O$ 5:2:2) pure, rf 0.65.

All the compounds of formula (I) were synthesised with the use of the same method (see the scheme given

above). Table 1 below gives some of the compounds obtained with some of their identifying characteristics.

TABLE 1 DERIVATIVES OF FORMULA



COMPOUND (*Note 1)	R1	R2	R3 -N-A	W
1	3,5-dichloro-phenyl	8-azaspiro[4.5]decan-8-yl	-----	4-methyl-1-piperazinyl
2	3,5-dichloro-phenyl	8-azaspiro[4.5]decan-8-yl	-----	4-methyl-1-piperazinyl
3	3,5-dichloro-phenyl	8-azaspiro[4.5]decan-8-yl	ethylenamino	4-morpholinyl
4	3,5-dichloro-phenyl	8-azaspiro[4.5]decan-8-yl	ethylenamino	dimethylamino
5	3,5-dichloro-phenyl	8-azaspiro[4.5]decan-8-yl	ethylenamino	dimethylamino
6	3,5-dichloro-phenyl	8-azaspiro[4.5]decan-8-yl	ethylenamino	4-methyl-1-piperazinyl
7	3-chloro-phenyl	8-azaspiro[4.5]decan-8-yl	-----	4-methyl-1-piperazinyl
8	2-pyridyl	8-azaspiro[4.5]decan-8-yl	ethylenamino	4-morpholinyl
9	3-trifluoromethyl-phenyl	8-azaspiro[4.5]decan-8-yl	ethylenamino	4-morpholinyl
10	2-furyl	8-azaspiro[4.5]decan-8-yl	ethylenamino	4-morpholinyl
11	3,5-dichloro-phenyl	8-azaspiro[4.5]decan-8-yl	-----	2-amino-quinuclidyl
12	2-naphthyl	8-azaspiro[4.5]decan-8-yl	-----	4-methyl-1-piperazinyl

COMPOUND (*Note 1)	FORMULA	MELTING POINT (C)°	TLC (Rf) (*Note 2)	SPECIFIC ROTATION (Configuration) (* Note 3,4)
1	C26H36C12N403 x HCl	119/22	0.56	-66.4 (R)
2	C26H36C12N403 x HCl	115/19	0.53	+66.5 (S)
3	C27H38C12N404	69/72	0.60	-36.99 (R)
4	C25H36C12N403 x C2H204	85/91	0.61	-18.4 * (R)
5	C27H40C12N403 x HCl	109/114	0.64	-52.2 (R)
6	C28H41C12N503 x C8H808	165/66	0.56	-11.9 * (R)
7	C26H37ClN403 x HCl	113/116	0.54	-69.1 (R)
8	C26H39N504 x 2HCl	69/71(dec)	0.53	-57.4 (R)
9	C28H39F3N304	87/90	0.57	-52.4 (R)
10	C25H38N405	101/103	0.58	-70.8 (R)
11	C28H38C12N403 x HCl	155/61	0.53	-39.5 (R)
12	C30H40N403 x HCl	110/113	0.58	-84.7 (R)

COMPOUND (*Note 1)	R1	R2	R3 / -N-A	W
13	3,5-dichloro-phenyl	3-azaspiro[5.5]-undecan-3yl	-----	4-methyl-1-piperazinyl
14	3,4-dimethyl-phenyl	butylamino	ethylenamino	4-morpholinyl
15	3,4-dimethyl-phenyl	butylamino	propylenamino	4-benzyl-1-piperazinyl
16	3,4-dimethyl-phenyl	pentylamino	ethylenamino	4-morpholinyl
17	4-nitrophenyl	pentylamino	ethylenamino	4-morpholinyl
18	3,4-difluoro-phenyl	pentylamino	ethylenamino	4-morpholinyl
19	3,4-dimethyl-phenyl	pentylamino	ethylenamino	4-benzyl-1-piperazinyl
20	3,4-dimethyl-phenyl	pentylamino	propylenamino	4-benzyl-1-piperazinyl
21	3,4-dimethyl-phenyl	hexylamino	ethylenamino	4-morpholinyl
22	3,4-dimethyl-phenyl	hexylamino	propylenamino	4-benzyl-1-piperazinyl
23	3-chloro-phenyl	(3,3-dimethylbutyl)amino	-----	4-methyl-1-piperazinyl
24	3-chloro-phenylamino	(3-ethyl-3-methyl-pentyl)-amino	ethylenamino	4-morpholinyl
25	3,4-dimethyl-phenyl	dibutylamino	ethylenamino	dimethylamino
26	3,4-dimethyl-phenyl	dibutylamino	ethylenamino	diethylamino
27	3,4-dimethyl-phenyl	dibutylamino	propylenamino	dimethylamino
28	3,4-dimethyl-phenyl	dibutylamino	ethylenamino	4-morpholinyl
29	3,4-dimethyl-phenyl	dibutylamino	propylenamino	4-morpholinyl
30	3,4-dimethyl-phenyl	dibutylamino	ethylenamino	1-piperidinyl

COMPOUND (*Note 1)	FORMULA	MELTING POINT (C)°	TLC (Rf) (*Note 2)	SPECIFIC ROTATION (Configuration) (* Note 3,4)	
13	C27H38C12N403 x HCl	121/26	0.66	-69.6	(R)
14	C24H38N404	127/30	0.51	0	(R,S)
15	C32H47N503 x 2 HCl	161/65	0.54	0	(R,S)
16	C25H40N404	118/20	0.55	0	(R,S)
17	C23H35N506	138/41	0.60	0	(R,S)
18	C23H34F2N404	135/38	0.52	0	(R,S)
19	C32H47N503	134/37	0.53	0	(R,S)
20	C33H49N503 x 2 HCl	100/07	0.57	0	(R,S)
21	C26H42N404	140/42	0.62	0	(R,S)
22	C34H51N503 x 2 HCl	140/44	0.60	0	(R,S)
23	C23H35ClN403 x HCl	113/15	0.58	-37.3	(R)
24	C26H42ClN504	165/67	0.59	+24.9	(R)
25	C26H44N403	110/11	0.51	0	(R,S)
26	C28H48N403	104/07	0.58	0	(R,S)
27	C27H46N403	96/9	0.53	0	(R,S)
28	C28H46N404	138/40	0.57	0	(R,S)
29	C29H48N404	61/63	0.56	0	(R,S)
30	C29H48N403	109/11	0.63	0	(R,S)

COMPOUND (*Note 1)	R1	R2	R3 | -N-A	W
31	3,4-dimethyl-phenyl	dibutylamino	methylamino	1-ethyl-pyrrolidin-2-yl
32	phenyl	dipentylamino	ethylenamino	4-morpholinyl
33	4-methyl-phenyl	dipentylamino	ethylenamino	4-morpholinyl
34	4-cyano-phenyl	dipentylamino	ethylenamino	4-morpholinyl
35	3,4-dimethoxy-phenyl	dipentylamino	ethylenamino	4-morpholinyl
36	4-isopropyl-phenyl	dipentylamino	ethylenamino	4-morpholinyl
37	3,4-dichloro-phenyl	dipentylamino	ethylenamino	4-morpholinyl
38	3,4-dichloro-phenyl	dipentylamino	propylenamino	4-morpholinyl
39	3,5-dichloro-phenyl	dipentylamino	ethylenamino	4-morpholinyl
40	3,4-dimethyl-phenyl	dipentylamino	ethylenamino	dimethylamino
41	3,4-dimethyl-phenyl	dipentylamino	propylenamino	dimethylamino
42	3,4-dimethyl-phenyl	dipentylamino	ethylenamino	diethylamino
43	3,4-dimethyl-phenyl	dipentylamino	propylenamino	diethylamino
44	3,4-dimethyl-phenyl	dipentylamino	ethylenamino	4-morpholinyl
45	3,4-dimethyl-phenyl	dipentylamino	ethylenamino	4-morpholinyl
46	3,4-dimethyl-phenyl	dipentylamino	ethylenamino	4-morpholinyl
47	3,4-dimethyl-phenyl	dipentylamino	propylenamino	4-morpholinyl
48	3,4-dimethyl-phenyl	dipentylamino	ethylenamino	4-methyl-1-piperazinyl
49	3,4-dimethyl-phenyl	dipentylamino	propylenamino	4-methyl-1-piperazinyl

COMPOUND (*Note 1)	FORMULA	MELTING POINT (C)°	TLC (Rf) (*Note 2)	SPECIFIC ROTATION (Configuration) (* Note 3,4)	
31	C29H48N403	73/76	0.51	0	(R,S)
32	C28H46N404	109/11	0.55	0	(R,S)
33	C29H48N404	109/12	0.60	0	(R,S)
34	C29H45N504	99/100	0.65	0	(R,S)
35	C30H50N406	129/39	0.63	0	(R,S)
36	C31H52N404	110/12	0.65	0	(R,S)
37	C28H44C12N404	116/19	0.65	0	(R,S)
38	C29H46C12N404	88/91	0.66	0	(R,S)
39	C28H44C12N404	129/31	0.67	0	(R,S)
40	C28H48N403	105/07	0.55	0	(R,S)
41	C29H50N403	70/72	0.60	0	(R,S)
42	C30H52N403	85/88	0.59	0	(R,S)
43	C31H54N403	64/65	0.60	0	(R,S)
44	C30H50N404 x HCl	150/53	0.65	0	(R,S)
45	C30H50N404	120/22	0.66	+12.4 *	(R)
46	C30H50N404	118/20	0.66	-12.0 *	(S)
47	C31H52N404	80/83	0.63	0	(R,S)
48	C31H53N503	98/100	0.50	0	(R,S)
49	C32H55N503	84/85	0.55	0	(R,S)

COMPOUND (*Note 1)	R1	R2	R3 / -N-A	W
50	3,4-dimethyl-phenyl	dipentylamino	ethylenamino	4-benzyl-1-piperazinyl
51	3,4-dimethyl-phenyl	dipentylamino	propylenamino	4-benzyl-1-piperazinyl
52	3,4-dimethyl-phenyl	dipentylamino	_____	4-methyl-1-piperazinyl
53	3,4-dimethyl-phenyl	dipentylamino	ethylenamino	1-pyrrolidinyl
54	3,4-dimethyl-phenyl	dipentylamino	propylenamino	1-piperidinyl
55	3,4-dimethyl-phenyl	dipentylamino	ethylenamino	1-piperidinyl
56	3,4-dimethyl-phenyl	dipentylamino	amino	4-methyl-1-piperazinyl
57	3,4-dimethyl-phenyl	dipentylamino	methylamino	1-methyl-4-piperidinyl
58	3,4-dimethyl-phenyl	dipentylamino	methylenamino	1-ethyl-pyrrolidin-2-yl
59	3-quinolinyl	dipentylamino	ethylenamino	4-morpholinyl
60	3,4-dichloro-phenyl	dipentylamino	-----	4-methyl-1-piperazinyl
61	2-naphthyl	dipentylamino	ethylenamino	4-morpholinyl
62	3-chloro-phenyl	[2-(1-adamantyl)ethyl] amino	ethylenamino	4-morpholinyl
63	3-chloro-phenylamino	[2-(1-adamantyl)ethyl] amino	ethylenamino	4-morpholinyl

COMPOUND (*Note 1)	FORMULA	MELTING POINT (C)°	TLC (Rf) (*Note 2)	SPECIFIC ROTATION (Configuration) (* Note 3,4)	
50	C37H57N503 x 2HCl	185/89	0.62	0	(R,S)
51	C38H59N503 x 2HCl	138/41	0.52	0	(R,S)
52	C29H48N403	81/83	0.59	0	(R,S)
53	C30H50N403	127/29	0.61	0	(R,S)
54	C32H54N403	92/94	0.56	0	(R,S)
55	C31H52N403	101/03	0.63	0	(R,S)
56	C29H49N503	118/20	0.59	0	(R,S)
57	C31H52N403 x HCl	173/76 dec	0.61	0	(R,S)
58	C31H52N403	77/80	0.65	0	(R,S)
59	C31H47N504	114/15	0.49	-16.3	(R)
60	C27H42C12N403 x HCl	81/83	0.64	-41.3	(R)
61	C32H48N404	126/27	0.54	- 8.4	(R)
62	C30H43ClN404	187/89	0.58	+11.5	(R)
63	C30H44ClN504	196(dec)	0.59	+22.3	(R)

COMPOUND (*Note 1)	R1	R2	R3 / -N-A	W
64	3,4-dimethyl-phenyl	(3-methoxypropyl)-pentylamino	ethylenamino	4-morpholinyl
65	3-chloro-phenyl	decahydroisoquinolin-2-yl	ethylenamino	4-morpholinyl
66	3-chloro-phenyl	cyclooctylamino	ethylenamino	4-morpholinyl
67	3-chloro-phenyl	octamethylenimino	ethylenamino	4-morpholinyl
68 *	3-chloro-phenyl	(3-ethyl-3methyl-pentyl)-amino	ethylenamino	4-morpholinyl
69 *	3,4-dichloro-phenyl	dipentylamino	ethylenamino	4-morpholinyl
70 *	3,5-dichloro-phenyl	8-azaspiro[4.5]decan8-yl	———	4-methyl-1-piperazinyl

COMPOUND (*Note 1)	FORMULA	MELTING POINT (C)°	TLC (Rf) (*Note 2)	SPECIFIC ROTATION (Configuration) (* Note 3,4)	
64	C29H48N4O5	111/12	0.67	0	(R,S)
65	C27H39ClN4O4 x HCl	116/18	0.51	-62.0	(R)
66	C26H39ClN4O4	152/54	0.57	0	(R,S)
67	C26H39ClN4O4 x HCl	54/47	0.49	0	(R,S)
68 *	C25H39ClN4O4	142/44	0.62	0	(R,S)
69 *	C27H42Cl2N4O4	135/36	0.65	+12.4	(R)
70 *	C25H34Cl2N4O3 x HCl	263/66	0.50	+2.6	(R)

Note: 1) The compounds 1-67 belong to the glutamic series (r=2)
The compounds 68-70 belong to the aspartic series (r=1)

2) The thin-layer chromatography (TLC) was carried out with the use of thin sheets of silica gel and with ButOH-Acetic acid - H_2(5/2/2:v/v) as the eluent.

3) The determination of the specific rotatory power was carried out in chloroform, except for the compounds 4, 6, 45 and 46, for which methanol was used, with the use of sodium as a yellow light source (D).

4) R and S denote the Rectus (R) and Sinister (S) configurations.

Description of pharmacological activity

1) Activity against gastric secretion in the rat

The investigation of the activity against gastric secretion performed by the compounds of the invention by means of an antigastrin mechanism was carried out in vivo in anaesthetized rats with the use of male animals weighing about 200g. Gastric secretion was stimulated with pentagastrin and the method of K.S. Lai [Gut 5, (1964), 327-341] was used, slightly modified.

After tracheotomy, the oesophagus and duodenum were cannulated. Perfusion was carried out with a tepid solution (37°C) of 0.25 mM NaOH which was passed through the stomach by means of a peristaltic pump at a constant flow rate of 1 ml/minute. After stabilisation for 20 minutes, the stimulant, dissolved in a physiological solution, was perfused for 120 minutes at a dose of 30 mcg/kg/h in a volume of 0.95 ml/hour. After perfusion for 60 minutes (the basal simulation), the product under test was administered intravenously (I.V.) as a bolus and the perfusion of the stimulant was continued for a further 60 minutes. The acid secretion was recorded continuously as a function of time.

The activity of the product was evaluated as the percentage reduction in the secreted acidity after the administration of the product compared with the basal acidity measured during the first 60 minutes of collection in the presence of pentagastrin alone.

The antagonistic compounds tested were administered in

different doses in order to be able to calculate an ID50, that is, the dose (in mg/kg I.V.) which can inhibit the effect of the pentagastrin by 50%.

The results obtained are shown in the table below (Tab. 2) in which the activities of the compounds are expressed as ID50s under the stimulus of 30 mcg/kg/h of pentagastrin.

TABLE 2: Antagonistic activity (ID50 mg/kg I.V.) towards acid secretion induced by pentagastrin (30 mcg/kg/h) in the rat.

Compounds	Activity (ID50)	Compounds	Activity (ID50)
1	9.0	44	IN (30)
2	24.8	68	31.0
3	12.8	70	18.9
4	IN(*) (30)	CR 2194	11.0
6	IN (20)	proglumide	500
13	8.5	lorglumide	IN (100)
23	25.0		

(*) Note: IN (inactive), when the antisecretive activity at the dose given is less than 20%.

It can be seen from an examination of this table that many of the basic compounds of the invention have potent antigastrin activity.

The antigastrin activity is particularly favourable in the case of the derivatives of glutamic acid (r=2) when R_1 is 3,5-dichloro-phenyl, when the amino group R_2 is the azaspiro[4.5]decan-8-yl group or the azaspiro[5.5]-undecan-3-yl group, A is a bond, and W is the

4-methyl-1-piperazinyl group (compounds 1 and 13). It can be seen that, in this experimental model, the most potent of the compounds of the invention are about 50 times more active than the reference antigastrin compound, proglumide. It is also interesting to note that the CCK-A antagonist, lorglumide, is completely inactive up to a dose of 100 mg/kg. The antigastrin activities of these compounds are stereospecific as can be seen by comparing the activity of the compound 1, derived from the R (rectus) series, which is about three times higher than that of its S (sinister) enantiomer, that is, the compound 2. The compound 1 is about 1.2 times more active than CR 2194, its acid "parent compound", and this ratio becomes about 1.5 when calculated on a molar basis. This shows that, contrary to what was known up to now, the gastrin (CCK-B) receptor is also sensitive to basic competitors.

2) Anticholecystokinin (anti-CCK-A) activity in vitro

In order to check the hypothesis that the molecular conformations of the compounds of the invention are such that, as well as their antagonistic activity towards gastrin (CCK-B), they also have antagonistic activity towards CCK-A, that is, the peripheral CCK which is active particularly at the level of the pancreas and the smooth musculature of the gall bladder, the pilorus and the intestine, the ability of some compounds of the invention and of some corresponding acid starting derivatives to inhibit the binding of [125-I]-[Bolton-Hunter]-CCK-8 to the cholecystokinin receptors of the pancreatic cells of the rat was tested, in comparison with the displacement induced by cold (unmarked) CCK-8.

The pancreatic cells of the rat were prepared as described by Makovec et al. (reference cited) so as to produce about $5x10^6$ cells/ml. The cells were then incubated together with the radioactive tracer and the compounds under test for 30 minutes at 37°C.

After the supernatant liquid had been discarded, the radioactivity associated with the pellet was determined with a gamma counter (80 % efficiency). The specific binding was determined as the difference between the binding in the absence and in the presence of 10^{-6}M CCK-8 (70% on average).

The results obtained are given in Table 3, in which the IC50, that is the concentration (in moles/litre) of the antagonist which can displace 50% of the [125-I]-CCK-8 from the receptor is given.

Table 3: Inhibition of the binding of (125-I)(B-H)-CCK-8 to the pancreatic cells of the rat.

Compounds	IC50 (moles/litre)
CCK-8	$0.5 . 10^{-9}$
Compound 1	$6.6 . 10^{-6}$
Compound 59	$1.2 . 10^{-6}$
Compound 61	$2.8 . 10^{-6}$
R-lorglumide	$0.05 . 10^{-6}$
CR 2194	$13.5 . 10^{-6}$

It can be seen from the data given in the table that some of the compounds claimed have a discrete anti-CCK A activity, antagonising the binding of CCK by 50% at concentrations of about 10^{-6}M, that is about 1000 times greater than those of the specific antagonist CCK-8.

Although it has a possible therapeutic significance, this activity is decidedly less than that of the most potent CCK-A antagonists of the acid series such as, for example, R-lorglumide which seems to be about 25 times more active than the compound 59. The introduction of an amino-amide group in position 1 of 4-benzamido-pentanoic acid for the gastrin antagonists (or CCK-B antagonists), on the other hand, slightly increases their CCK-A-antagonistic activity as can be seen by examining the activity of the compound 1 which is about twice as active as its acidic "parent compound" CR 2194.

3) Anticholecystokinin (anti CCK-B) activity in vitro

Since the radioligand [I-125][B-H]-CCK-8 does not discriminate between the CCK-A and CCK-B receptors present in the brain, in order better to evaluate the abilities of the compounds of the invention to interact with the central CCK-B receptors, a new ligand, non-sulphated [3-H][N-methyl-N-leucine]CCK-8 was used which had been found [Knapp et al.; J. Pharmacol. and Exp. Therap. 255 (3) (1990), 1278-1286) to be a very selective ligand for the CCK-B receptors, its affinity for the receptors of the cortex (CCK-B) being about 4000 times greater than for those of the pancreas (CCK-A) in the guinea-pig.

Cerebral cortices of white male guinea pigs were therefore used, according to the method mentioned above, so as to obtain a membrane content/ml corresponding to about 300 mcg of proteins/ml. The membranes were incubated together with the radioactive tracer and the compounds under test for 150 minutes at 25°C. After the supernatant liquid had been

discarded, the radioactivity associated with the pellet was determined with a liquid scintillator. The specific binding was determined as the difference between the binding in the absence and in the presence of 5 . 10^{-6}M CCK-8. The results obtained are given in Table 4 which gives the IC50, that is, the concentration (in moles/litre) of the antagonist which can displace 50% of the (3-H)[N-methyl-N-leucine]CCK-8 from the receptor.

Table 4: Inhibition of binding of (3-H)[N-methyl-N-leucine] CCK-8 to the guinea pig cortical membrane.

Compounds	IC50 (moles/litre)	Compounds	IC50 (moles/litre)
1	0.7 . 10^{-6}	23	IN
2	IN*	36	81.3 . 10^{-6}
3	2.8 . 10^{-6}	44	65.4 . 10^{-6}
4	12.5 . 10^{-6}	55	IN
5	2.6 . 10^{-6}	60	50.0 . 10^{-6}
6	3.3 . 10^{-6}	61	2.9 . 10^{-6}
7	6.5 . 10^{-6}	R-lorglumide	9.2 . 10^{-6}
11	3.8 . 10^{-6}	CR 2194	2.4 . 10^{-6}
13	0.6 . 10^{-6}	pentagastrin	3.0 . 10^{-9}

Note (*): IN (inactive) when the IC50 is < 10^{-4}M.

It can be seen from the data given in Table 4 that some of the compounds of the invention, such as, for example, the compounds 1 and 13, are potent inhibitors of the binding of [N-methyl-N-leucine]CCK-8 to the receptors of the cortical membranes of guinea-pigs. In fact they are about 3 times more potent than the gastrin antagonist CR 2194 and about 10 times more potent than the CCK-A antagonist R-lorglumide, whereas

they are about 200 times less active than the specific antagonist, pentagastrin. It can also be seen that the displacing activity is greatly affected by the stereochemistry of the molecule of the invention. In fact the S enantiomer of the compound 1 (compound 2) is practically inactive in this test, having an IC50 of more than 10^{-6}M.

4) Anxiolytic activity in the mouse

In order to confirm the hypothesis that the potent activity of some of the compounds of the invention against central CCK-B may be correlated with a possible anxiolytic activity, this potential activity was evaluated in the mouse with the use of the "Black and White Box test". This experimental model, which was carried out according to Costall et al. [Pharm. Biochem. Behav. 32 (1989), 777-785] used a box with dimensions of 45 x 21 x 21 (h) cm. divided into two compartments which communicated with each other by means of a 13 x 5 cm hole. The smaller compartment (1/3 of the total area) had black walls, whereas the larger had transparent walls and was illuminated by a lamp which was placed 20 cm above the box and supplied light at 20 W. Under the floor was an activity meter which registered the movements performed by the animal in the individual compartments. The experiment was started by placing the animal in the centre of the illuminated box; as well at its movements, the time which the animal spent in the dark and in the light and the number of times it moved between the 2 compartments were recorded for five minutes. In general, a control animal tended preferably to stay in the dark compartment where it felt better protected from an unusual enviromental situation which put it in a state

of anxiety. In this experimental model (see the reference cited above), a compound having anxiolytic activity decreased the % of movements into the dark in comparison with the total movements, increased the movements between the two light-dark compartments, and increased the % of the total time time spent in the light. The results obtained are given in Table 5 below in which the activities obtained with the compound 1 (the rectus series) and its enantiomer 2 (sinister) tested in comparison with diazepam and the CCK-B antagonist L365-260.

Table 5: ANXIOLYTIC ACTIVITY IN THE MOUSE IN THE "BLACK AND WHITE BOX TEST"

	DOSE mg/kg IP	No. animals	TOTAL MOV.	MOV. DARK(%) TOTAL MOV.	% EFF.VS CONTROL
CONTROL	-	15	483	50	-
COMPOUND 1	0.01	15	478	50	0
COMPOUND 1	0.1	15	461	47	-5
COMPOUND 1	1	15	471	45	-9
CONTROL	-	10	473	52	-
COMPOUND 2	0.1	10	477	50	-4
COMPOUND 2	1.0	10	462	50	-4
CONTROL *	-	10	439	50	-
L-365-260	0.01	10	417	57	12
"	0.1	10	446	54	18
CONTROL *	-	15	459	56	-
DIAZEPAM	1	15	508#	53	-5
DIAZEPAM	3	15	539#	52	-7

	LIGHT-DARK MOVEMENTS	% EFF.VS CONTROL	LIGHT TIME (%) TOTAL TIME	% EFF.VS CONTROL
CONTROL	12.8	-	27.7	-
COMPOUND 1	13.2	3	32.3#	17
COMPOUND 1	15.0#	17	35.4#	28
COMPOUND 1	12.9	0	30.5	10
CONTROL	13.3	-	28.2	-
COMPOUND 2	13.2	0	28.3	0
COMPOUND 2	12.8	0	27.5	0
CONTROL *	16.2	-	27.0	-
L-365-260	14.2	-12	27.0	0
"	13.3	-18	31.8	18
CONTROL *	14.5	-	24.6	-
DIAZEPAM	19.9	+37.2	29.3	19
DIAZEPAM	22.3	+53.8#	33.6	36.7

Note: The control group (*) did not consist of a physiological solution, but of a suspension of methyl cellulose (0.5%) in a 5% (v/v) solution of dimethylsulphoxide-C which was used to dissolve the compounds under test. (#) A significant difference in comparison with the controls ($P<0.01$).

It can be seen from Table 5 that the compound 1 is active for all the parameters tested. Thus, it has anxiolytic activity which results in a reduction in the percentage of movements into the dark in comparison with the total movements, an increase in the number of light-dark movements, and an increase in the time spent in the light, in comparison with the control group. The dose at which the compound is most active is 0.1 mg/kg (I.P.). The effect of the compound has a bell-shaped curve which result is not rare for compounds which are active on the central nervous system. Its S enantiomer (compound 2) was completely inactive in this model, confirming the results obtained in vitro on the binding of the guinea-pig cortex. The potent benzodiazepine-type CCK-B antagonist L-365-260 (Pakard et al TIPS 11 (1990), 271-273) was also active at a dose of 0.1 mg/kg but only for the parameter which relates to the increase in the time spent in the light. The conventional anxiolytic, diazepam, which was tested at doses of 1 and 3 mg/kg was active in a dose-dependent manner for all the parameters tested. Its activity, however, was qualitatively different since this compound also significantly increased the total movements whereas neither of the putative CCK-B antagonists, that is, the compound 1 and the compound L-365-260, seemed to affect this parameter.

5) Antispastic activity in vitro: guinea-pig ureters.

Another interesting aspect of the activity of these products is the potent spasmolytic activity which some of them have on the smooth musculature of mammals. Their activity in the ureters of guinea pigs is given below by way of example. The method of Mitolo-Chieppa et al (Pharm. Res. Comm: 14, 807-814/1992) was used, slightly modified. The guinea-pig ureter, cleaned of fat and of renal tissue, was placed in a bath for

isolated organs in the presence of Krebs at a temperature of 37°C and oxygenated continuously with an oxygen-CO_2 mixture (95-5 v/v). The isotonic contractions were detected by means of a force transducer and recorded. After a re-equilibration period of about 45 minutes, the prepared specimen showed a spontaneous rhythmic contractility. A given concentration of the product under test was then introduced into the bath and left in contact with the prepared specimen for five minutes, after which the ureter was washed until its own spontaneous activity was re-established. The myorelaxant activities of the compounds were determined with the use of various concentrations thus determining the IC50 values, that is, the concentration in mcg/l of the compound which could antagonise the spontaneous activity of the prepared specimen by 50% in terms of both the frequency and the force of the contractions. The results obtained are set out in Table 6 below which gives the compounds tested and the IC50s found, which were calculated by the regression method on a set of at least 3 tests at 3 different concentrations for each compound tested.

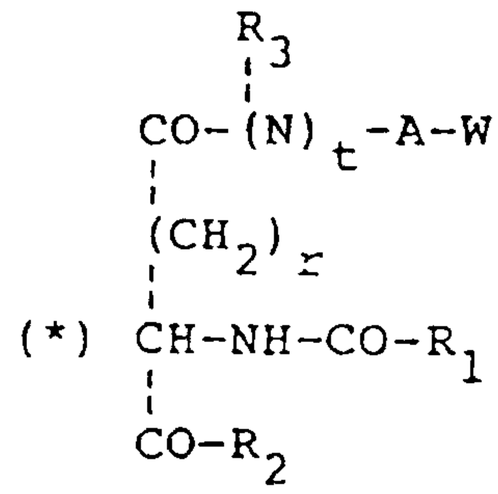
TABLE 6: Inhibition (IC50) of the spontaneous motility of guinea-pig ureters in vitro

Compound	IC50 (frequency)	IC50 (force)	Compound	IC50 (frequency)	IC50 (force)
1	29	23	37	7	8
2	20	25	40	44	27
3	4.3	4.5	41	28	20
4	121	IN	42	22	18
6	IN	IN	44	4	5
16	IN	IN	45	6	8
25	IN	36	46	1.5	1.6
27	IN	33	47	15	12
28	43	18	51	100	100
29	17	18	55	18	11
31	IN	23	58	19	14
32	22	IN	61	100	32
33	16	18	64	IN	59
34	12	12	Papaverine	27	23
35	16	16	Flavoxate	IN	29
36	1.5	2	Verapamil	2.2	3

It can be seen from Table 6 that, whereas some of the compounds of the invention are not very effective in this model, others such as, for example, the compounds 3, 36, 44 and 46, are extremely active (IC50 about 1-2 mcg/ml for the most active).

For example, the compound 46 is about 20 times more active than Papaverine and Flavoxate and about twice as active as an extremely potent calcium antagonist such as Verapamil. In general, it can be said that the myolytic activity performed in this model is particularly high when R_1 is 3,4 dimethylphenyl or 4-isopropylphenyl, R_2 is dipentylamino or 8-azaspiro[4.5]decan-8-yl, A is ethylenamino, and W is 4-morpholinyl. The preferred configuration in this case is S (sinister) as can be deduced by comparing the activities of the compound 46 with those of its R enantiomer, the compound 45.

1. A compound which is represented by the general formula I:



(I)

and in which r is 1 or 2;

R_1 is selected independently from:

unsubstituted phenyl;

mono- or di-substituted phenyl groups in which the substituents are selected from the group consisting of halogens (chloro, fluoro, and bromo), linear or branched C_1-C_4 alkyl groups, nitro, cyano, methoxy, and trifluoromethyl groups;

an unsubstituted phenylamino group;

phenylamino groups mono- or di-substituted as described above for the phenyl group;

2(beta)-naphthyl; and

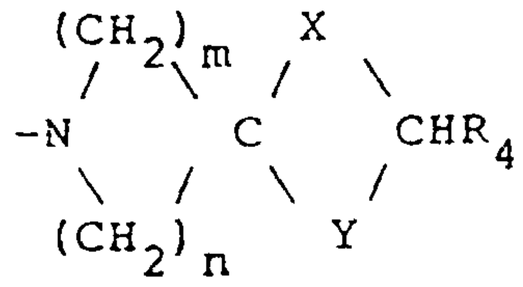
heterocyclic, monocyclic or bicyclic groups selected from:

an unsubstituted pyridyl group, and

a pyridyl group mono- or di-substituted with one or two substituents independently selected from the group consisting of methyl, chloro, furyl (2- or 3-yl), indolyl (2- or 3-yl),isoindolyl (3-yl), benzofuranyl (2- or 3-yl), quinolinyl (2- or 3-yl) and isoquinolinyl (3-yl);

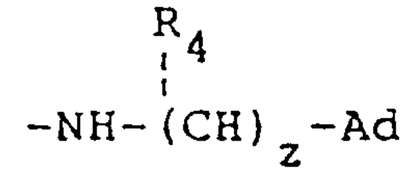
R_2 is selected independently from:

a_1) a heterocyclic spiro group represented by:



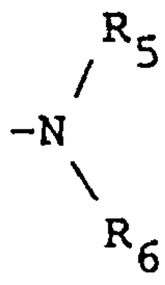
in which m and n are independently a value selected from 1, 2 and 3 provided that the ring formed consists of at least 5 atoms, X and Y are selected independently from $(CH\text{-}R_4)_z$, TCH_2 and CH_2T in which T is O or S, and in which R_4 is a group selected independently from H, linear and branched C_1-C_4 alkyl groups, OCH_3, and OH, and z is a value selected from 0, 1, 2 and 3 provided that the ring formed consists of at least 3 atoms;

b_1) an aminoalkyladamantyl group represented by:



in which z and R_4 have the meanings given above and Ad is adamantyl (1- or 2-yl);

c_1) an alkylamino group represented by:

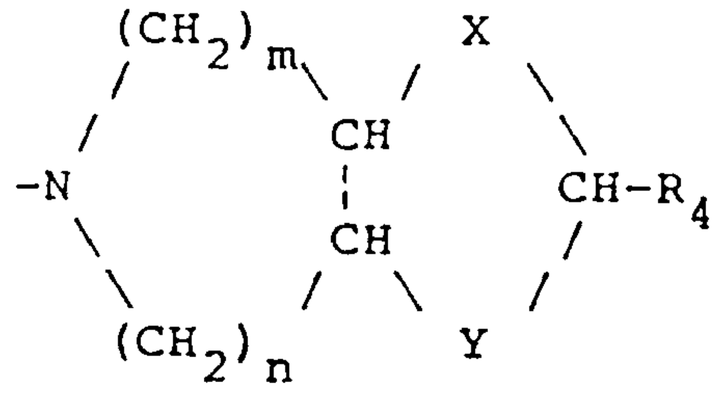


in which R_5 is a linear or branched alkyl chain containing from 4 to 10 carbon atoms or a C_5-C_{10} cycloalkyl group, or a linear or branched alkoxyalkyl group containing from 4 to 7 carbon atoms, and R_6 is selected independently from H, alkyl groups, linear and branched alkoxyalkyl groups containing from 4 to 7

carbon atoms, and C_5-C_{10} cycloalkyl groups;

d_1) a C_4-C_{10} cycloalkylamine; and

e_1) a dicyclic amino group (condensed) represented by:



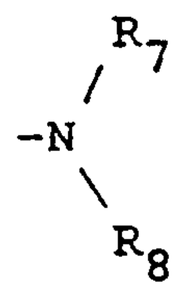
and in which m, n, X, Y, and R_4 have the meanings given above;

R_3 is H, CH_3 or C_2H_5;

A is a bond or a linear or branched alkylene group comprising from 1 to 4 carbon atoms; and

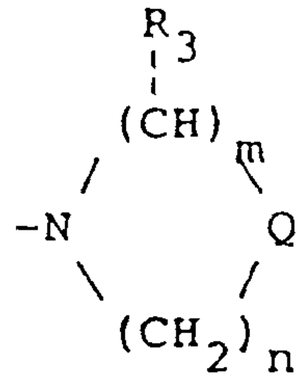
W is selected from the group consisting of:

a_2) a tertiary amino group represented by:



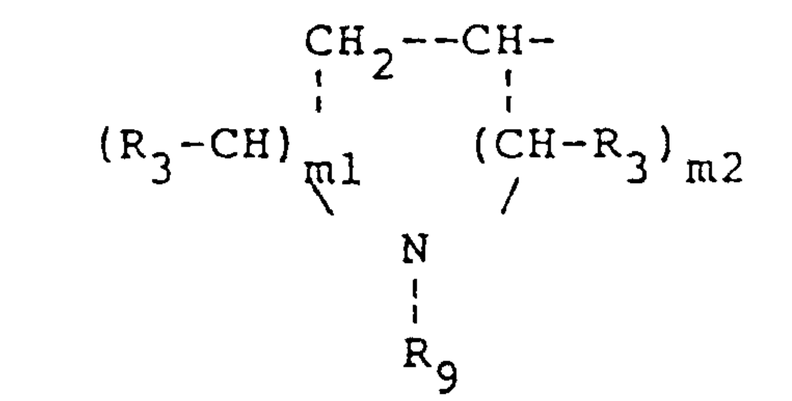
in which R_7 and R_8 are, independently, hydrogen or a linear or branched alkyl group comprising from 1 to 5 carbon atoms, provided that R_7 and R_8 are not both hydrogen;

b_2) a heterocyclic group represented by:



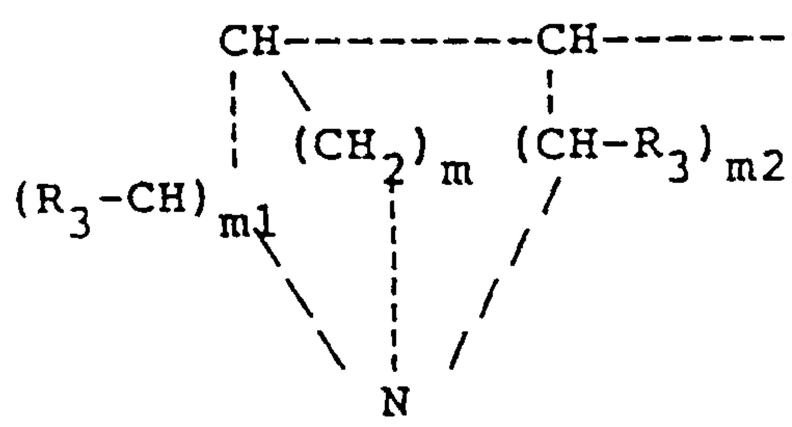
in which R_3, m and n have the meanings given above and Q is a bond, CH_2, oxygen, sulphur or nitrogen, N-substituted with R_9, R_9 being a group selected independently from H, linear and branched C_1-C_4 alkyl groups, phenyl and benzyl groups, of which the aromatic groups may be unsubstituted, or mono- or di-substituted as described for the phenyl group in R_1;

c_2) a heterocyclic group represented by:



in which m1 and m2 are independently a value selected from 0, 1, 2 and 3 and R_3 and R_9 have the meanings given above; and

d_2) a heterocyclic group represented by:



in which m, m1, m2 and R_3 have the meanings given above;

t is always 1, except that in b_2, when Q is N-R_9, it is 0 or 1, and pharmaceutically acceptable salts thereof.

2. A compound according to Claim 1 in which R_1 is 3-chlorophenyl or 3,5-dichlorophenyl, R_2 is 8-azaspiro [4.5]decano-8-yl or 3-azaspiro[5.5]undecano-3-yl, t is zero, A is a bond, W is 4-methyl-1-piperazinyl, and R_3 is hydrogen, and the stereochemistry of the chiral centre may be racemic (R, S) or R (rectus).

3. A compound according to Claim 2 wherein r is 2.

4. A compound according to Claim 2 or 3 wherein the stereochemistry of the chiral centre is R (rectus).

5. A compound according to Claim 1 in which R_1 is 3,4-dimethylphenyl or 4-isopropylphenyl, R_2 is a dipentylamino group, -NR3A is ethylenamino, W is 4-morpholinyl, and the stereochemisry of the chiral centre may be racemic (R, S) or S (sinister).

6. A compound according to Claim 5 wherein r is 2.

7. A compound according to Claim 5 or 6 wherein the stereochemistry of the chiral centre is S (sinister).

8. A compound according to Claim 1 in which R_1 is 3,4-dichlorophenyl, 2-naphthyl or 3-quinolinyl, R_2 is a dipentylamino group, A is a bond or an ethylene group, W is 4-morpholinlyl or 4-methyl-1-piperazinyl in which case t is zero, and R_3 is hydrogen, and the steriochemistry of the chiral centre may be racemic or R (rectus).

9. A compound according to Claim 8 wherein r is 2.

10. A compound according to Claim 8 or 9 wherein the stereochemistry of the chiral centre is R (rectus).

11. A pharmaceutical preparation comprising at least one of the compounds according to Claim 1 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

12. A pharmaceutical preparation according to Claim 11 for use in treatment of ulcers.

13. A pharmaceutical preparation according to Claim 11 for use in the treatment of tumourous conditions which are sustained by gastrin or other biologically active polypeptides related thereto.

14. A pharmaceutical preparation according to Claim 11 for the treatment of pathological conditions of the CNS linked to imbalances in the physiological neurone levels of gastrin or of other biologically active polypeptides related thereto.

15. A pharmaceutical preparation according to Claim 11 for use in the treatment of disorders of the digestive system due to disturbances of motility and of mucotrophism.

16. A pharmaceutical preparation according to Claim 11 for use in the treatment of biliary dyskinesia, colitis or pancreatitis.

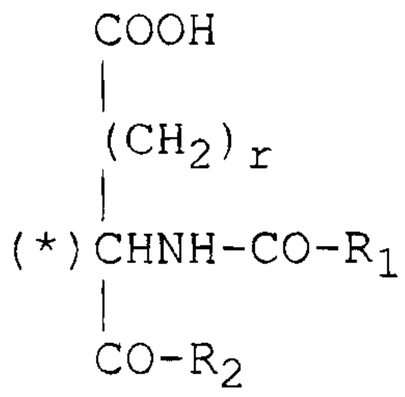
17. A pharmaceutical preparation according to Claim 11 for use in the treatment and prevention of eye conditions induced by the surgical treatment of cataracts or by chronic eye inflammation, or in the treatment of pathological conditions of other sensory organs in which gastrin, cholecystokinin or other related biologically active peptides have physiological or pathological activity.

18. A pharmaceutical preparation according to Claim 11 for use in the treatment of conditions of the urino-genital system.

19. A pharmaceutical preparation according to Claim 11 for use in the treatment of urinary incontinence, neurogenic bladder, urinary calculus and painful spastic conditions of the vesico-ureteral and uterine musculature in general.

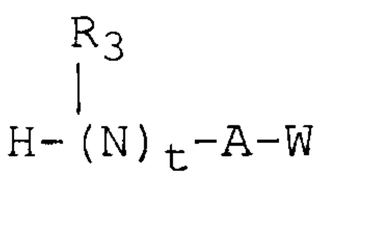
20. A pharmaceutical preparation according to Claim 11 wherein the pharmaceutically acceptable carrier is selected from the group consisting of vehicles, binders, flavourings, dispersants, preservatives, humectants and mixtures thereof.

21. A method of preparing a compound of formula (I) as defined in Claim 1 in which r, t, R_1, R_2, R_3, A and W have the meanings given in Claim 1 and in which the substituents at the chiral centre [marked with an asterisk in formula (I)] have the (R,S), R or S conformation, consisting of reacting acid derivatives of formula (II):



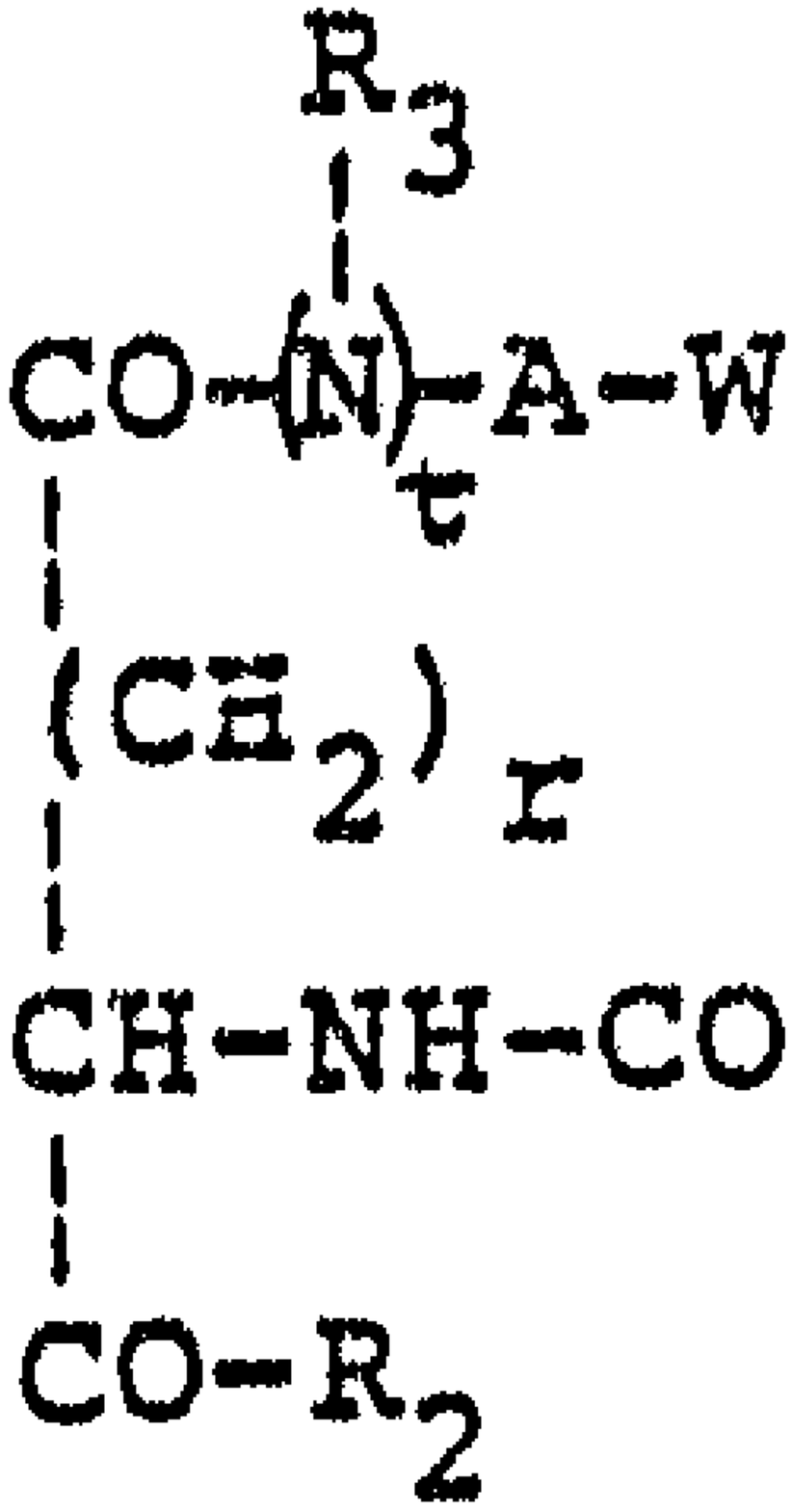
(II)

in which r, R_1 and R_2 have the meanings given above, with suitable amines of formula (III):



(III)

in which R_3, t, A and W have the meanings given in Claim 1, in a molar ratio of from 1 to 3 at a temperature of between -15°C and +20°C by the mixed anhydride method or by other equivalent conventional methods of synthesis, and in recovering the basic compounds (I) from the reaction mass either as such or by salification carried out in an inert solvent by suitable pharmaceutically-acceptable organic or inorganic acids.



(I)