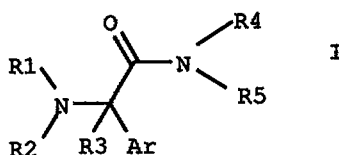


S016772J.66

New arylglycinamide derivatives, processes for
preparing them and pharmaceutical compositions
containing these compounds

The invention relates to new arylglycinamide derivatives
of general formula

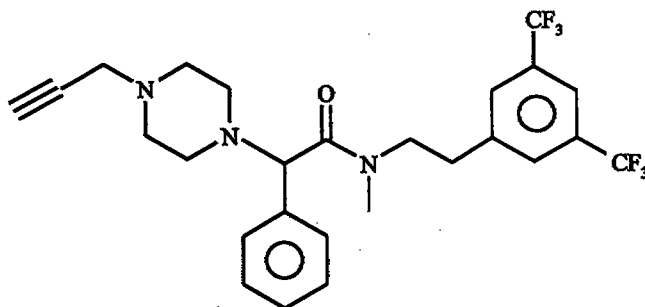


15 and the pharmaceutically acceptable salts thereof,
processes for preparing them and pharmaceutical
compositions containing these compounds. The
compounds are valuable neurokinin (tachykinin)
antagonists.

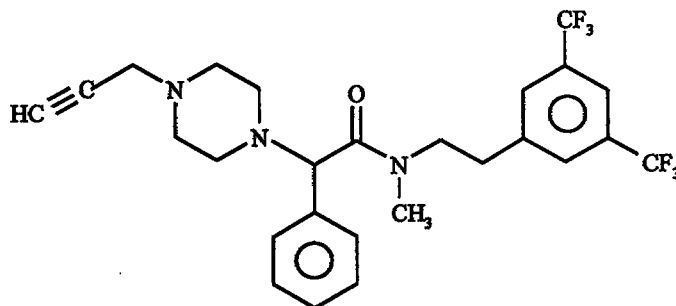
20 The abbreviations used in this specification and
claims are explained as follows:

25	CDI	=	Carbonyldiimidazole
	DCCI	=	Dicyclohexylcarbodiimide
	HOBt	=	1-Hydroxybenzotriazole
	THF	=	Tetrahydrofuran
	DMF	=	Dimethylformamide
	RT	=	Room temperature
30	DMAP	=	4-Dimethylaminopyridine
	TBTU	=	O-Benzotriazolyl-tetramethyluronium- tetrafluoroborate

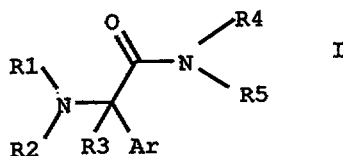
35 The formulae are shown in simplified form. In
representing the compounds, for example, all the CH₃-
substituents are represented by a hyphen and CH is
represented by =, thus, for example:



denotes



The invention relates to new arylglycinamide derivatives of general formula I

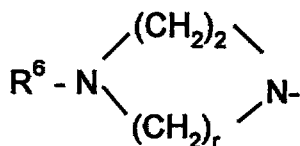


or the pharmaceutically acceptable salts thereof, wherein

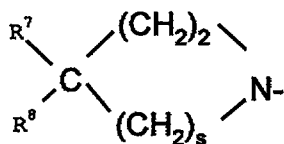
Ar denotes unsubstituted or mono- to penta-substituted phenyl, or unsubstituted or mono- or disubstituted naphthyl [wherein the substituents of the phenyl and naphthyl independently of one another denote halogen (F, Cl, Br, I), (C₁₋₄)alkyl, O-(C₁₋₄)alkyl, CF₃, OCF₃ or NR¹²R¹³ (wherein R¹² and R¹³ independently of one another denote H, methyl or acetyl)] or Ar is phenyl substituted by -O-CH₂-O- or -O-(CH₂)₂-O-;

R¹ and R² together with the N to which they are bound
denote a ring of the formula

5

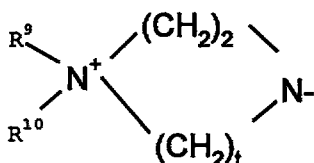


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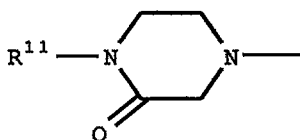
20



25

or

30



35

wherein

r, s and t are 2 or 3;

R⁶ denotes

40

H,

(C₁₋₅) alkyl,

(C₃₋₅) alkenyl,

propynyl,

hydroxy (C₂₋₄) alkyl,

45

methoxy (C₂₋₄) alkyl,

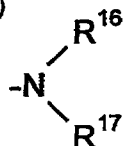
di (C₁₋₃) alkylamino (C₂₋₄) alkyl,

amino (C₂₋₄) alkyl,

amino,

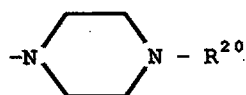
di(C₁₋₃)alkylamino,
monofluoro- to perfluoro(C₁₋₂)alkyl,
N-methylpiperidinyl,
pyridyl,
5 pyrimidinyl,
pyrazinyl,
pyridazinyl
or the group -CH₂-C(O)NR¹⁴R¹⁵,
wherein
10 R¹⁴ is H or (C₁₋₄)alkyl and
R¹⁵ is H, (C₁₋₄)alkyl, (C₃₋₆)cycloalkyl, hydroxy(C₂₋₄)alkyl,
alkoxy(C₂₋₃)alkyl, phenyl(C₁₋₄)alkyl, or R¹⁴ and R¹⁵
together with the N to which they are bound form a ring
15 (1-pyrrolidinyl, piperidino, morpholino or 1-
methylpiperazin-4-yl);

R⁷ has one of the definitions (a) to (d),
(a) hydroxy
(b) 4-piperidinopiperidyl,
20 (c)



25 wherein R¹⁶ and R¹⁷ independently of one another denote
H,
(C₁₋₄)alkyl,
(C₃₋₆)cycloalkyl,
hydroxy(C₂₋₄)alkyl,
30 (C₁₋₃)alkoxy(C₂₋₄)alkyl,
phenyl(C₁₋₄)alkyl or
di(C₁₋₃)alkylamino(C₂₋₄)alkyl,
or if R¹⁶ is H or (C₁₋₄)alkyl,
R¹⁷ may also be -CH₂C(O)NR¹⁸R¹⁹, wherein R¹⁸ and R¹⁹ are
35 defined as R¹⁴ and R¹⁵ hereinbefore;

(d)



- 5 wherein R²⁰ denotes
 H,
 (C₁₋₄) alkyl,
 (C₄₋₆) cycloalkyl or
 -CH₂C(O)NR²¹R²²,
- 10 wherein R²¹ and R²² are defined as R¹⁴ and R¹⁵
 hereinbefore;
- R⁸ is H
- 15 R⁹ and R¹⁰ independently of each other denote (C₁₋₄) alkyl;
- R¹¹ denotes
 H,
 (C₁₋₅) alkyl,
 (C₃₋₅) alkenyl,
 propynyl,
 hydroxy(C₂₋₄) alkyl,
 methoxy(C₂₋₃) alkyl,
 di(C₁₋₃) alkylamino(C₂₋₃) alkyl,
 amino(C₂₋₃) alkyl,
 amino,
 di(C₁₋₃) alkylamino,
 monofluoro- to perfluoro(C₁₋₂) alkyl,
 N-methylpiperidinyll,
 pyridyl,
 pyrimidinyl,
 pyrazinyl,
 pyridazinyl
 or the group -CH₂-C(O)NR²³R²⁴,
- 20 wherein R²³ and R²⁴ are defined as R¹⁴ and R¹⁵
 hereinbefore;
- 25
- 30
- 35

R^3 denotes H, (C_{1-4}) alkyl, unsubstituted or mono- to trisubstituted phenyl, wherein the substituents independently of one another denote halogen (F, Cl, Br, I), (C_{1-4}) alkyl, O- (C_{1-4}) alkyl, CF_3 , OCF_3 or $NR^{25}R^{26}$ (wherein R^{25} and R^{26} independently of one another denote H, methyl or acetyl);

R^4 denotes phenyl (C_{1-4}) alkyl or naphthyl (C_{1-4}) alkyl, wherein phenyl may be substituted by 1 to 3 substituents, wherein the substituents independently of one another denote halogen (F, Cl, Br, I), (C_{1-4}) alkyl, O- (C_{1-4}) alkyl, CF_3 , OCF_3 or $NR^{27}R^{28}$ (wherein R^{27} and R^{28} independently of one another denote H, methyl or acetyl);

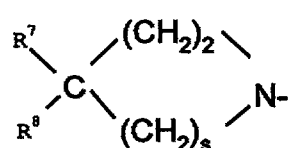
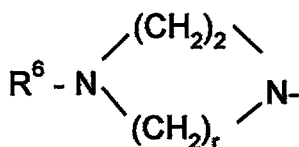
and

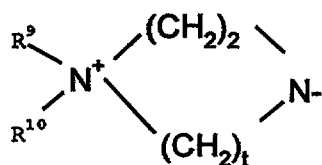
R^5 denotes H, (C_{1-4}) alkyl, (C_{3-6}) cycloalkyl, CH_2COOH , $CH_2C(O)NH_2$, OH or phenyl (C_{1-4}) alkyl.

Preferred compounds of general formula I are those wherein

Ar denotes unsubstituted or mono- or disubstituted phenyl, or unsubstituted naphthyl, or Ar is phenyl substituted by -O- CH_2 -O- or -O- $(CH_2)_2$ -O-;

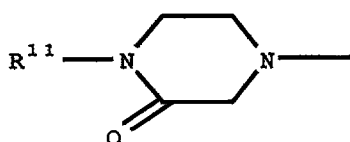
R^1 and R^2 together with the N to which they are bound denote a ring of the formula





5

or



10

wherein

r is 2 or 3 and

s and t are 2;

15 $\text{R}^6, \text{R}^7, \text{R}^8, \text{R}^9, \text{R}^{10}$ and R^{11} are as hereinbefore defined;

R^3 is H or (C_{1-4}) alkyl,

20 R^4 denotes phenyl (C_{1-4}) alkyl or naphthyl (C_{1-4}) alkyl, wherein phenyl may be substituted by 1 or 2 substituents, wherein the substituents independently of one another are halogen (F, Cl, Br, I), (C_{1-4}) alkyl, O- (C_{1-4}) alkyl, CF_3 or OCF_3 ;

25 and

R^5 denotes H, (C_{1-4}) alkyl, (C_{3-6}) cycloalkyl, OH or (C_{1-4}) alkylphenyl.

30 Particular mention should be made of compounds of formula I wherein

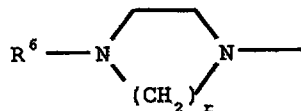
Ar is unsubstituted or mono- or disubstituted phenyl, or unsubstituted naphthyl [wherein the substituents of the phenyl independently of one another are halogen (F, Cl, Br, I), methyl, methoxy, CF_3 or OCF_3] or Ar is phenyl substituted by -O- CH_2 -O- or -O- $(\text{CH}_2)_2$ -O-;

35

particularly those wherein Ar is phenyl, naphthyl,
phenyl substituted in position 3 and/or 4 by methoxy or
halogen, or phenyl in which positions 2 and 3 or 3 and 4
are linked by -O-CH₂-O-, preferably those compounds
5 wherein

Ar is phenyl,
phenyl substituted by methoxy in positions 3 and 4 or
phenyl wherein positions 3 and 4 or 2 and 3 are linked
10 by -O-CH₂-O-.

Of the compounds defined above, special mention should
be made of those wherein, in the ring



r is 2 or 3 and

R⁶ denotes

20 H,

(C₁₋₅) alkyl,

(C₃₋₅) alkenyl,

propynyl,

hydroxy (C₂₋₄) alkyl,

25 methoxy (C₂₋₄) alkyl,

di (C₁₋₃) alkylamino (C₂₋₄) alkyl,

amino (C₂₋₄) alkyl,

amino,

di (C₁₋₃) alkylamino,

30 monofluoro- to perfluoro (C₁₋₂) alkyl,

N-methylpiperidinyl,

pyridyl,

pyrimidinyl,

or

35



particularly those wherein

r is 3 and R⁶ is methyl;

and those wherein

r is 2 and

5 R⁶ is

H,

(C₁₋₄) alkyl,

propenyl,

propynyl,

10 hydroxy (C₂₋₃) alkyl,

methoxyethyl,

di (C₁₋₂) alkylamino (C₂₋₃) alkyl,

aminoethyl,

amino,

15 dimethylamino,

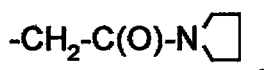
CH₂CF₃,

N-methylpiperidinyll,

pyridyl,

pyrimidinyl,

20 or



preferably those wherein

r is 2 and

25 R⁶ is H, (C₁₋₃) alkyl, allyl, 2-propynyl, -CH₂CH₂OCH₃,
-CH₂CH₂N(CH₃)₂, N-methylpiperidinyll, 2-pyrimidinyl

or

30 -CH₂-C(O)-N $\square$, particularly those wherein

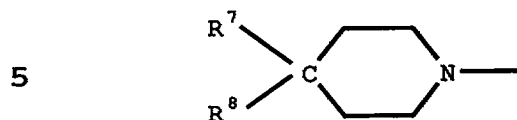
r is 2 and

R⁶ is H, CH₃, C₃H₇, CH(CH₃)₂, CH₂CH₂OH, CH₂CH₂OCH₃ or
CH₂CH₂N(CH₃)₂.

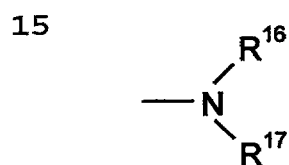
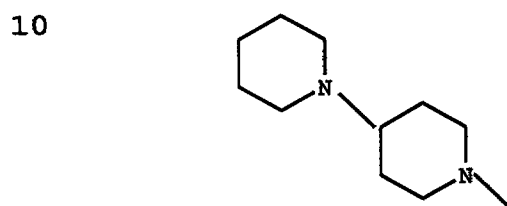
35 Of the compounds defined above, mention should also be
made of those wherein

R¹ and R² together with the N to which they are bound

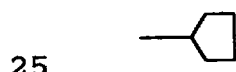
form the ring



wherein R^8 is H and
 R^7 is OH



20 wherein R^{16} and R^{17} independently of one another denote:
 H
 (C_{1-3}) alkyl,



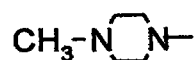
$(CH_2)_nOH$ wherein n is 2, 3 or 4

$(CH_2)_2OCH_3$

$-(CH_2)_nPh$ wherein n is 2 or 4

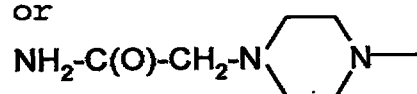
$(CH_2)_2N(CH_3)_2$

30



35

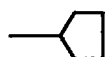
or



particularly those wherein

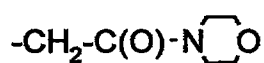
R^{16} and R^{17} are both CH_3 or C_2H_5 or

5 R^{16} is H or CH_3 and R^{17} is
(C_{1-3}) alkyl,



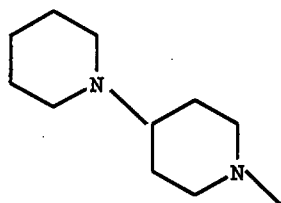
(CH_2)₂OH,

10 (CH_2)₄OH or



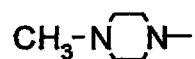
and those wherein

15 R^7 denotes

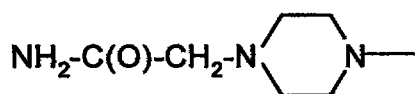


20

$N(CH_3)_2$

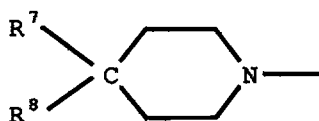


25 or



especially those wherein

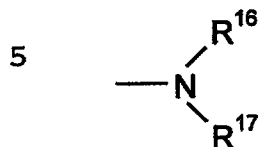
30 R^1 and R^2 together with the N to which they are bound
form the ring



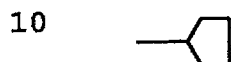
35

wherein

- (a) R^8 is H and
 R^7 is

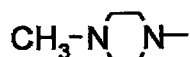


wherein R^{16} and R^{17} both represent CH_3 , C_2H_5 or CH_2CH_2OH or
 R^{16} is H or CH_3 and R^{17} is (C_{1-3}) alkyl,

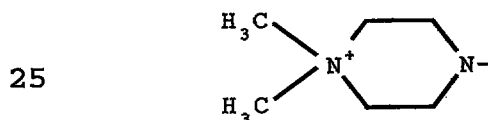


$(CH_2)_2OH$ or
 $(CH_2)_4OH$ or

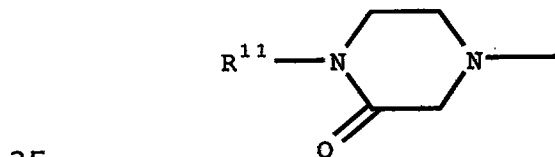
- 15 (b) R^8 is H and
 R^7 denotes



- 20 Of the compounds defined above, mention should also be
made of those wherein
 R^1 and R^2 together with the N to which they are bound
form the ring



- Of the compounds defined above, special mention should
also be made of those wherein
30 R^1 and R^2 together with the N to which they are bound
form the ring



wherein R^{11} is H or (C_{1-3}) alkyl, particularly those
wherein

R¹¹ is -CH(CH₃)₂.

Of the compounds defined above, the ones of particular interest are those wherein R³ is H;

5

and/or

10 R⁴ denotes phenyl(C₁₋₄)alkyl, wherein phenyl may be substituted by 1 or 2 substituents, wherein the substituents independently of one another denote halogen (F, Cl, Br, I), (C₁₋₄)alkyl, O-(C₁₋₄)alkyl, CF₃ or OCF₃;

and/or

15

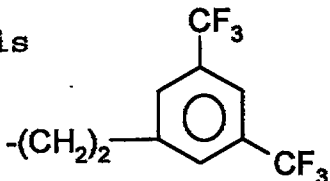
R⁵ denotes H, (C₁₋₄)alkyl, (C₃₋₆)cycloalkyl, -OH or phenyl(C₁₋₄)alkyl,

particularly those wherein

20 R⁴ denotes phenyl(C₂₋₄)alkyl, wherein the substituents are in positions 3 and/or 5 of the phenyl ring and/or

R⁵ is H, methyl, OH or phenethyl,

25 preferably those wherein

R⁴ is  and R⁵ is methyl.

30

Compounds of general formula I may have acid groups, chiefly carboxyl groups, and/or basic groups such as amino functions, for example. Compounds of general formula I may therefore be present either as internal salts, as salts with pharmaceutically acceptable inorganic acids such as hydrochloric acid, sulphuric acid, phosphoric acid, sulphonic acid or organic acids

35

(such as maleic acid, fumaric acid, citric acid, tartaric acid or acetic acid) or as salts with pharmaceutically acceptable bases such as alkali or alkaline earth metal hydroxides or carbonates, zinc or ammonium hydroxides or organic amines such as dimethylamine, triethylamine, triethanolamine, etc.

The compounds according to the invention may occur as racemates but may also be obtained as pure enantiomers, i.e. in the (R)- or (S)-form.

The term naphthyl used hereinbefore includes both 1-naphthyl and 2-naphthyl.

Test results for compounds according to the invention:

The receptor affinity for the NK₁-receptor (substance P-receptor) is determined on human lymphoblastoma cells (IM-9) with cloned NK₁-receptors, by measuring the displacement of ¹²⁵I-labelled substance P. The K_i-values thus obtained show the efficacy of the compounds:

		Ki [nM]
	Example 1	1.2
	Example 2	1.0
	Example 3	19
5	Example 4	1.4
	Example 5	1.5
	Example 8	1.8
	Example 9	2.5
	Example 11	3.8
10	Example 12	5.0
	Example 13	2.4
	Example 15	0.98
	Example 16	0.90
	Example 17	7.75
15	Example 18	0.96
	Example 19	1.17
	Example 20	2.0
	Example 22	2.2
	Example 23	2.5
20	Example 24	2.2
	Example 25	6.0
	Example 26	1.6
	Example 28	1.3
	Example 30	1.8
25	Example 32	1.3
	Example 33	7.4
	Example 34	2.9
	Example 47	1.7
	Example 55	1.25
30	Example 63	1.4
	Example 64	1.1
	Example 65	5.7
	Example 73	2.0
	Example 74	1.5
35	Example 75	0.44
	Example 76	2.0

The compounds according to the invention are valuable neurokinin (tachykinin) antagonists which have both substance P antagonism and also neurokinin A and neurokinin B antagonistic properties. They are useful
5 for the treatment and prevention of neurokinin-mediated diseases:
for the treatment or prevention of inflammatory and allergic diseases of the respiratory tract, such as asthma, chronic bronchitis, hyperreactive respiratory
10 tract, emphysema, rhinitis and cough,
and of the eyes, such as conjunctivitis and iritis,
of the skin, such as dermatitis in contact eczema,
15 urticaria, psoriasis, sunburn, insect bites and stings, itching, sensitive or hypersensitive skin,
of the gastrointestinal tract, such as gastric and duodenal ulcers, ulcerative colitis, Crohn's disease,
20 irritable bowel and Hirschsprung's disease,
of the joints, such as rheumatoid arthritis, reactive arthritis and Reiter syndrome;
25 for treating diseases of the central nervous system such as dementia, Alzheimer's disease, schizophrenia, psychoses, depression, headache (e.g. migraine or tension headaches), epilepsy, Parkinson's disease and stroke;
30 for treating herpes zoster and postherpetic pain, tumours, collagenoses, dysfunction of the deferent urinary tract, haemorrhoids, nausea and vomiting, caused for example by radiation or cytostatic therapy or motion
35 and pain of all kinds.

The invention therefore also relates to the use of the

compounds according to the invention as therapeutic agents and pharmaceutical preparations which contain these compounds. They are preferably used in humans. The compounds according to the invention may be administered by intravenous, subcutaneous, intramuscular, intraperitoneal or intranasal route, by inhalation, by transdermal route, optionally aided by iontophoresis or enhancers known from the literature, and by oral route.

For parenteral administration the compounds of formula I or the physiologically acceptable salts thereof, possibly with the conventional substances such as solubilisers, emulsifiers or other adjuvants, are dissolved, suspended or emulsified. Solvents which may be used include: water, physiological saline solutions or alcohols, e.g. ethanol, propanediol or glycerol, sugar solutions such as glucose or mannitol solutions or a mixture of several solvents.

In addition, the compounds may be administered by means of implants, e.g. of polylactide, polyglycolide or polyhydroxybutyric acid or intranasal preparations.

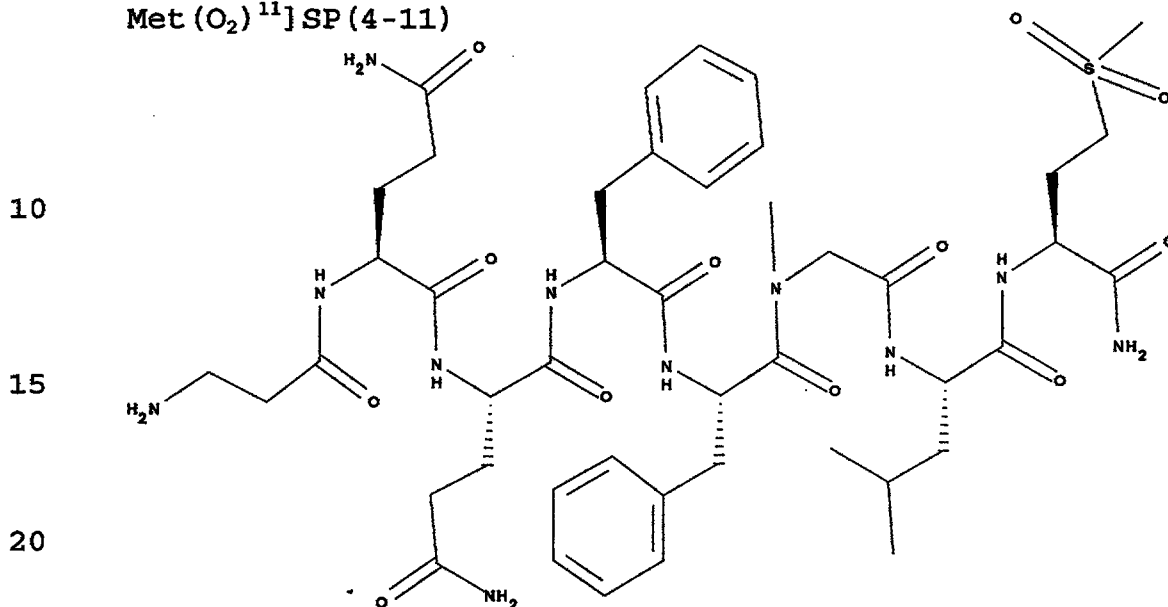
The oral efficacy of compounds of general formula I can be demonstrated by the following standard test:

Inhibition of lowering of blood pressure caused by NK_1 in anaesthetised guinea pigs.

Guinea pigs weighing 300-500 grams were anaesthetised with pentobarbital (50 mg/kg i.p.), intubated and artificially ventilated. They were ventilated with 10 ml/kg of air at a frequency of 60 breaths per minute. The carotid artery was cannulated and the arterial blood pressure was recorded. A polyethylene tube was inserted into the jugular vein for the intravenous supply of

substances.

A temporary reduction in blood pressure was brought about at intervals of 10 minutes by intravenous administration of the NK₁-agonist [β Ala⁴, Sar⁹, Met(O₂)¹¹]SP(4-11)



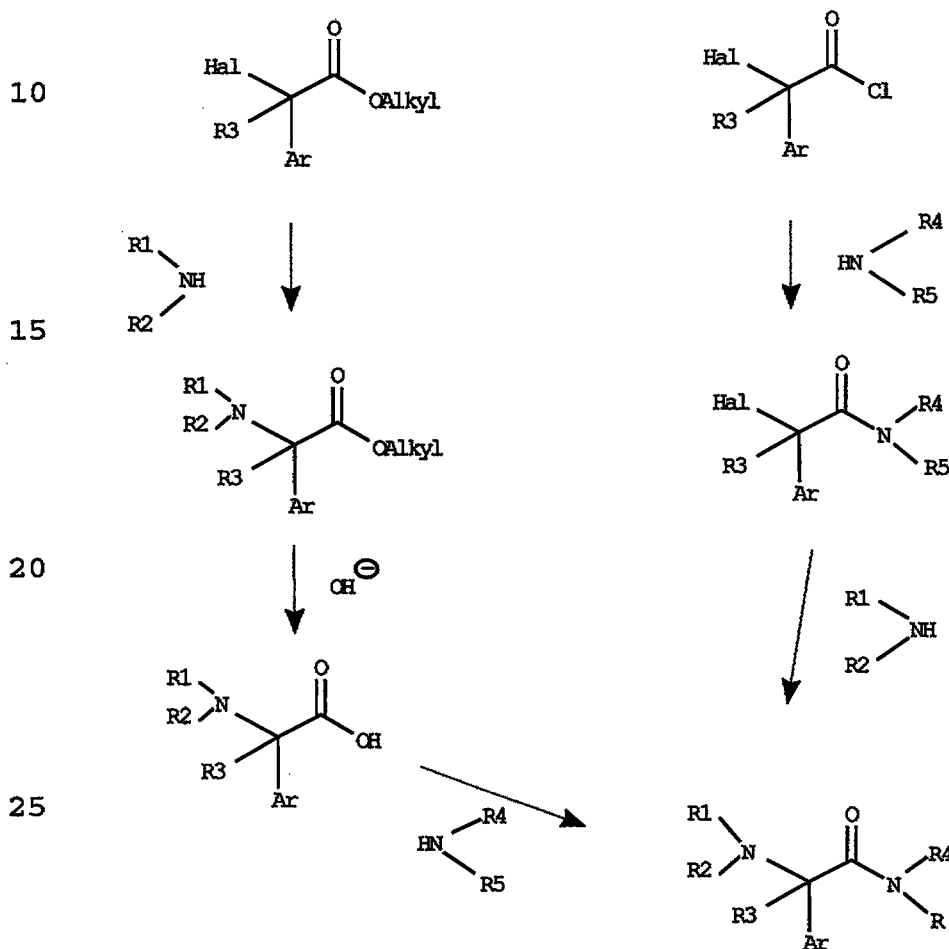
25 in a dose of 0.2 μ mol/kg. After the blood pressure thus produced had been measured, the test compound was introduced into the duodenum and the NK₁-agonist was again injected every 10 minutes.

30 The results were expressed as a % inhibition of the reduction in blood pressure caused by the NK₁-agonist specified.

In a dosage of 1 mg/kg (administered into the duodenum) the compound of Example 1 inhibited the lowering of blood pressure caused by the NK₁-agonist by 80%.

The compounds according to the invention can be produced using generally known methods.

5 The compounds may be prepared in various ways. The two most common procedures are represented by the following diagram:



35 Method A. The carboxylic acid may be linked to the amine $\text{HN}(\text{R}^5)\text{R}^4$ by various methods. Conventional methods are coupling processes such as those used in peptide chemistry. A coupling reagent such as TBTU, DCCI/HOBt, CDI, etc., is added to the coupling partners in substantially equivalent quantities. Suitable solvents are DMF, THF, CH_2Cl_2 , CHCl_3 , acetonitrile or other inert solvents or mixtures thereof. The suitable temperature

range is between -50°C and $+120^{\circ}\text{C}$, preferably between 0°C and 40°C .

5 The carboxylic acid may also initially be converted into the corresponding acid halide by known methods using SOCl_2 , SO_2Cl_2 , PCl_3 , PCl_5 or PBr_3 or mixtures thereof, and the acid halide is then reacted with the amine $\text{HN}(\text{R}^5)\text{R}^4$ in an inert solvent such as CH_2Cl_2 , THF or dioxane at temperatures between -50°C and $+100^{\circ}\text{C}$, typically at 0° to
10 20°C .

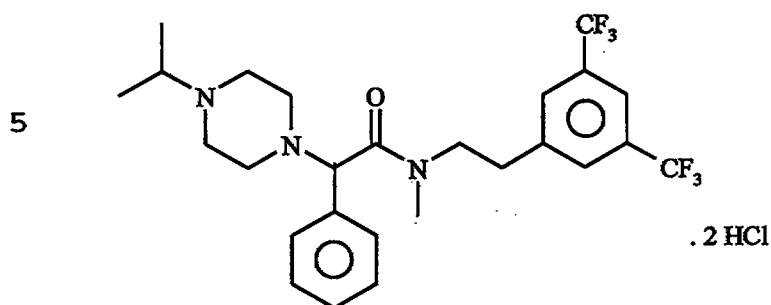
Another alternative is to convert the carboxylic acid initially into the alkylester, usually the methylester, by known methods and this ester is then reacted with the
15 amine $\text{HN}(\text{R}^5)\text{R}^4$ in an inert solvent such as DMF, dioxane or THF. The reaction temperatures are between 20°C and 150°C , typically between 50°C and 120°C . The reaction may also be carried out in a pressurized container.

20 Method B. Here, the α -halo-arylacetamide derivative obtained by known methods is reacted with the amine $\text{R}^1(\text{R}^2)\text{NH}$, thereby cleaving hydrogen halide. Inorganic bases such as K_2CO_3 , NaHCO_3 or CaCO_3 or organic bases such as triethylamine, Hünig base, pyridine or DMAP are used
25 to mop up the cleaved (or excess) hydrogen halide, or an excess of the amine $\text{R}^1(\text{R}^2)\text{NH}$ may be used. DMF, THF, dioxane or other inert solvents are used. The temperature range for the reaction is from 0 to 100°C , typically between 10 and 80°C .

30 Method C. The compounds according to the invention wherein R^5 is not H may also be prepared as follows: first of all, the corresponding compound in which R^5 is H is synthesised using method A or B. Then, N-alkylation
35 is carried out as follows in order to introduce alkyl, cycloalkyl or CH_2COOH . The compounds according to the invention wherein R^5 is H are deprotonated with an equivalent quantity of NaH, NaNH_2 ,

KOH, NaOCH₃ or another strong base. Anhydrous inert solvents such as THF, dioxane or diethylether are used for this. Then the corresponding alkylating agent is added slowly in the form of the corresponding halide, 5 tosylate or mesylate. The reaction is carried out at a temperature within the range from -50°C to +100°C, typically between 0°C and +50°C.

Example 1:



10

Mp.: 105 - 115°C
FAB-MS: (M+H)⁺ = 516.3.

1st step: 0.71 g of 1-isopropylpiperazine were
15 dissolved in 55 ml of anhydrous DMF, mixed with 0.64 g
of Na₂CO₃, stirred for 20 minutes at RT and then cooled
to 5°C. 1.15 g of methyl (R,S)-α-bromophenylacetate
were added and the suspension was stirred overnight at
RT. The precipitate was filtered off and the filtrate
20 was evaporated down. The residue was taken up in ethyl
acetate, extracted twice with 10% KHCO₃ solution and once
with saturated NaCl solution. The organic phase was
dried over Na₂SO₄, filtered and evaporated down, to yield
1.23 g of methyl (R,S)-1-isopropyl-4-(2-phenylacetate)
25 piperazine as a viscous oil.
Yield: about 89%.

2nd step: 1.23 g of the product from the 1st step were
dissolved in 10 ml of methanol and 10 ml of THF, mixed
with 10 ml of 1N NaOH and the mixture was stirred
30 overnight at ambient temperature. The clear reaction
solution was neutralised by the addition of 10 ml of 1N
HCl, evaporated to dryness, the residue was treated with
DMF and the solid was separated by suction filtering.
The filtrate was evaporated down and the residue was
35 triturated with ether, the solid substance removed by
suction filtering and dried in a desiccator. In this
way, 1.1 g of (R,S)-1-i-propyl-4-(2-phenylacetic acid)-
piperazine were obtained as a solid white substance.
Yield: 92%.

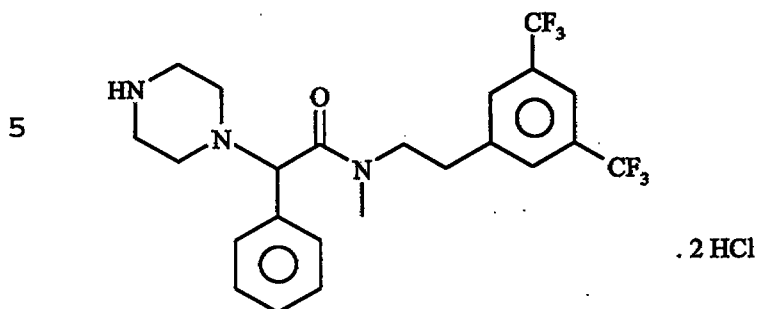
40 3rd step: 0.37 g of the product of the 2nd step and

0.42 g of N-methyl-3,5-bis-(trifluoromethyl)-phenylethylamine were dissolved in 14 ml of DMF and adjusted to pH 8.5 by the addition of about 0.4 ml of TEA. 0.48 g of TBTU were added and the mixture was stirred overnight at room temperature. The clear reaction solution was evaporated down *in vacuo*, the residue was stirred with NaHCO₃ solution and extracted twice with ethyl acetate. The combined organic phases were filtered and the filtrate was evaporated down. The residue was chromatographed over silica gel using CH₂Cl₂/MeOH (9:1) as eluant. The uniform fractions obtained were evaporated down, dissolved in a little MeOH, acidified with ethereal HCl and evaporated down again. The residue was triturated with ether and dried in a desiccator. 0.58 g of (R,S)-1-i-propyl-4-[2-phenylacetic acid-N-methyl-N-(3,5-bistrifluoromethyl-phenylethyl)]-amide dihydrochloride were obtained as a solid white substance.

Yield: 75%.

The other compounds of the invention may be prepared analogously, e.g. the following:

Example 2:



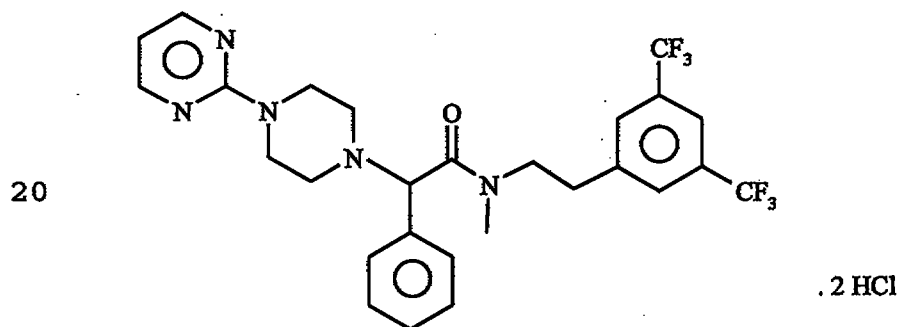
10

Mp. 141 - 146°C

FAB-MS: (M+H)⁺ = 474.3

Example 3:

15



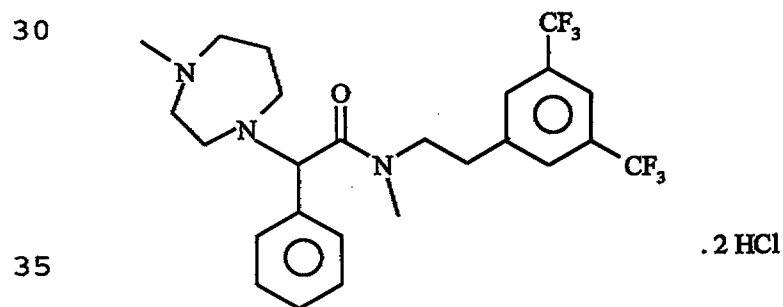
25

Mp.: 122 - 132°C

FAB-MS: (M+H)⁺ = 552.4

Example 4:

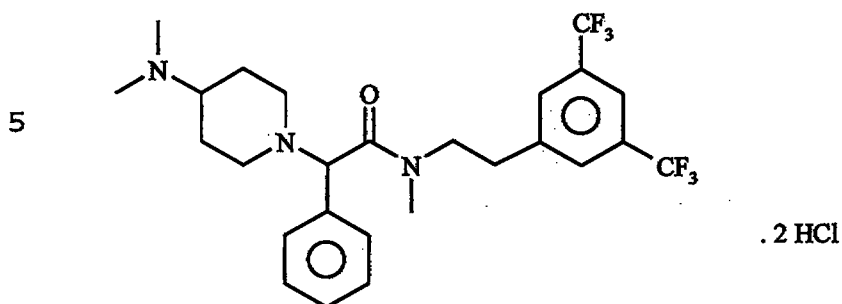
30



Mp.: 138 - 148°C

FAB-MS: (M+H)⁺ = 502.3

Example 5:



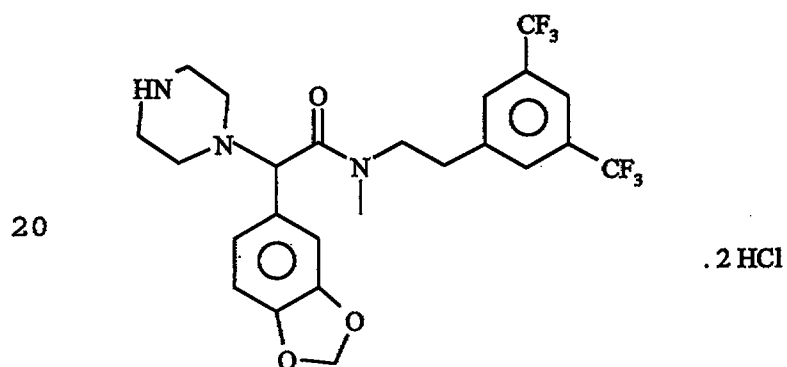
10

Mp.: 231 - 241°C (Decomp.)

FAB-MS: $(M+H)^+ = 516.4$

Example 6:

15



20

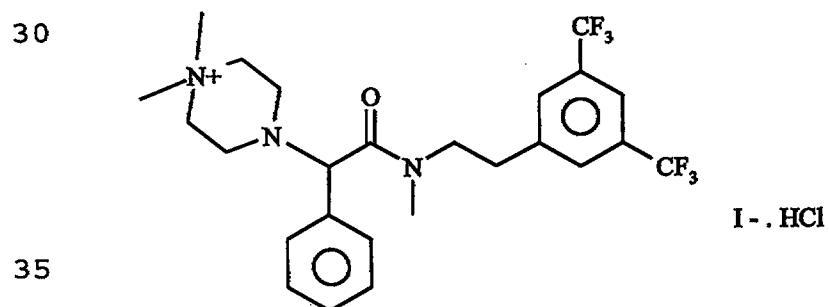
25

Mp.: 122 - 132°C

FAB-MS: $(M+H)^+ = 518.1$

Example 7:

30

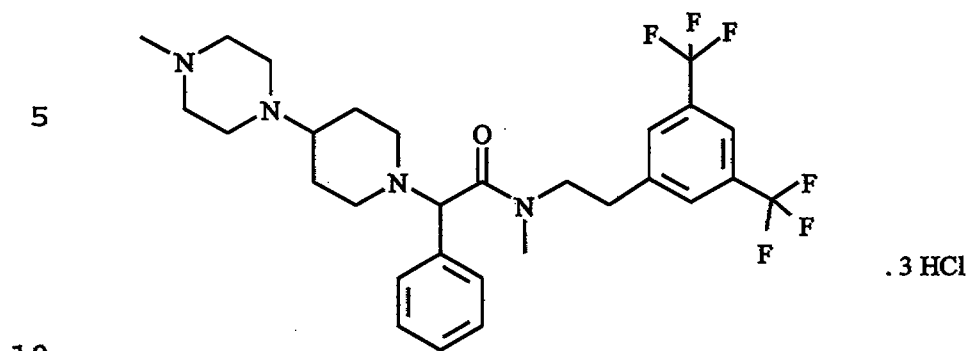


35

Mp.: 168 - 174°C (Decomp.)

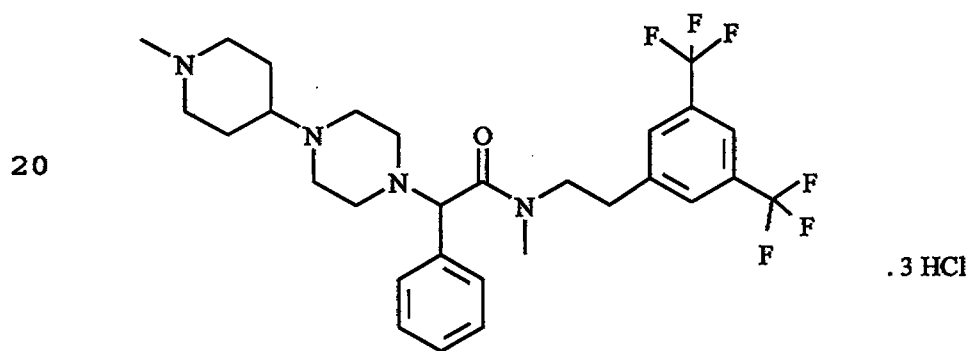
FAB-MS: $M^+ = 502.3$

Example 8:



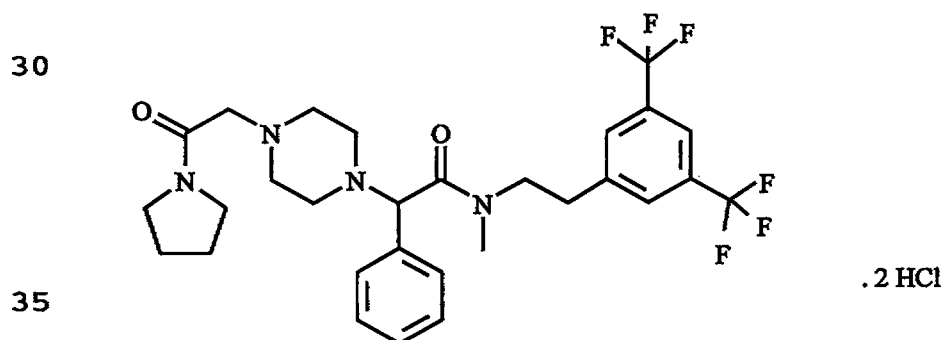
Mp.: >240°C

Example 9:



Mp.: >230°C

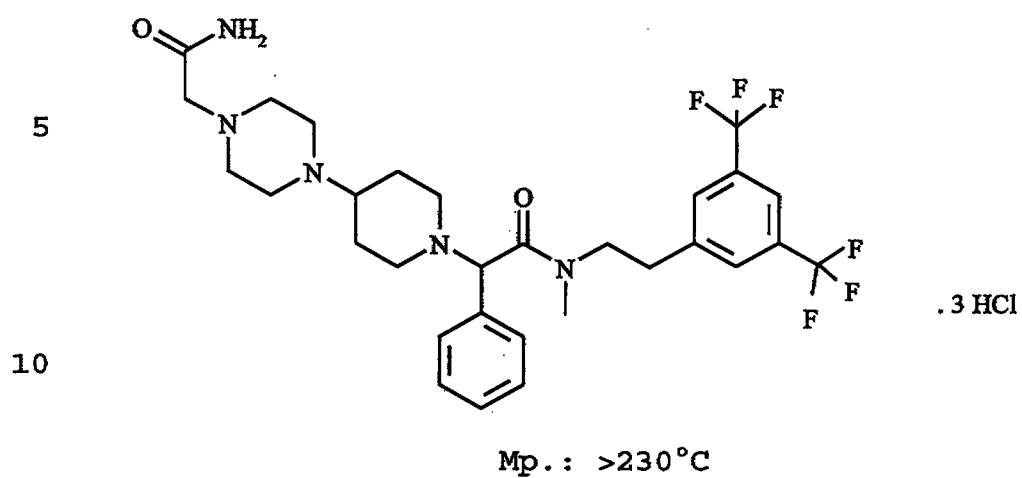
Example 11:



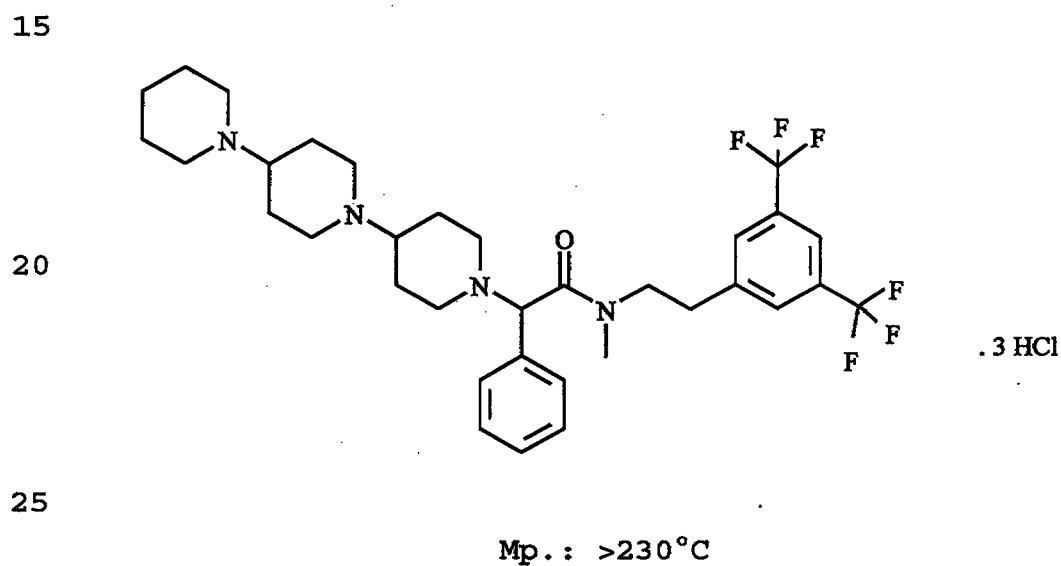
Bp.: 130 - 160°C

Mp.: 215 - 218°C (Decomp.)

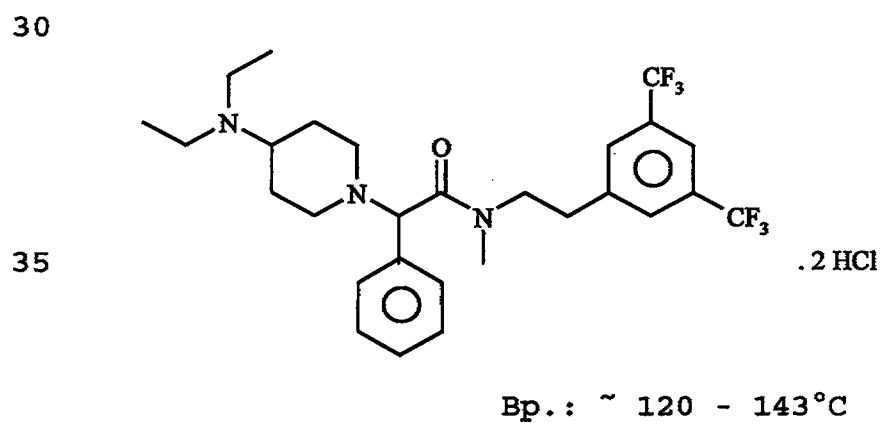
Example 12:



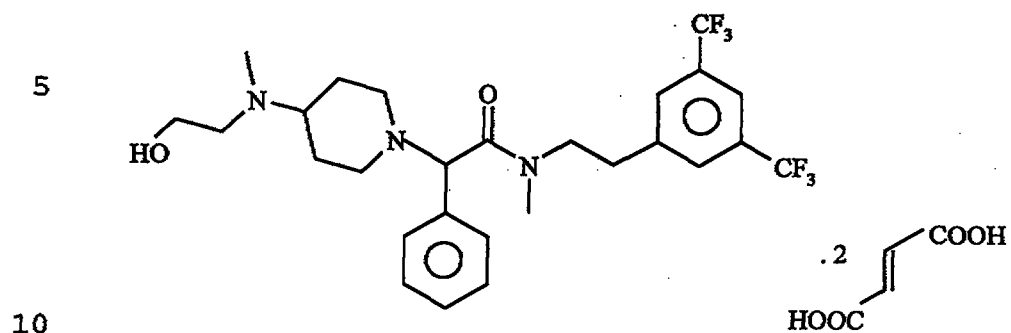
Example 13:



Example 15:

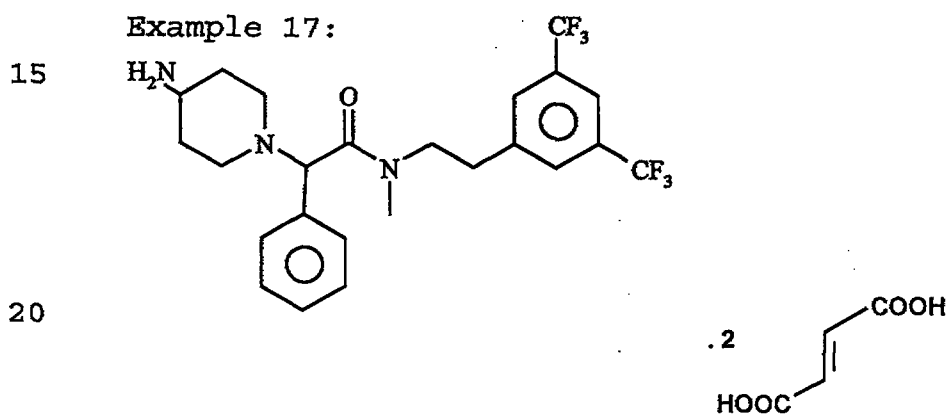


Example 16:



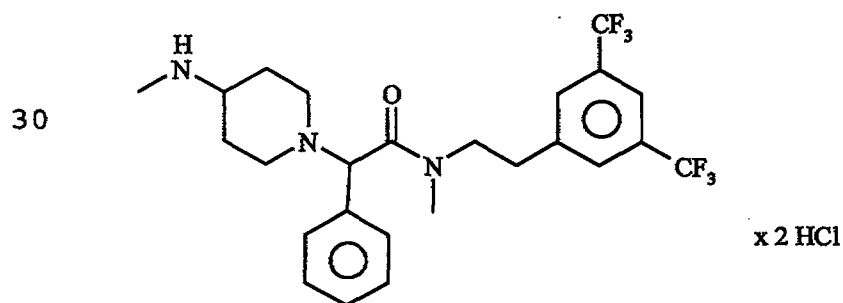
Mp.: 168 - 170°C

Example 17:



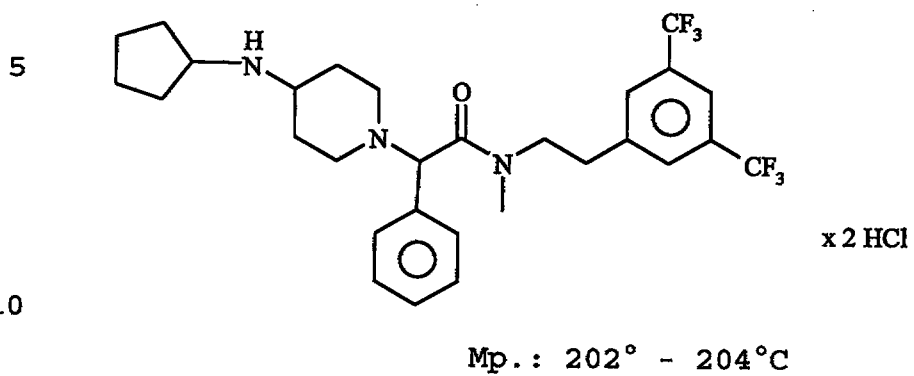
Mp.: 142 - 150°C

Example 18:

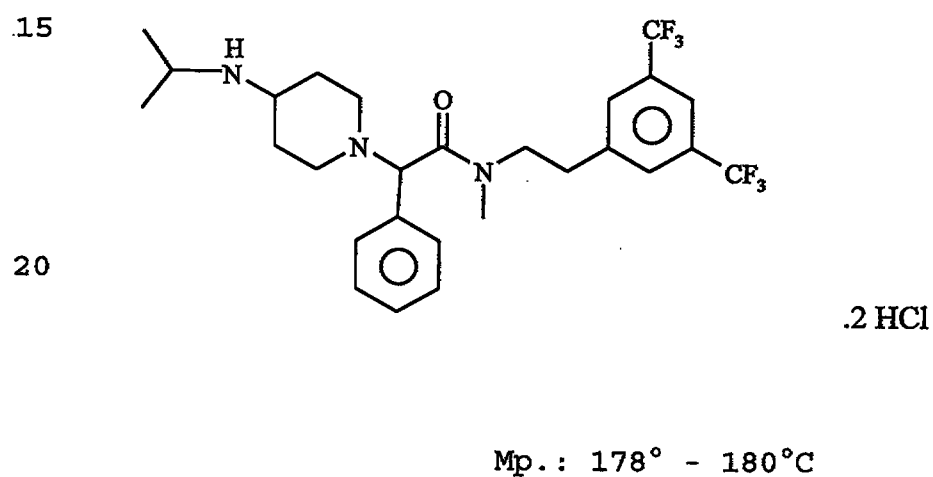


Mp.: >230°C

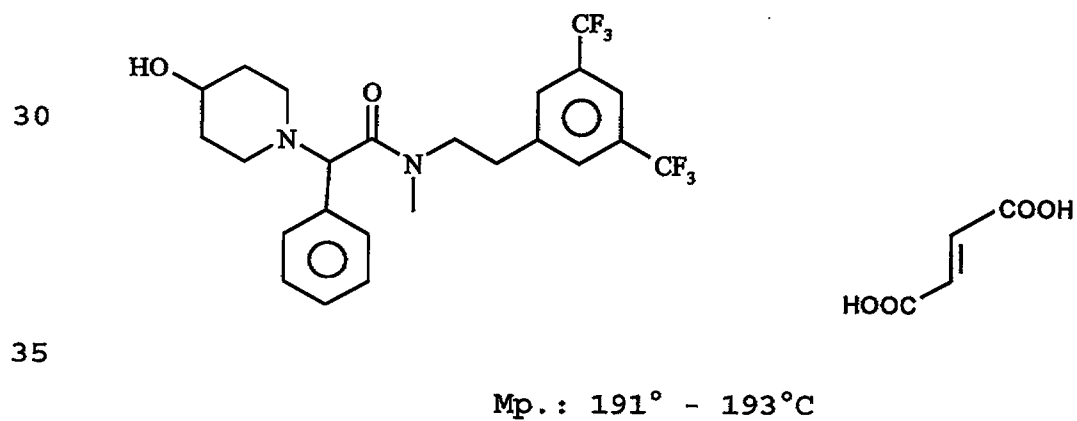
Example 19:



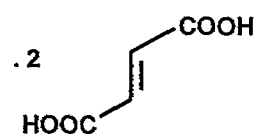
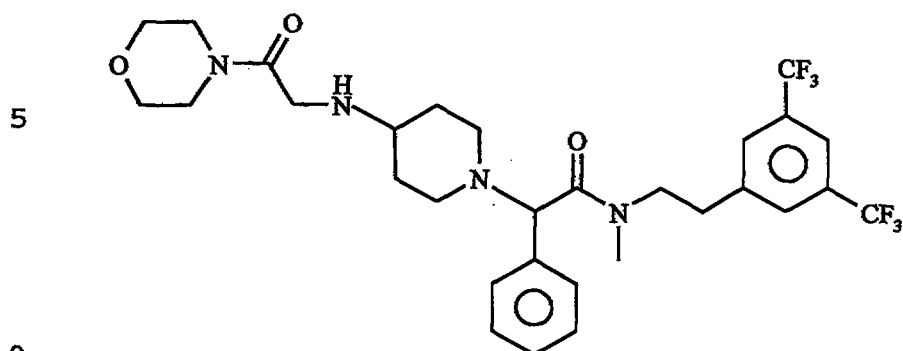
Example 20:



Example 22:

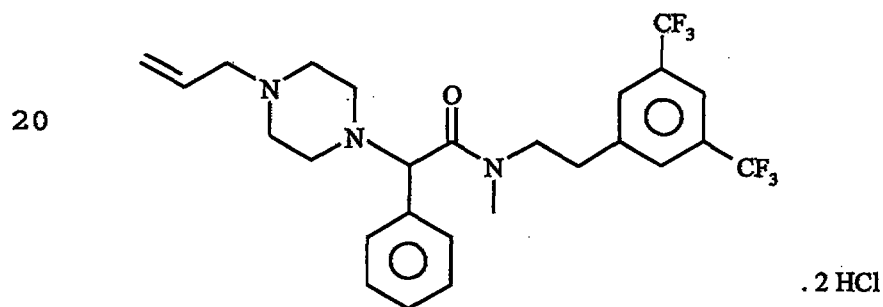


Example 23:



Mp.: 162 - 164°C

Example 24:

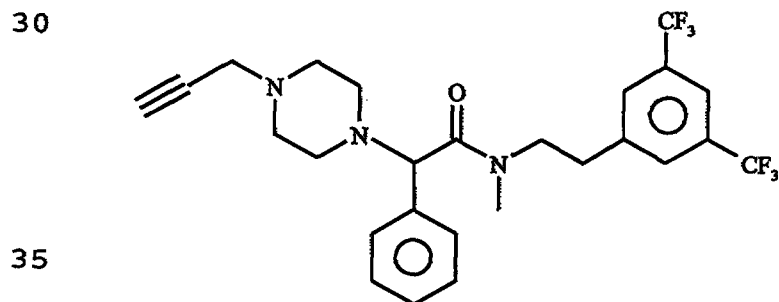


.2 HCl

Mp.: 220 - 224°C (Decomp.);

FAB-MS: (M+H)⁺ = 514.3

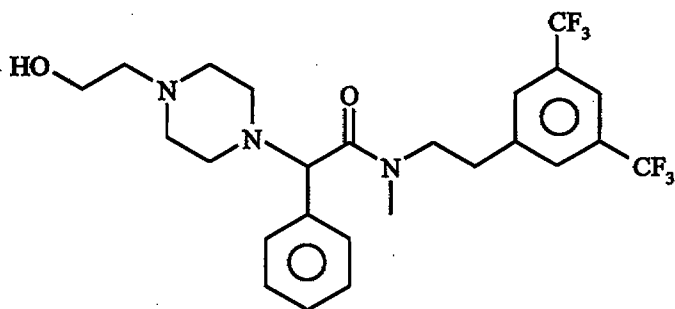
Example 25:



Mp.: 102 - 117°C;

FAB-MS: (M+H)⁺ = 512.4

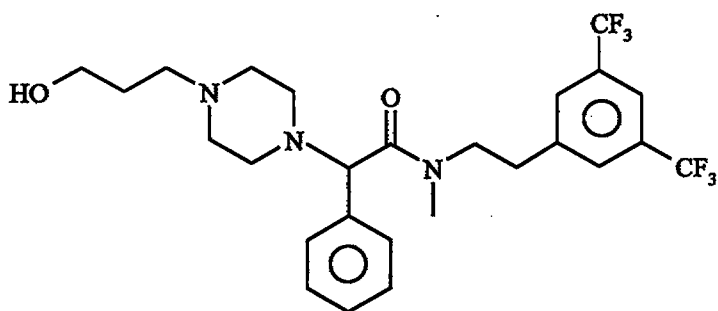
Example 26:



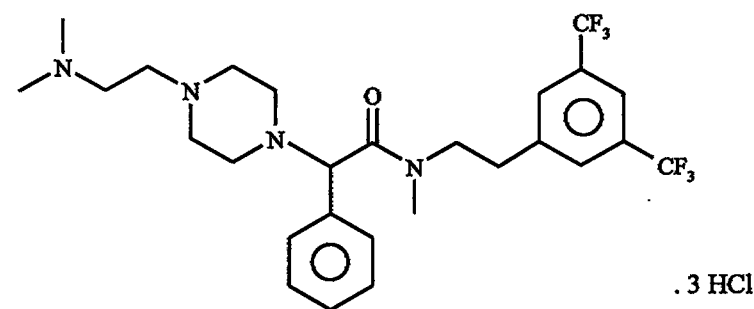
Mp.: 225° - 232°C (Decomp.);

FAB-MS: (M+H)⁺ = 518.3

Example 27:



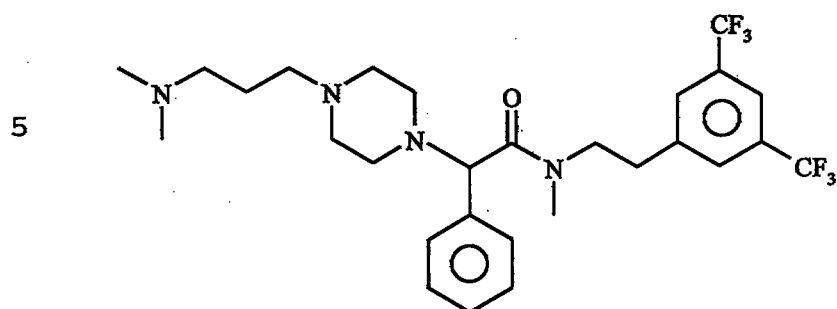
Example 28:



Mp.: 242 - 245°C (Decomp.)

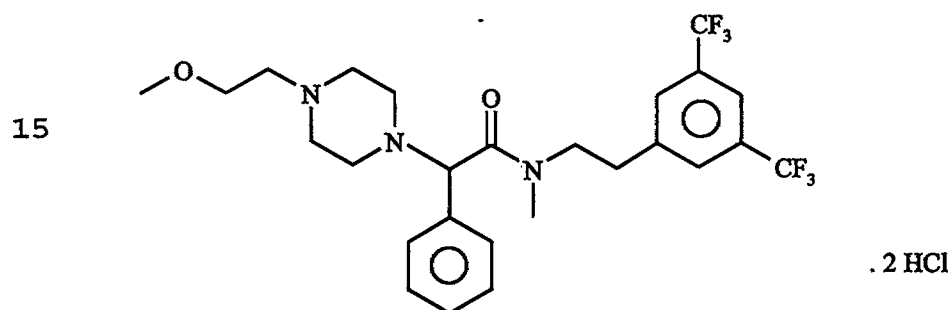
FAB-MS: (M+H)⁺ = 545.2

Example 29:



10

Example 30:

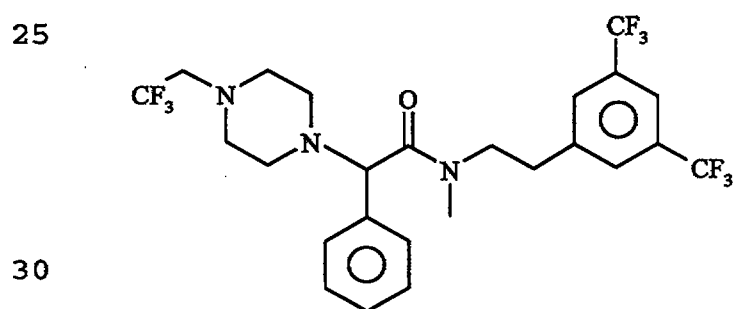


20

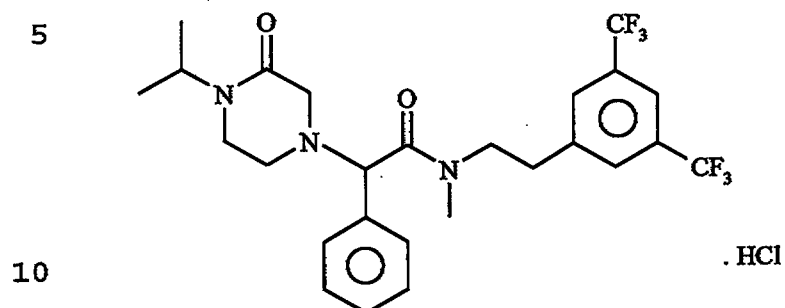
Mp.: 115° - 124°C;

FAB-MS: (M+H)⁺ = 532.3

Example 31:



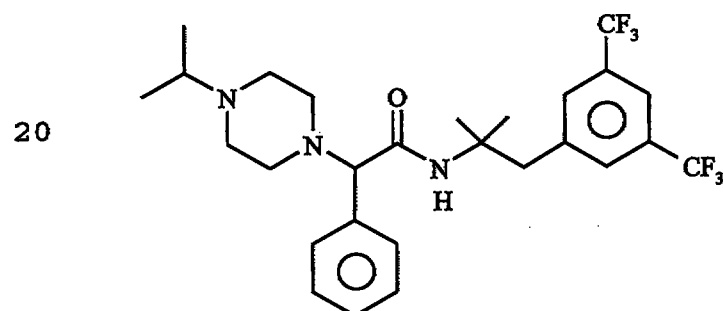
Example 32:



Mp.: 107 - 112°C;

FAB-MS: (M+H)⁺ = 530.2

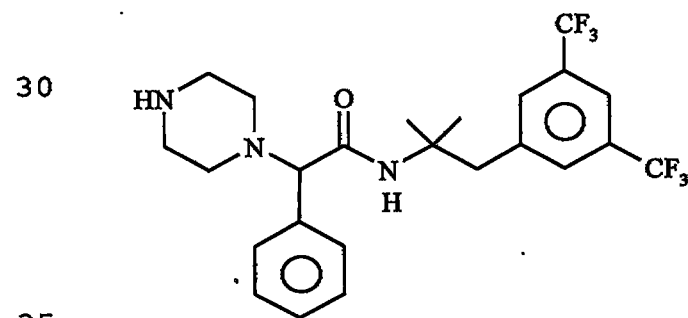
Example 33:



Mp.: 133 - 143°C;

FAB-MS: (M+H)⁺ = 530.4

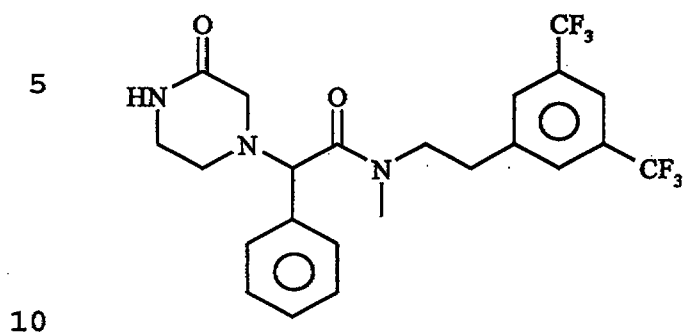
Example 34:



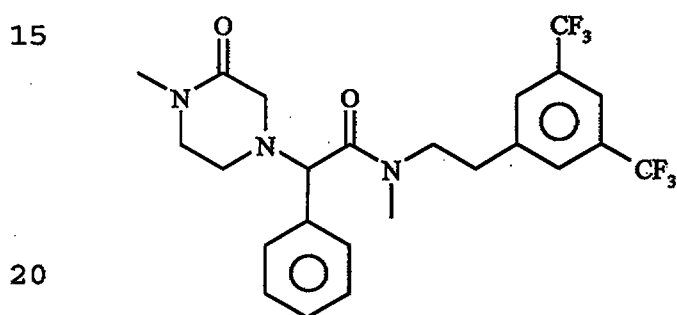
Mp.: 178 - 182°C;

FAB-MS: (M+H)⁺ = 488.3

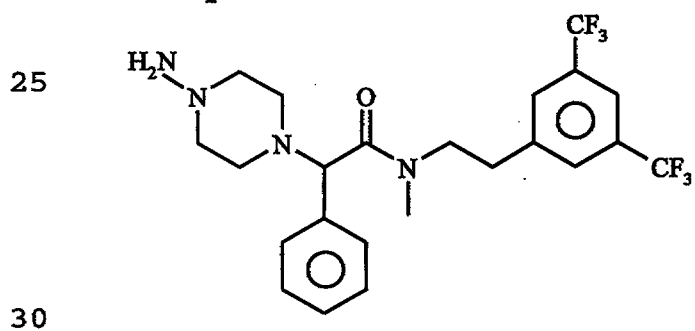
Example 35:



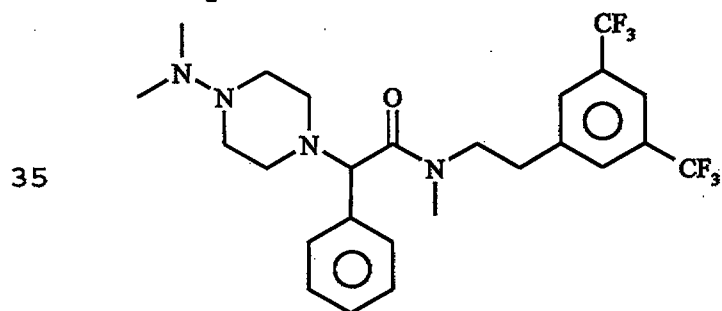
Example 36:



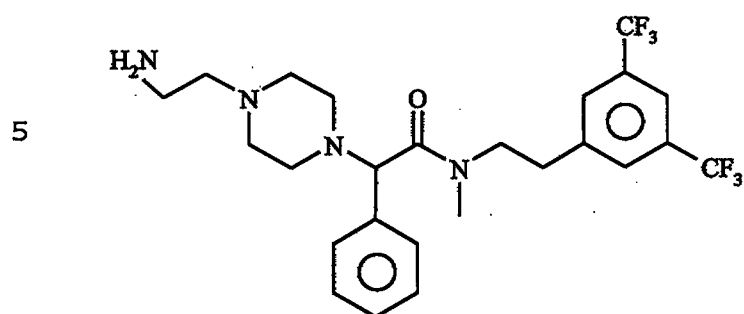
Example 37:



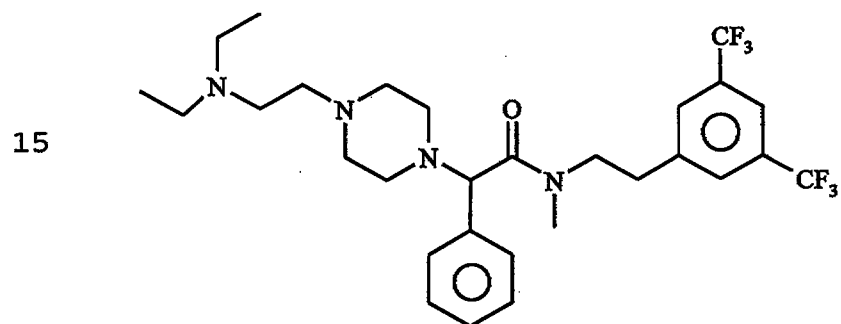
Example 38:



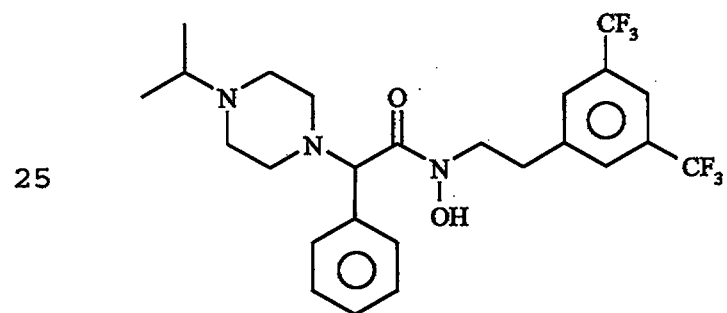
Example 39:



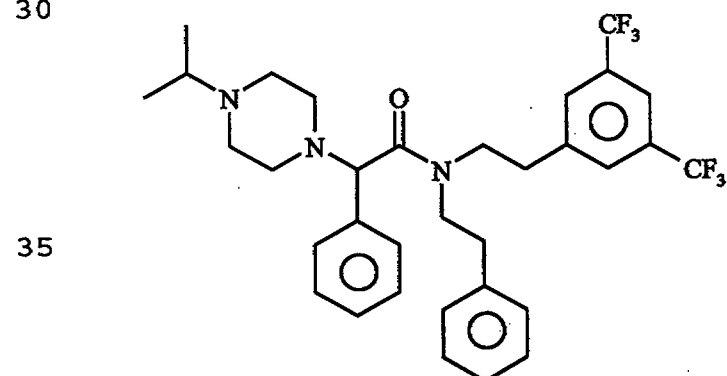
10 Example 40:



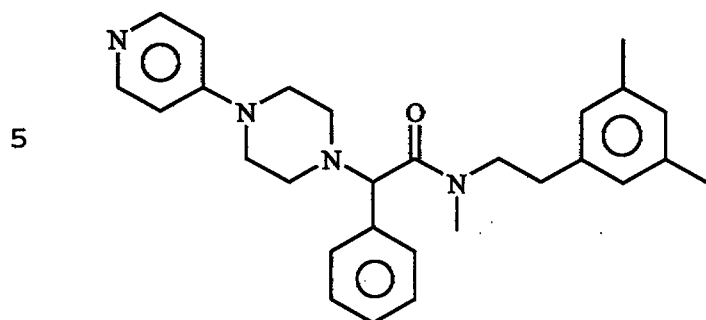
20 Example 41:



Example 42:

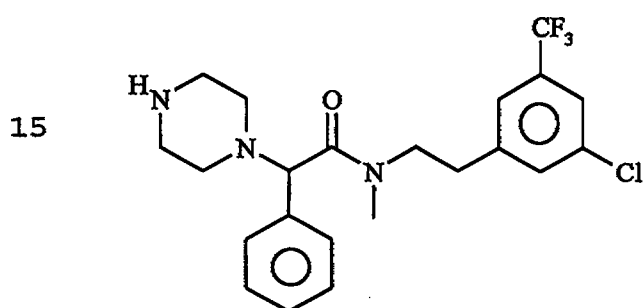


Example 43:



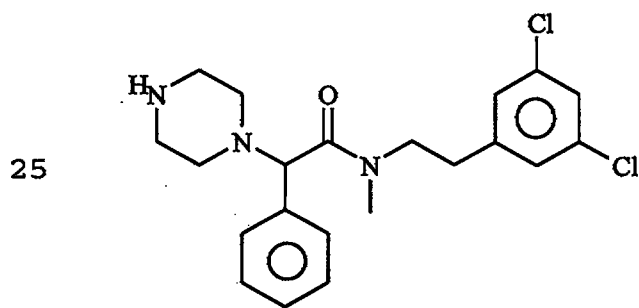
10

Example 44:



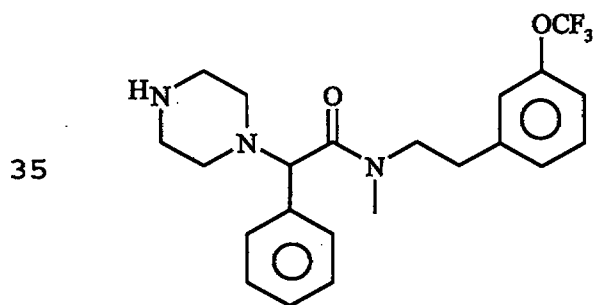
20

Example 45:

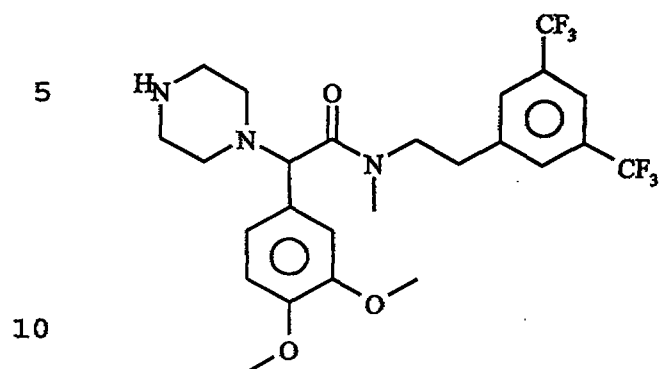


30

Example 46:



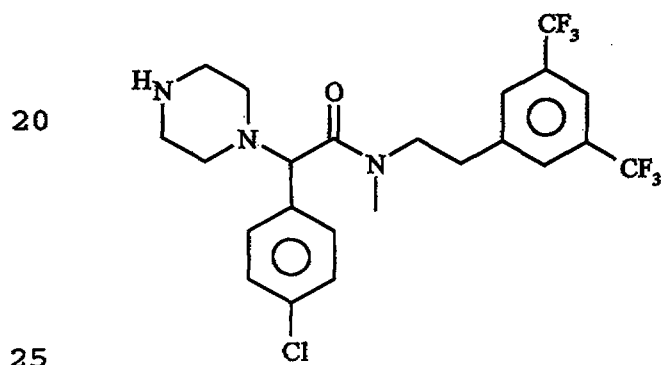
Example 47:



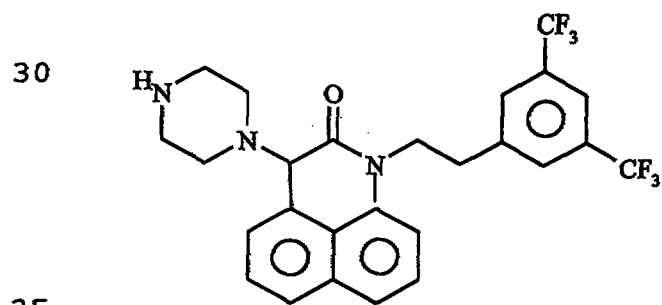
Mp.: 149-159°C

FAB-MS: (M+H)⁺ = 534.4

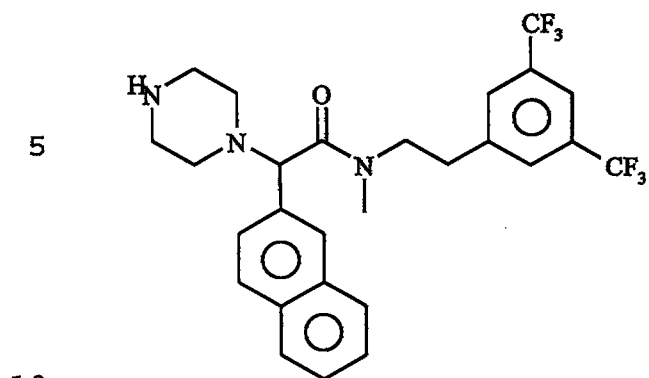
Example 48:



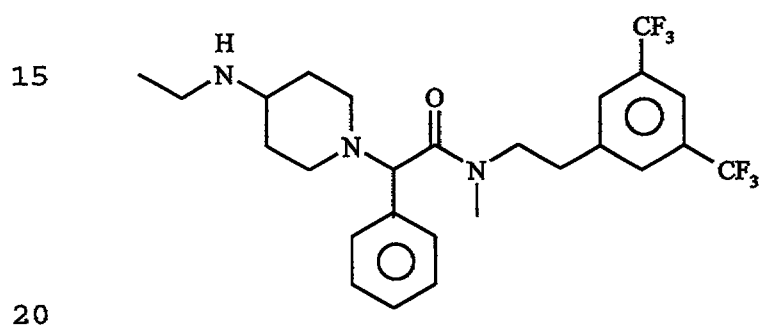
Example 49:



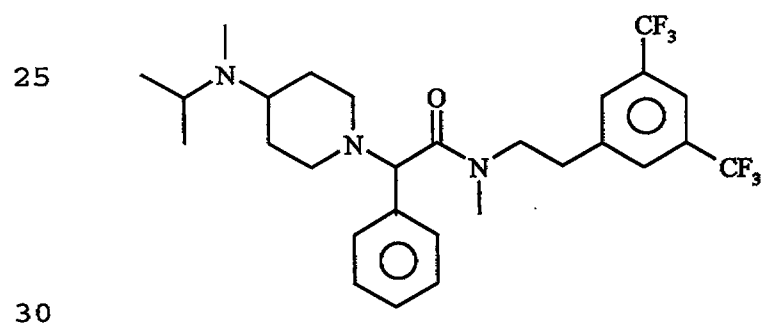
Example 50:



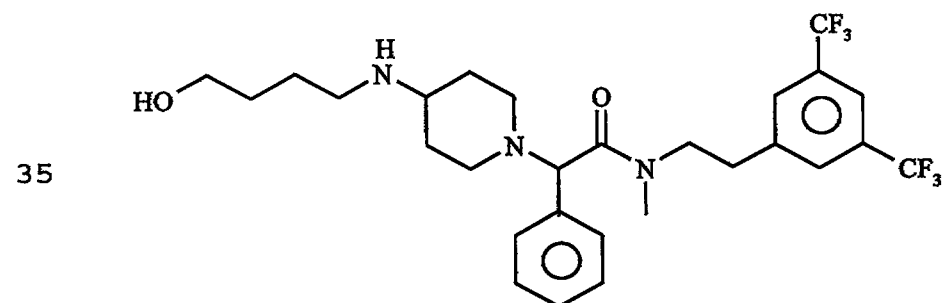
Example 51:



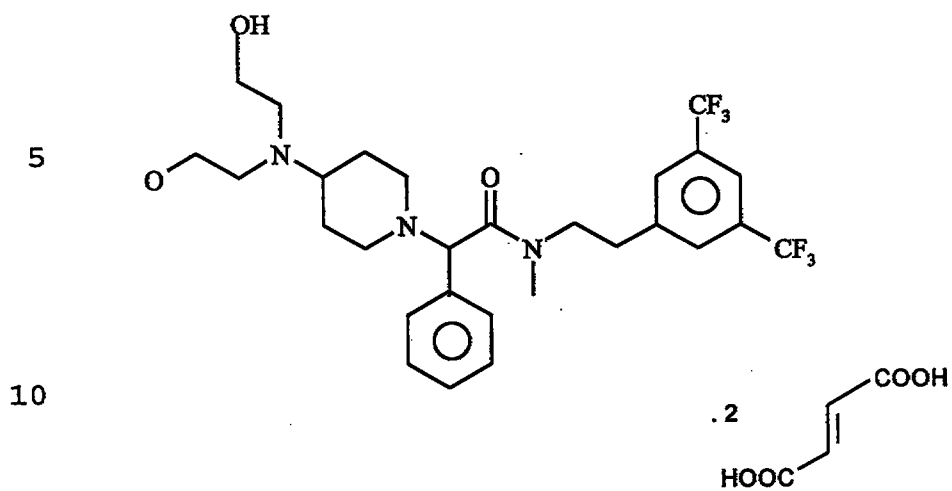
Example 53:



Example 54:

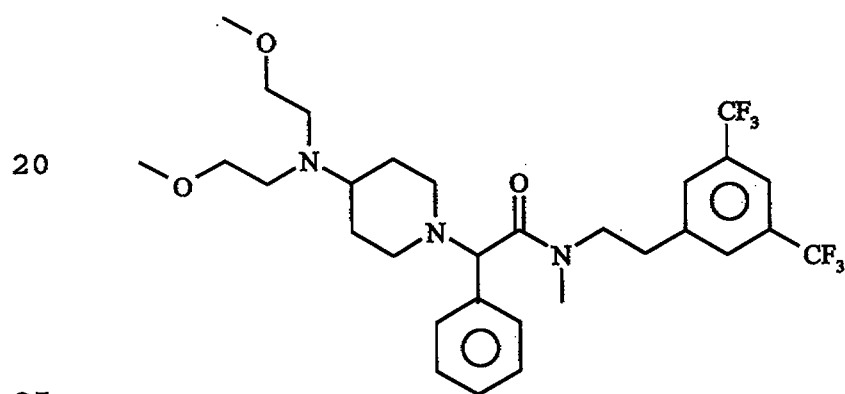


Example 55:

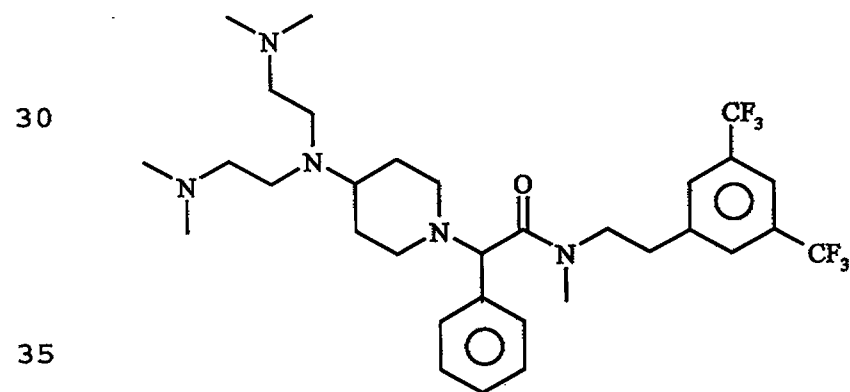


Mp.: 115 - 119°C

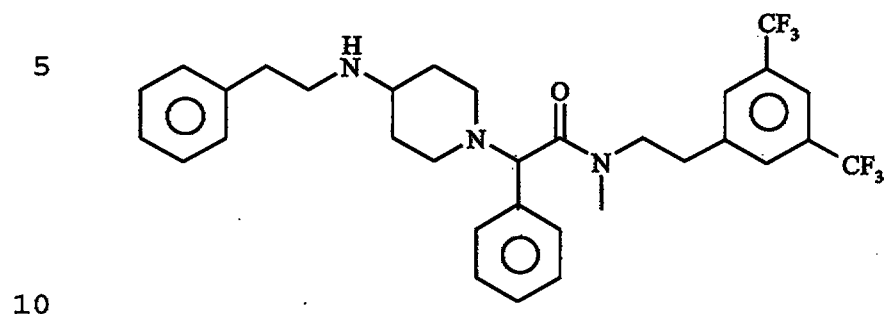
15 Example 56:



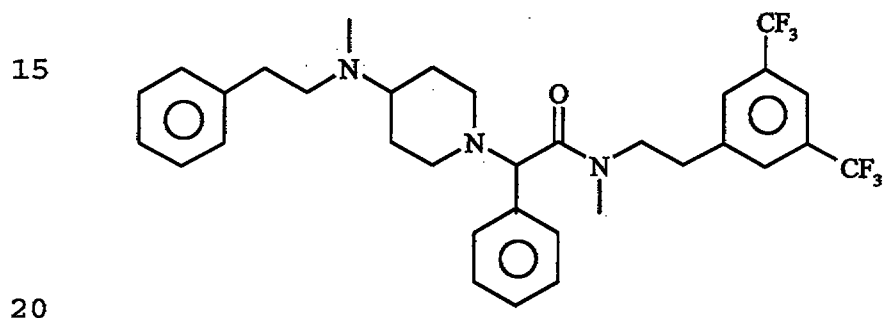
Example 57:



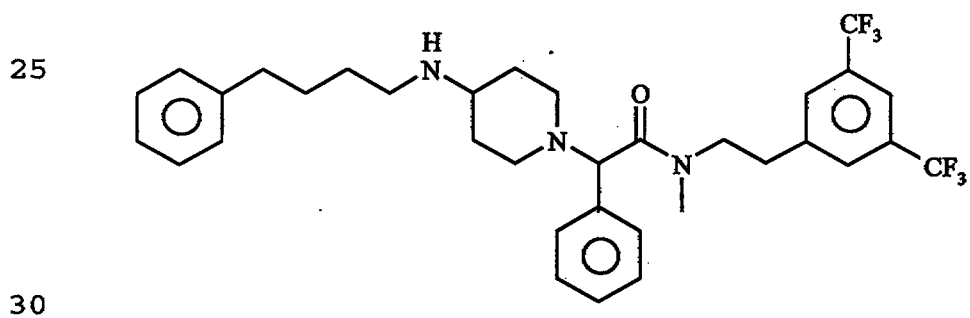
Example 58:



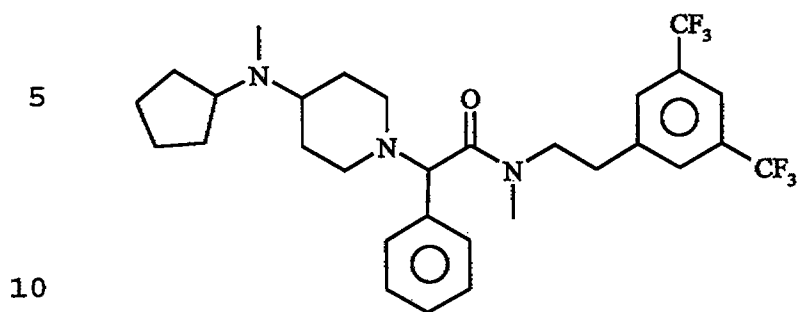
Example 59:



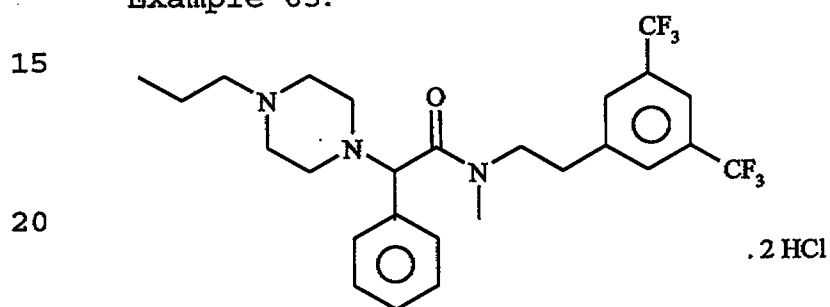
Example 60:



Example 61:



Example 63:



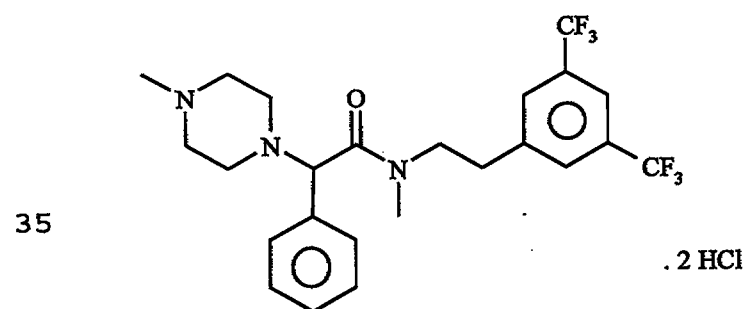
25

Mp.: 218 - 228°C (Decomp.)

FAB-MS: (M+H)⁺ = 516.3

Example 64:

30

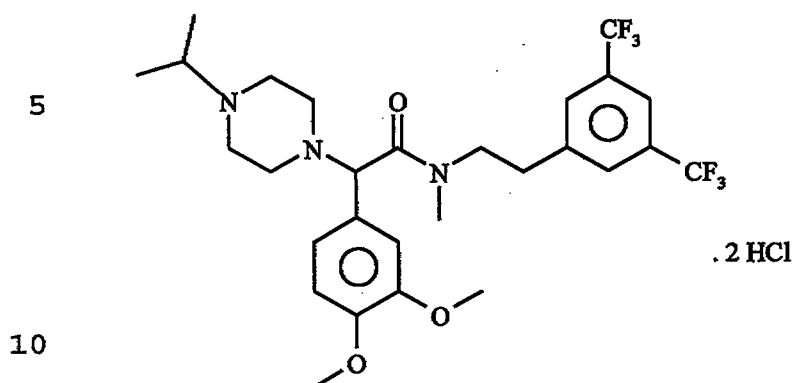


35

Mp.: 92 - 96°C

FAB-MS: (M+H)⁺ = 488.2

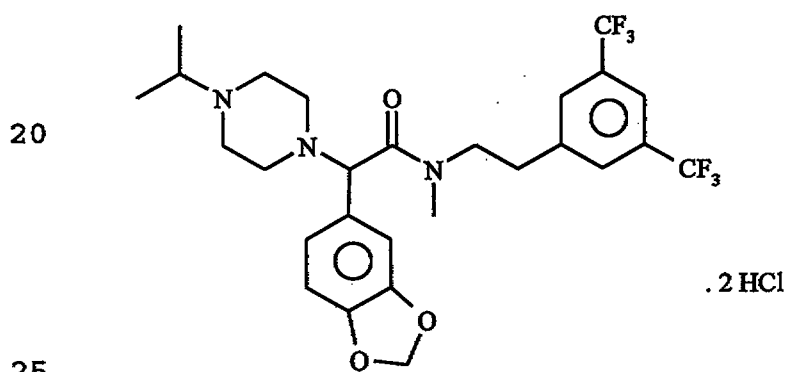
Example 65:



Mp.: 132 - 142°C

FAB-MS: (M+H)⁺ = 576.5

Example 66:

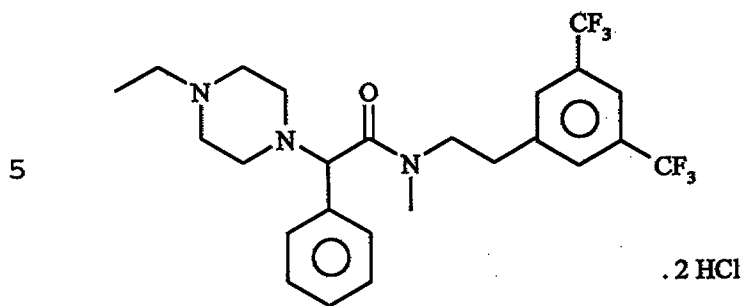


Mp.: 131 - 141°C

FAB-MS: (M+H)⁺ = 560.1.

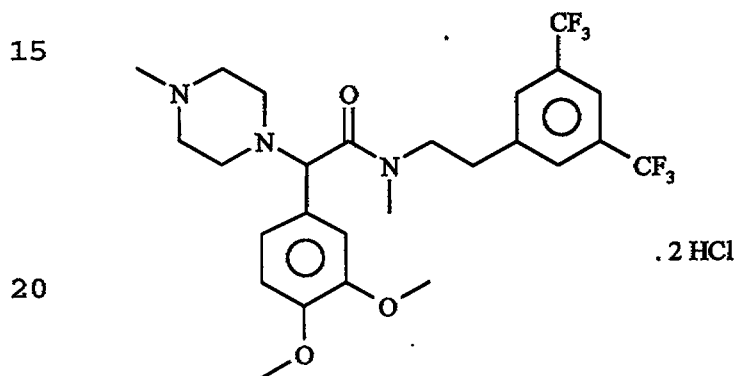
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Example 67:

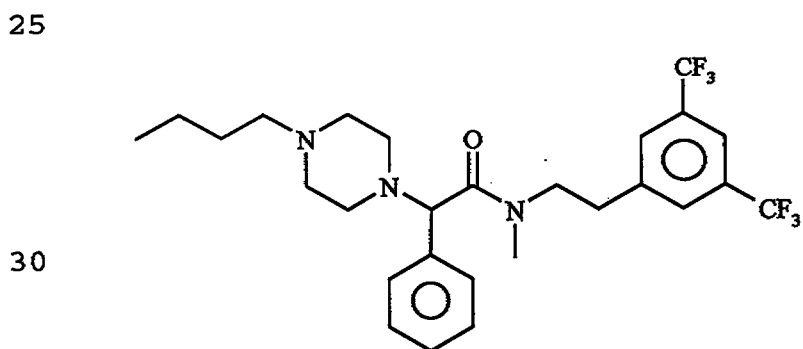


10
Mp.: 228 - 231°C (Decomp.)
FAB-MS: (M+H)⁺ = 502.3

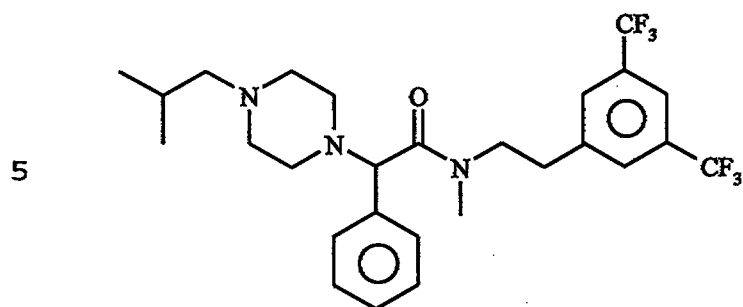
Example 68:



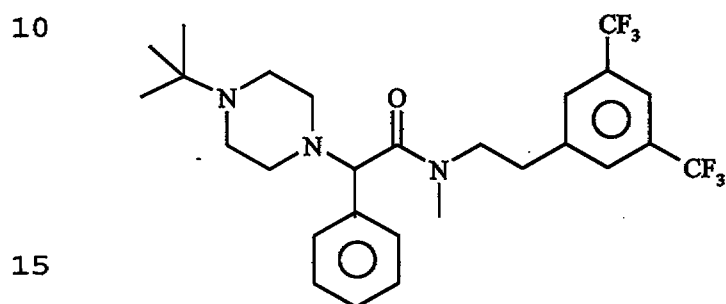
Example 69:



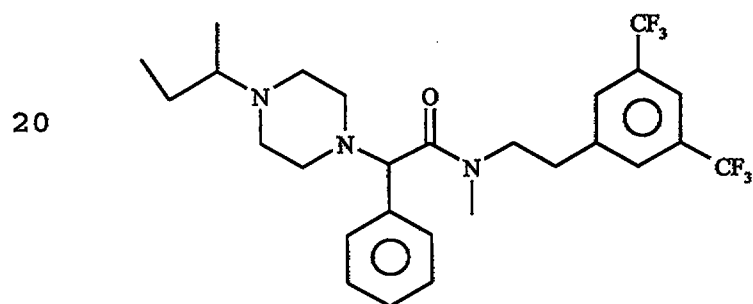
Example 70:



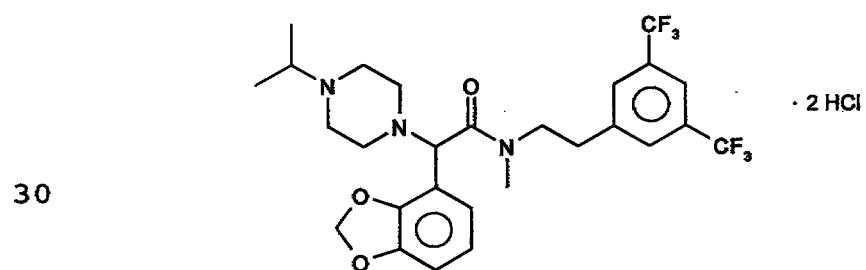
Example 71:



Example 72:



25 Example 73:

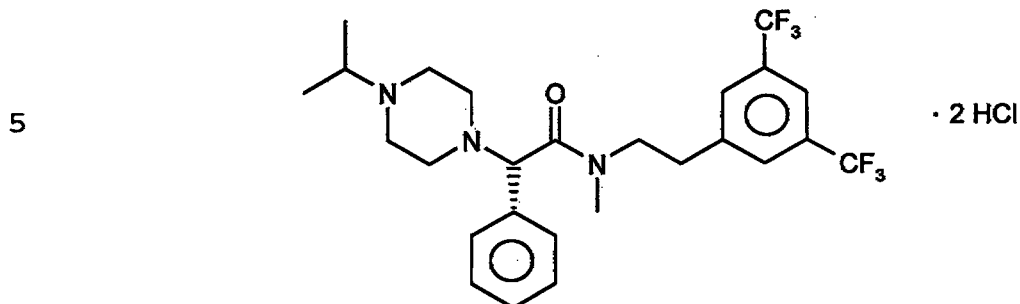


35

Mp.: 108 - 118°C

FAB-MS: (M+H)⁺ = 560.4

Example 74:



10

Fp.: 138 - 148°C.

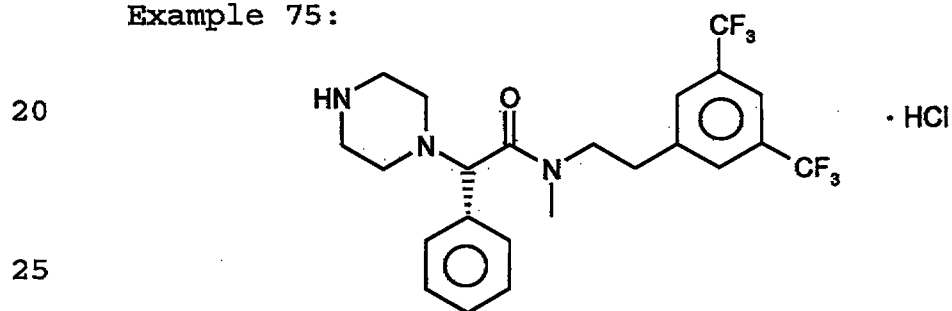
$[\alpha]_D^{20} = +45.5^\circ$ (MeOH)

Mp.: 138 - 148°C

$[\alpha]_D^{20} = +45.5^\circ$ (MeOH)

15

Example 75:



Fp.: 166 - 176°C.

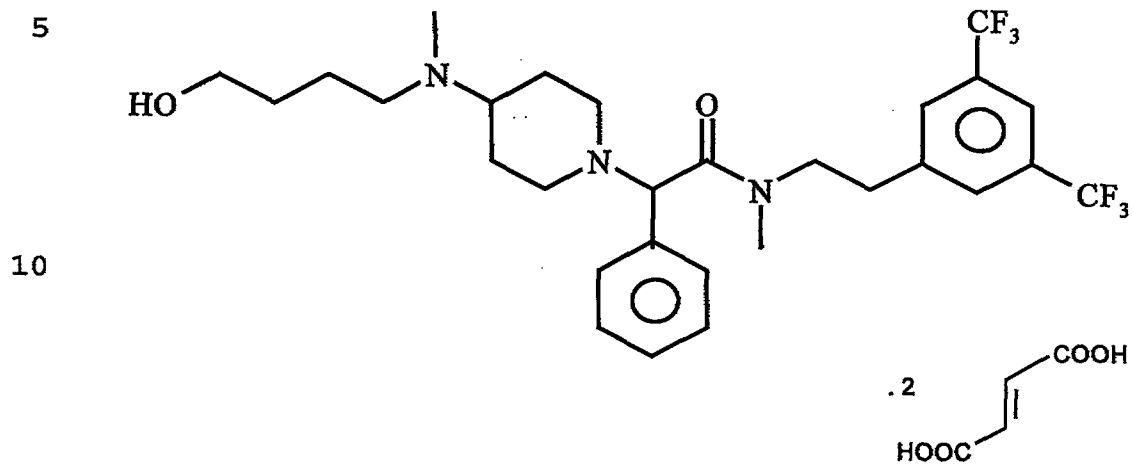
$[\alpha]_D^{20} = +19.0^\circ$ (DMSO).

Mp.: 166-176°C

$[\alpha]_D^{20} = +19.0^\circ$ (DMSO)

35

Example 76:



Mp.: 132 - 134°C

20 Of these compounds, the compounds of Examples 1 and 8 are preferred.

In the foregoing representations of the formulae, the CH₃ groups are not drawn in full.

25 Compound 1, for example, contains a methyl group as the group R⁵.

Pharmaceutical preparations:

Injectable solution

200 mg of active substance*
5 1.2 mg of monopotassium dihydrogen
phosphate = KH_2PO_4)
0.2 mg of disodium hydrogen phosphate =) (buffer)
 $\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$)
94 mg sodium chloride) (isotonic agents)
10 or)
520 mg glucose)
4 mg albumin (protease protection)
q.s. sodium hydroxide solution)
q.s. hydrochloric acid) ad pH 6
15 ad 10 ml water for injections

Injectable solution

200 mg active substance*
94 mg sodium chloride
20 or
520 mg glucose
4 mg albumin
q.s. sodium hydroxide solution)
q.s. hydrochloric acid) ad pH 9
25 ad 10 ml water for injections

Lyophilisate

200 mg of active substance*
520 mg of mannitol (isotonic agent/framework
30 agent)
4 mg albumin

Solvent 1 for lyophilisate

10 ml of water for injections

35 Solvent 2 for lyophilisate

20 mg of Polysorbate®80 = Tween®80
(surfactant)

10 ml of water for injections

- 5 * Active substance: compound according to the
 invention, e.g. one of
 Examples 1 to 76

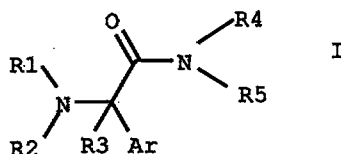
Dosage for humans weighing 67 kg: 1 to 500 mg



Claims:

1. Arylglycinamide derivatives of general formula I

5



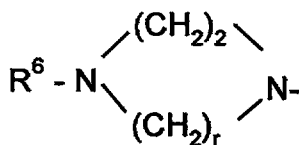
10

or the pharmaceutically acceptable salts thereof,
wherein

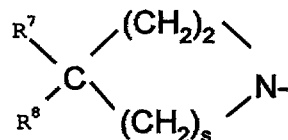
- Ar denotes unsubstituted or mono- to penta-
substituted phenyl, or unsubstituted or mono-
or disubstituted naphthyl [wherein the
substituents of the phenyl and naphthyl
independently of one another denote halogen (F,
Cl, Br, I), (C₁₋₄)alkyl, O-(C₁₋₄)alkyl, CF₃, OCF₃
or NR¹²R¹³ (wherein R¹² and R¹³ independently of
one another denote H, methyl or acetyl)] or Ar
is phenyl substituted by -O-CH₂-O- or
-O-(CH₂)₂-O-;

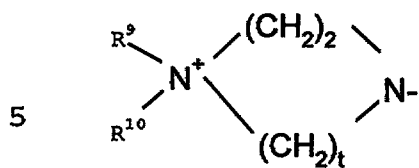
- 25 R¹ and R² together with the N to which they are bound
denote a ring of the formula

30



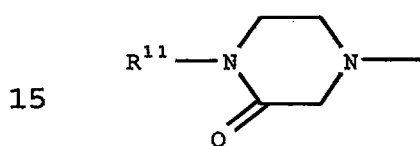
35





or

10



wherein

20

r, s and t are 2 or 3;

R⁶ denotes

H,

25

(C₁₋₅) alkyl,

(C₃₋₅) alkenyl,

propynyl,

hydroxy(C₂₋₄) alkyl,

methoxy(C₂₋₄) alkyl,

30

di(C₁₋₃) alkylamino(C₂₋₄) alkyl,

amino(C₂₋₄) alkyl,

amino,

di(C₁₋₃) alkylamino,

monofluoro- to perfluoro(C₁₋₂) alkyl,

35

N-methylpiperidinyl,

pyridyl,

pyrimidinyl,

pyrazinyl,



pyridazinyl

or the group $-\text{CH}_2-\text{C}(\text{O})\text{NR}^{14}\text{R}^{15}$,

wherein

R^{14} is H or (C_{1-4}) alkyl and

5 R^{15} is H, (C_{1-4}) alkyl, (C_{3-6}) cycloalkyl, hydroxy (C_{2-4}) alkyl, alkoxy (C_{2-3}) alkyl, phenyl (C_{1-4}) alkyl, or R^{14} and R^{15} together with the N to which they are bound form a ring (1-pyrrolidinyl, piperidino, morpholino or 1-methylpiperazin-4-yl);

10

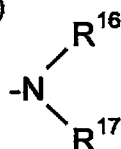
R^7 has one of the definitions (a) to (d),

(a) hydroxy

(b) 4-piperidinopiperidyl,

(c)

15



wherein R^{16} and R^{17} independently of one another
20 denote

H,

(C_{1-4}) alkyl,

(C_{3-6}) cycloalkyl,

hydroxy (C_{2-4}) alkyl,

25

(C_{1-3}) alkoxy (C_{2-4}) alkyl,

phenyl (C_{1-4}) alkyl or

di (C_{1-3}) alkylamino (C_{2-4}) alkyl,

or if R^{16} is H or (C_{1-4}) alkyl,

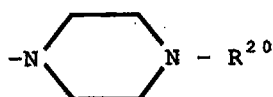
R^{17} may also be $-\text{CH}_2\text{C}(\text{O})\text{NR}^{18}\text{R}^{19}$, wherein R^{18} and R^{19} are

30

defined as R^{14} and R^{15} hereinbefore;

(d)

35



wherein R^{20} denotes

H,



(C₁₋₄) alkyl,
(C₄₋₆) cycloalkyl or
-CH₂C(O)NR²¹R²²,
wherein R²¹ and R²² are defined as R¹⁴ and R¹⁵
5 hereinbefore;

R⁸ is H

R⁹ and R¹⁰ independently of each other denote
10 (C₁₋₄) alkyl;

R¹¹ denotes
H,
(C₁₋₅) alkyl,
15 (C₃₋₅) alkenyl,
propynyl,
hydroxy(C₂₋₄) alkyl,
methoxy(C₂₋₃) alkyl,
di(C₁₋₃) alkylamino(C₂₋₃) alkyl,
20 amino(C₂₋₃) alkyl,
amino,
di(C₁₋₃) alkylamino,
monofluoro- to perfluoro(C₁₋₂) alkyl,
N-methylpiperidinyll,
25 pyridyl,
pyrimidinyl,
pyrazinyl,
pyridazinyl
or the group -CH₂-C(O)NR²³R²⁴,
30 wherein R²³ and R²⁴ are defined as R¹⁴ and R¹⁵
hereinbefore;

R³ denotes H, (C₁₋₄) alkyl, unsubstituted or mono-
to trisubstituted phenyl, wherein the
35 substituents independently of one another
denote halogen (F, Cl, Br, I), (C₁₋₄) alkyl, O-
(C₁₋₄) alkyl, CF₃, OCF₃ or NR²⁵R²⁶ (wherein R²⁵ and
R²⁶ independently of one another denote H,



methyl or acetyl);

R⁴ denotes phenyl(C₁₋₄)alkyl or naphthyl(C₁₋₄)alkyl, wherein phenyl may be substituted by 1 to 3 substituents, wherein the substituents independently of one another denote halogen (F, Cl, Br, I), (C₁₋₄)alkyl, O-(C₁₋₄)alkyl, CF₃, OCF₃ or NR²⁷R²⁸ (wherein R²⁷ and R²⁸ independently of one another denote H, methyl or acetyl);

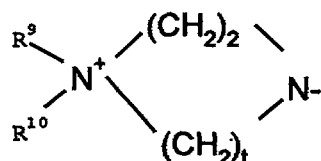
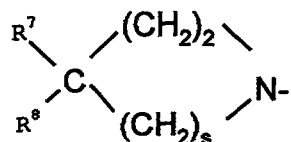
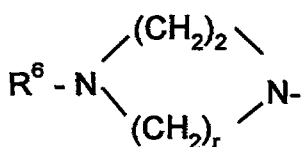
and

R⁵ denotes H, (C₁₋₄)alkyl, (C₃₋₆)cycloalkyl, CH₂COOH, CH₂C(O)NH₂, OH or phenyl(C₁₋₄)alkyl.

2. Compound according to claim 1 wherein

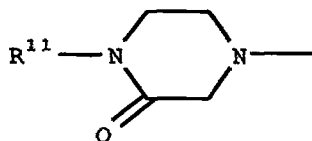
Ar denotes unsubstituted or mono- or disubstituted phenyl, or unsubstituted naphthyl, or Ar is phenyl substituted by -O-CH₂-O- or -O-(CH₂)₂-O-;

R¹ and R² together with the N to which they are bound denote a ring of the formula





or



wherein

r is 2 or 3 and

s and t are 2;

10

R^6 , R^7 , R^8 , R^9 , R^{10} and R^{11} are defined as in claim 1;

R^3 is H or (C_{1-4}) alkyl,

15 R^4 denotes phenyl (C_{1-4}) alkyl or naphthyl (C_{1-4}) alkyl,
wherein phenyl may be substituted by 1 or 2
substituents, wherein the substituents
independently of one another are halogen (F,
Cl, Br, I), (C_{1-4}) alkyl, O- (C_{1-4}) alkyl, CF_3 or
20 OCF_3 ;

and

25 R^5 denotes H, (C_{1-4}) alkyl, (C_{3-6}) cycloalkyl, OH or
phenyl (C_{1-4}) alkyl.

3. Compound according to claim 1 or 2, wherein

30 Ar is unsubstituted or mono- or disubstituted
phenyl, or unsubstituted naphthyl [wherein the
substituents of the phenyl independently on one
another denote halogen (F, Cl, Br, I), methyl,
methoxy, CF_3 or OCF_3] or Ar is phenyl
substituted by -O- CH_2 -O- or -O- $(CH_2)_2$ -O-.

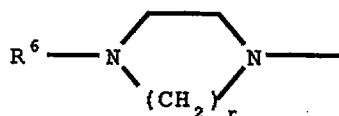
35

4. Compound according to claim 3, wherein Ar is
phenyl, naphthyl, phenyl substituted by methoxy or



halogen in position 3 and/or 4 or phenyl wherein positions 2 and 3 or 3 and 4 are linked by -O-CH₂-O-.

- 5 5. Compound according to claim 4, wherein Ar is phenyl, phenyl substituted by methoxy in positions 3 and 4 or phenyl in which positions 3 and 4 or 2 and 3 are linked by -O-CH₂-O-.
- 10 6. Compound according to one of claims 1 to 5, wherein in the ring



- r is 2 or 3 and
 R^6 denotes
H,
20 (C₁₋₅)alkyl,
 (C₃₋₅)alkenyl,
 propynyl,
 hydroxy(C₂₋₄)alkyl,
 methoxy(C₂₋₄)alkyl,
25 di(C₁₋₃)alkylamino(C₂₋₄)alkyl,
 amino(C₂₋₄)alkyl,
 amino,
 di(C₁₋₃)alkylamino,
 monofluoro- to perfluoro(C₁₋₂)alkyl,
30 N-methylpiperidinyl,
 pyridyl,
 pyrimidinyl,
 or
35 -CH₂-C(O)-N $\square$.

7. Compound according to claim 6, wherein r is 3 and R^6 is methyl.



8. Compound according to claim 6, wherein

r is 2 and

R⁶ is

5

H,

(C₁₋₄) alkyl,

propenyl,

propynyl,

hydroxy (C₂₋₃) alkyl,

10

methoxyethyl,

di (C₁₋₂) alkylamino (C₂₋₃) alkyl,

aminoethyl,

amino,

dimethylamino,

15

CH₂CF₃,

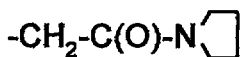
N-methylpiperidiny1,

pyridyl,

pyrimidinyl

or

20



9. Compound according to claim 8, wherein

25

r is 2 and

R⁶ is H, (C₁₋₃) alkyl, allyl, 2-propynyl, -CH₂CH₂OCH₃,

-CH₂CH₂N(CH₃)₂, N-methylpiperidiny1, 2-pyrimidinyl

or

30



10. Compound according to claim 9, wherein

r is 2 and

35

R⁶ is H, CH₃, C₃H₇, CH(CH₃)₂, CH₂CH₂OH, CH₂CH₂OCH₃ or
CH₂CH₂N(CH₃)₂.

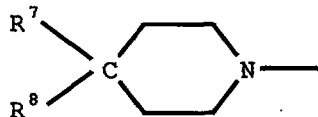
11. Compound according to one of claims 1 to 5,



wherein

R^1 and R^2 together with the N to which they are bound form the ring

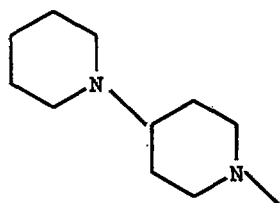
5



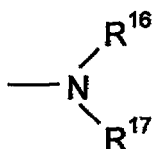
wherein R^8 is H and

10

R^7 is OH



15



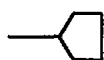
20

wherein R^{16} and R^{17} independently of one another denote:

H

25

(C_{1-3}) alkyl,



(CH_2)_nOH wherein n is 2, 3 or 4

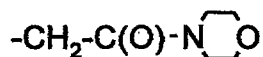
30

(CH_2)₂OCH₃

-(CH_2)_nPh wherein n is 2 or 4

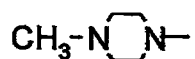
(CH_2)₂N(CH₃)₂

35

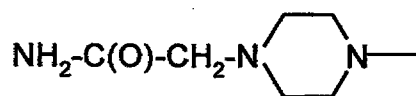




- 58 -



or



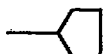
5

12. Compound according to claim 11, wherein

R^{16} and R^{17} are both CH_3 or C_2H_5 or

10

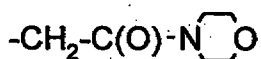
R^{16} is H or CH_3 and R^{17} is
(C_{1-3}) alkyl,



15

$(\text{CH}_2)_2\text{OH}$,

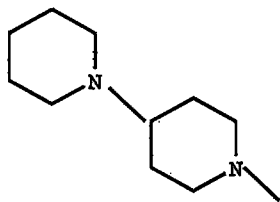
$(\text{CH}_2)_4\text{OH}$ or



20

13. Compound according to claim 11 wherein

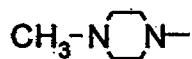
R^7 denotes



25

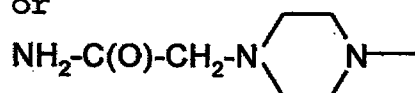
30

$\text{N}(\text{CH}_3)_2$



35

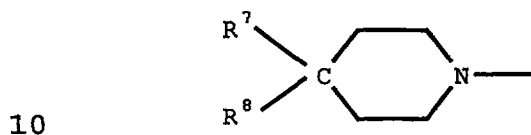
or





14. Compound according to claim 11,
wherein

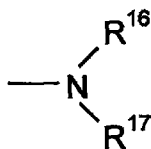
5 R^1 and R^2 together with the N to which they are bound
form the ring



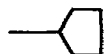
wherein

(a) R^8 is H and
 R^7 is

15



wherein R^{16} and R^{17} both represent CH_3 , C_2H_5 or
20 CH_2CH_2OH or
 R^{16} is H or CH_3 and R^{17} is (C_{1-3}) alkyl,



$(CH_2)_2OH$ or

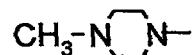
25

$(CH_2)_4OH$

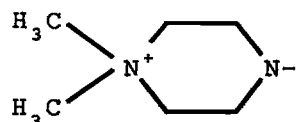
or

(b) R^8 is H and
 R^7 denotes

30

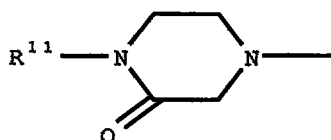


15. Compound according to one of claims 1 to 5,
35 wherein R^1 and R^2 together with the N to which they
are bound form the ring



- 60 -

16. Compound according to one of claims 1 to 5,
wherein R^1 and R^2 together with the N to which they
are bound form the ring



wherein R^{11} is H or (C_{1-3}) alkyl.

17. Compound according to claim 16, wherein
 R^{11} is $-CH(CH_3)_2$.

18. Compound according to one of claims 1 to 17,
wherein R^3 is H.

19. Compound according to one of claims 1 to 18,
wherein

R^4 denotes phenyl (C_{1-4}) alkyl, wherein phenyl may be
substituted by 1 or 2 substituents, in which
the substituents independently of one another
are halogen (F, Cl, Br, I), (C_{1-4}) alkyl, O-
 (C_{1-4}) alkyl, CF_3 or OCF_3 ;

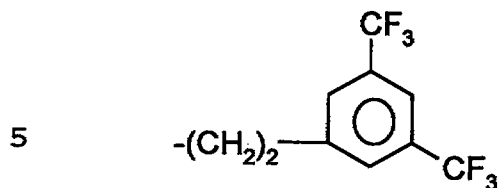
and

- R^5 denotes H, (C_{1-4}) alkyl, (C_{3-6}) cycloalkyl, -OH or
phenyl (C_{1-4}) alkyl.

20. Compound according to claim 19, wherein
 R^4 denotes phenyl (C_{2-4}) alkyl, wherein the
substituents are in positions 3 and/or 5 of the
phenyl ring and
 R^5 is H, methyl, OH or phenethyl.



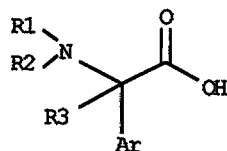
21. Compound according to claim 20, wherein R^4 is



and R^5 is methyl.

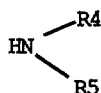
10 22. Process for preparing a compound of general formula I according to one of claims 1 to 21, characterised in that

15 a) an acid

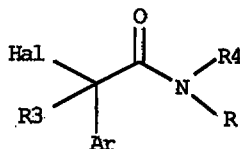


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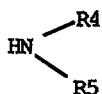
or a halide or alkylester thereof is reacted with an amine



b) an α -haloarylacetamide



is reacted with an amine



; or

c) a compound I wherein R^5 is H is N-alkylated;

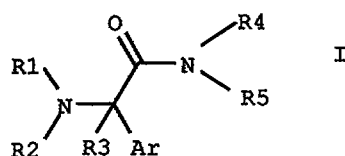


and a compound thus obtained is isolated as a free compound or as a pharmaceutically acceptable salt thereof.

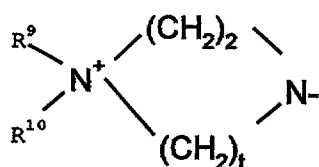
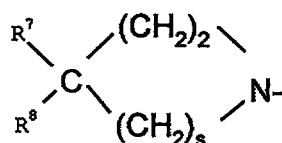
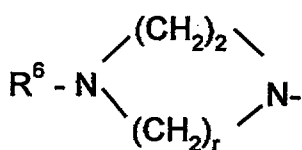
- 5 23. Pharmaceutical preparation containing a compound according to one of claims 1 to 21 and pharmaceutically acceptable carriers and excipients.
- 10 24. Use of a compound according to one of claims 1 to 22 for preparing a pharmaceutical preparation for the treatment and prevention of neurokinin-mediated diseases.
- 15 25. Use of a compound according to one of claims 1 to 22 for the treatment and prevention of neurokinin-mediated diseases.

Abstract:

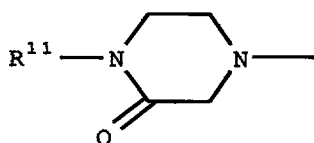
The invention relates to new arylglycinamide
5 derivatives of general formula I



and the pharmaceutically acceptable salts thereof,
wherein R¹ and R² together with the N to which they
are bound form a ring of the formula



or



in which
R³, R⁴, R⁵, Ar, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, r, s
and t
have the meanings given in the
specification and the preparation and use
thereof. The new compounds are valuable
neurokinin (tachykinin) antagonists.