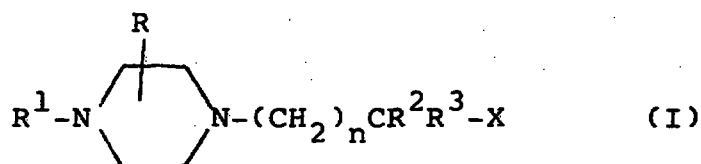


PIPERAZINE DERIVATIVES

This invention relates to piperazine derivatives, to processes for their preparation, to their use and to pharmaceutical compositions containing them. The novel compounds act on the central nervous system by binding to 5-HT receptors (as more fully explained below) and hence can be used as medicaments for treating humans and other mammals.

The novel compounds of the invention are those of the general formula



and the pharmaceutically acceptable acid addition salts thereof.

In formula (I)

n is one of the integers 1 or 2.

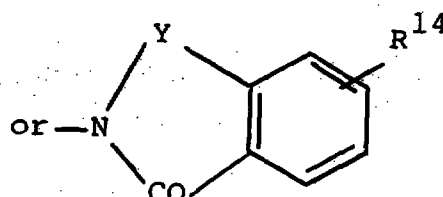
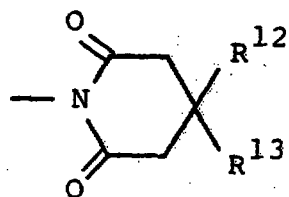
R is hydrogen or lower alkyl,

R^1 is an aryl or nitrogen containing heteroaryl radical,

R^2 is hydrogen or lower alkyl,

R^3 is an aryl radical, an alkyl radical containing 4 to 8 carbon atoms or an aryl(lower)alkyl radical,

X is $-\text{OCOR}^{10}$, $-\text{CO}_2\text{R}^6$, $-\text{CONR}^5\text{R}^9$, $-\text{OCO}_2\text{R}^6$, $-\text{NR}^4\text{COR}^6$, OCONHR^{11} , $-\text{NHCO}_2\text{R}^6$, $-\text{NR}^4\text{CONHR}^6$, $-\text{CONHNHR}^6$, $-\text{CONHOR}^6$,



R^4 and R^5 are each hydrogen or lower alkyl

R^6 is $-\text{CHR}^7\text{R}^8$, cycloalkyl of 3 to 12 carbon atoms or aryl(lower)alkyl (where R^7 and R^8 are each hydrogen or lower alkyl),

- 5 R^9 is hydrogen, an alkyl group of 1 to 8 carbon atoms other than a tertiary alkyl group, cycloalkyl of 3 to 12 carbon atoms, cycloalkyl(lower)alkyl, aryl, aryl(lower)alkyl or 8-azaspiro[4.5]deca-7,9-dione-8-yl-(lower)alkyl [with the proviso that when R^3 is aryl or
- 10 aralkyl, R^9 is not a phenyl group substituted in the ortho position by halogen, nitro, trifluoroalkyl, cyano, sulphonic acid, sulphonamido, carboxy, carbalkoxy, carboxylanilino or a 4-carboxylamino-benzosulphonamido group and that when R^9 is hydrogen,
- 15 alkyl, aryl or aryl(lower)alkyl R^5 is hydrogen or a primary or secondary lower alkyl group],

- or R^5 and R^9 together with the nitrogen atom to which they are attached represent an azetidino, pyrrolidino, piperidino, hexahydroazepino, morpholino or piperazino
- 20 ring which may be optionally substituted by lower alkyl, aryl or aryl(lower)alkyl.

- R^{10} is cycloalkyl of 3 to 12 carbon atoms, or 2,3-dihydro[1,4]benzodioxinyl optionally substituted by lower alkyl, lower alkoxy or halogen or, when R^3 is an
- 25 alkyl radical containing 4 to 8 carbon atoms, R^{10} can also be aryl;

R^{11} is cycloalkyl of 3 to 12 carbon atoms, aryl or aryl(lower)alkyl,

R^{12} and R^{13} are each lower alkyl or together with the carbon atom to which they are both attached represent C_{4-6} cycloalkyl,

R^{14} represents hydrogen, halogen, lower alkyl or lower alkoxy and

Y is CO or SO_2

with the further proviso that n is 1 when X is $-COOC_2H_5$, $-CONH_2$ or $-CON(CH_3)_2$, R^2 is hydrogen and R^3 is aryl.

- 10 The term "lower" as used herein means that the radical referred to contains 1 to 6 carbon atoms. Preferably such radicals contain 1 to 4 carbon atoms. Examples of "lower alkyl" are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert.-butyl, pentyl and isopentyl.
- 15 When R^3 is an alkyl group of 4 to 8 carbon atoms it may be a straight or branched chain group; a preferred example is tert.-butyl. Preferably R^3 is an aryl radical.

- 20 When used herein "aryl" means an aromatic radical having 6 to 12 carbon atoms (eg phenyl, naphthyl) which optionally may be substituted by one or more substituents commonly used in medicinal chemistry, eg substituents such as lower alkoxy, halogen, trifluoromethyl, nitro, carbalkoxy, carboxamido, cyano,
- 25 amino, (lower)alkylamino and di(lower)alkylamino.

Examples of aryl(lower)alkyl and aryl(lower)alkoxy include, for example, benzyl and benzyloxy in which the phenyl group may be substituted as defined above.

- 30 When used herein "nitrogen containing heteroaryl radical" means an aromatic ring containing one or more nitrogen atoms as heteroatoms (eg pyridinyl,

pyrimidinyl or pyrazinyl) which may optionally be substituted by one or more lower alkyl, lower alkoxy, halogen, trifluoromethyl, amino, (lower)alkylamino or di(lower)alkylamino substituents. Preferably the heteroaryl radical is monocyclic.

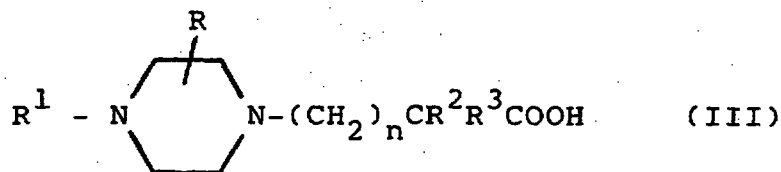
Preferred compounds are:-

- those in which n is 1;
- those in which R^1 is aryl particularly an optionally substituted phenyl such as o-methoxyphenyl;
- those in which R is hydrogen;
- those in which R^2 is hydrogen;
- those in which R^3 is aryl particularly optionally substituted phenyl;
- those in which X is an ester grouping of formula $-CO_2R^6$ or an amide grouping of formula $-CONR^5R^9$ particularly where $-NR^5R^9$ represents a cyclic grouping eg piperidino or hexahydroazepino.

The compounds of the invention may be prepared by a number of methods known in the art from known starting materials or starting materials that may be prepared by conventional methods. In one method for preparing an amide of formula (I), where X represents $-CONR^5R^9$ an amine of formula



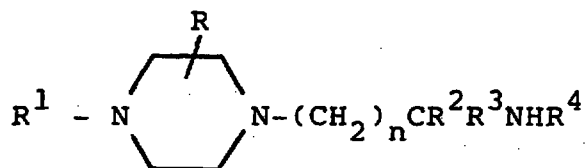
where R^5 and R^9 are as defined above is acylated with an acid of formula



(where R, R^1 , R^2 and R^3 are as defined above) or with an acylating derivative thereof. Examples of acylating

derivatives include the acid halides (eg acid chlorides), azides, anhydrides, imidazolides (eg obtained from carbonyldiimidazole), activated esters or O-acyl ureas obtained from a carbodiimide such as a dialkylcarbodiimide particularly dicyclohexylcarbodiimide. Preferably the amine is acylated with the acid in presence of a coupling agent such as 1,1'-carbonyldiimidazole, iso-butylchloroformate or diphenylphosphinyl chloride.

10 The reverse amides, ie the compounds of the invention in which X is $-NR^4COR^6$ may be prepared in an analogous manner to the amides mentioned above by acylating the piperazine alkylamine

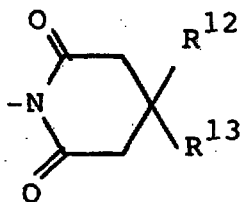


with an acid of formula

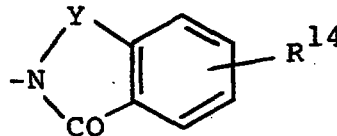


15 or with an acylating derivative thereof.

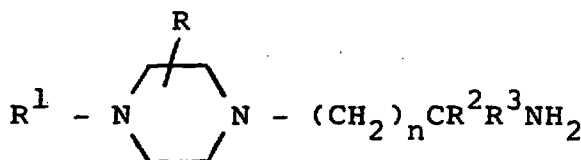
Similarly, the compounds of the invention in which X is



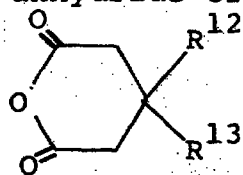
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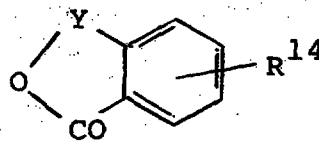
may be prepared by reacting an amine of formula



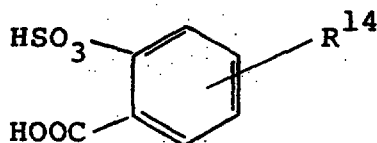
with an anhydride of formula



or

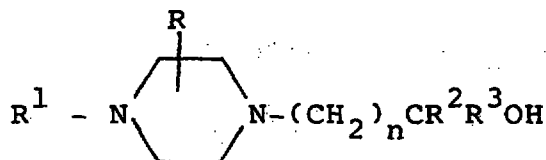


or with an acid of formula



An ester of the invention in which $-X$ is $-\text{CO}_2\text{R}^6$ may be prepared by esterification of the acid of formula (III) above with an alcohol of formula R^6OH .

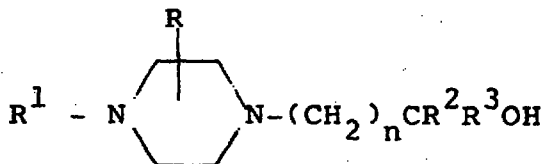
The reverse esters, ie the compounds in which X is $-\text{OCOR}^{10}$, may be prepared by esterifying a piperazine alcohol of formula



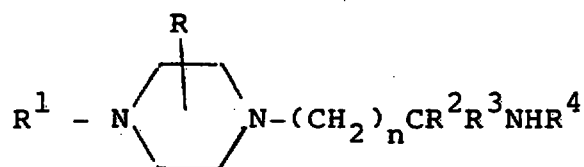
with an acid of formula R^{10}COOH .

Both types of esterification may be carried out by methods known in the art. For example an acid halide may be reacted with the appropriate alcohol.

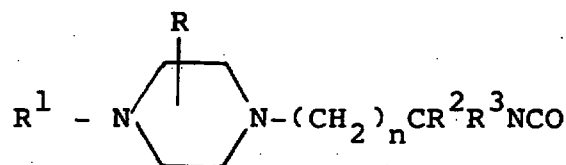
The ureas, ie compounds in which X is $-\text{NR}^4\text{CONHR}^6$ and the carbamates, ie compounds in which X is $-\text{O.CO.NHR}^{11}$ may be prepared by reacting the piperaziny-alkan-ol or -alkylamine of formula



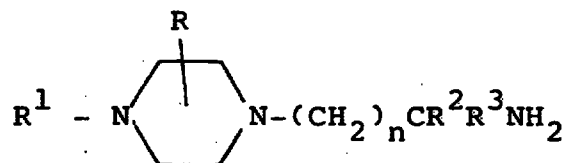
or



with the appropriate isocyanate. The reverse carbamates, ie the compounds in which X is $-\text{NHCO}_2\text{R}^6$ may be prepared in a similar manner from the piperazine isocyanate derivative



and the alcohol R^6OH , or by reacting an amine of formula



with a compound of formula R^6OCOHal (where Hal is halogen, eg chlorine).

10

The hydroxylamine compounds of the invention, ie compounds in which X is CONHOR^6 may be prepared by reacting the acid of formula (III) above with a hydroxylamine of formula NH_2OR^6 .

15

The hydrazide compounds of the invention, ie compounds in which X is $-\text{CONHNHR}^6$ may be prepared by reacting the acid of formula (III) with a hydrazide of formula NH_2NHR^6 .

20

An alternative method of preparing the compounds of the invention comprises alkylation of a piperazine of formula



(where R and R¹ are as defined above) with an alkylating agent providing the group



(where n, R², R³ and X are as defined above).

5

The alkylating agent may be, for example, a compound of formula



10

where R², R³ and X are as defined above and Z is a leaving group such as halogen or an alkyl- or aryl-sulphonyloxy group. Alternatively the alkylating agent may be an unsaturated compound of formula

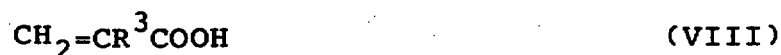


15

(where R³ and X are as defined above) and the compound of formula (VII) is reacted with the piperazine of formula (IV) by means of a Michael reaction. The reaction may be carried out at elevated temperature in the presence of an alcohol. A small quantity of an acid catalyst may be employed in the reaction when X represents -CONR⁵R⁹.

20

The starting materials for the processes described above may be prepared by methods known in the art. For example certain acids of formula (III) may be prepared by Michael reaction of an acid of formula

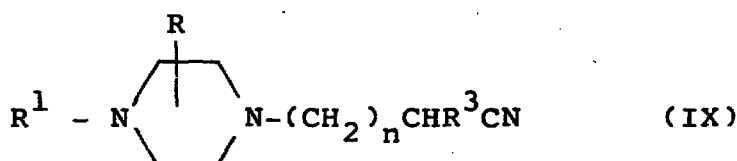


and a piperazine of formula



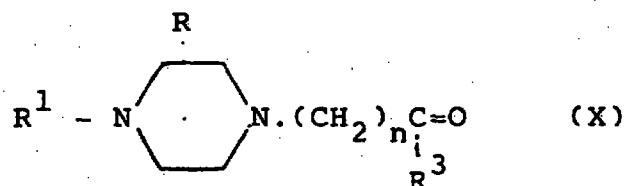
in a method similar to the Michael reaction described above. The unsaturated compound of formula (VII) may be prepared from the acid of formula (VIII) by the known methods of obtaining amides and esters from acids. In a preferred method the acid is reacted with an amine in the presence of a condensing agent such as isobutylchloroformate or the acid is esterified, eg by reaction with an alcohol in presence of 2-chloro-1-methylpyridinium iodide. The acids of formula (VIII) are known or may be prepared by methods known in the art.

The amides of formula (I) in which X is $-\text{CONR}^5\text{R}^9$ where R^5 is hydrogen and R^9 is a secondary (lower)alkyl group may be prepared by an alternative method comprising reacting a nitrile of formula



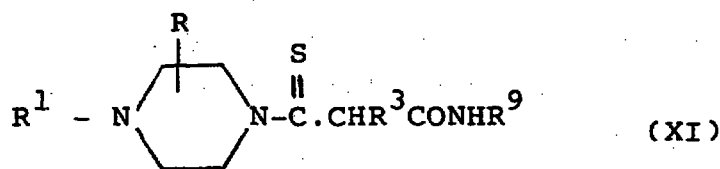
with a secondary alcohol under acidic conditions as in the Ritter reaction. The nitrile (IX) may also be subjected to acid hydrolysis to give an amide of formula (I) in which X is CONH_2 . Furthermore the nitrile may be hydrolysed to the acid (III) which may then be converted to compounds of formula (I) by the methods given above. The nitrile of formula (IX) may be prepared by known methods such as reacting an unsaturated nitrile of formula $\text{CH}_2=\text{CR}_3\text{CN}$ with a

piperazine of formula (IV) under Michael conditions or reacting a ketone of formula



with p-toluenesulphonylisocyanide.

- 5 A further method of preparing the amides of formula (I) in which X is $-\text{CONHR}^9$ comprises the desulphurisation of a sulphur containing compound of formula



- 10 where R, R^1 and R^9 are as defined above and R^3 is aryl. The desulphurisation may be carried out in presence of a nickel catalyst. The compound of formula (XI) may be prepared by a Willgerodt reaction, eg an aryl alkyl ketone of formula $\text{CH}_3\text{CO} \cdot \text{R}^3$ is reacted with sulphur and a piperazine of formula (IV) and the resulting thioamide is treated with a base and with a isocyanate of formula R^9NCO .

- 15 The processes described above may be carried out to give a compound of the invention in the form of a free base or as an acid addition salt. If the compound of the invention is obtained as an acid addition salt, the free base can be obtained by basifying a solution of
20 the acid addition salt. Conversely, if the product of the process is a free base an acid addition salt, particularly a pharmaceutically acceptable acid addition salt, may be obtained by dissolving the free

base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds.

5 Examples of acid addition salts are those formed from inorganic and organic acids, such as sulphuric, hydrochloric, hydrobromic, phosphoric, tartaric, fumaric, maleic, citric, acetic, formic, methanesulphonic, p-toluenesulphonic, oxalic and
10 succinic acids.

The compounds of the invention may contain one or more asymmetric carbon atoms, so that the compounds can exist in different stereoisomeric forms. The compounds can be for example, racemates or optically
15 active forms. The optically active forms can be obtained by resolution of the racemates or by asymmetric synthesis.

The compounds of the present invention possess pharmacological activity. In particular, they act on
20 the central nervous system by binding to 5-HT receptors. In pharmacological testing it has been shown that the compounds particularly bind to receptors of the 5-HT_{1A} type. In general, the compounds selectively bind to receptors of the 5-HT_{1A} type to a
25 much greater extent than they bind to other receptors such as α_1 and D₂ receptors. Many exhibit activity as 5-HT_{1A} antagonists in pharmacological testing. The pharmacological testing of the compounds indicates that they can be used for the treatment of CNS disorders,
30 such as anxiety in mammals, particularly humans. They may also be useful as antidepressants, hypotensives and as agents for regulating the sleep/wake cycle, feeding behaviour and/or sexual function.

The compounds of the invention were tested for 5-HT_{1A}

receptor binding activity in rat hippocampal membrane homogenate by the method of B S Alexander and M D Wood, J Pharm Pharmacol, 1988, 40, 888-891. The results for representative compounds of the invention are given below.

5

10

15

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25

30

Compounds of Example	IC ₅₀ (nM)
6	127
8	45
19	24
21	49
22	45
23	59
24	75
26	46
29	25
31	28
32	21
33	8
34	9
35	16.5
37	45
39	22
40	78
42	88
43	37

The affinity for D₂ receptor sites (as measured by the procedure of A A Hancock et al, Mol Pharmacol, 1984, 26, 439) and for α_1 sites (as measured by the procedure of A L Morrow et al, Mol Pharmacol, 1986, 29, 321) for various compounds is given below:

	Compound of Example	Affinity for D ₂ site IC ₅₀ (nM)	Affinity for α_1 site IC ₅₀ (nM)
5	19	6290	976
	21		1200
	22		1230
	24		> 10 ⁴
	26		1090
10	29		1140
	32	>10000	851
	37		7310
	42		2850
	43		988

15 The compounds are tested for 5-HT_{1A} receptor antagonism activity in a test involving the antagonism of 5-carboxamidotryptamine in the guine-pig ileum in vitro (based upon the procedure of Fozard et al, Br J Pharmac 1985, 86, 601P). The results for compounds of the invention are given below.

20	Compound of Example	pA ₂
25	19	6.9
	21	6.9
	23	7.0
	26	6.8
	31	7.4
25	32	6.8
	37	7.6
	43	6.9

30 The invention also provides a pharmaceutical composition comprising a compound or a pharmaceutically acceptable acid addition salt thereof in association

with a pharmaceutically acceptable carrier. Any suitable carrier known in the art can be used to prepare the pharmaceutical composition. In such a composition, the carrier is generally a solid or liquid or a mixture of a solid or liquid.

Solid form compositions include powders, granules, tablets, capsules (eg hard and soft gelatine capsules), suppositories and pessaries. A solid carrier can be, for example, one or more substances which may also act as flavouring agents, lubricants, solubilisers, suspending agents, fillers, glidants, compression aides, binders or tablet-disintegrating agents; it can also be an encapsulating material. In powders the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets the active ingredient is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain up to 99%, eg from 0.03 to 99%, preferably 1 to 80% of the active ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidone, low melting waxes and ion exchange resins.

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

Liquid form compositions include, for example, solutions, suspensions, emulsions, syrups, elixirs and pressurised compositions. The active ingredient, for

example, can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both or pharmaceutically acceptable oils or fats. The liquid carrier can contain other suitable pharmaceutical additives such as solubilisers, emulsifiers, buffers, preservatives, sweeteners, flavouring agents, suspending agents, thickening agents, colours, viscosity regulators, stabilisers or osmo-regulators. Suitable examples of liquid carriers for oral and parenteral administration include water (particularly containing additives as above, eg cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols, eg glycerol and glycols) and their derivatives, and oils (eg fractionated coconut oil and arachis oil). For parenteral administration the carrier can also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are used in sterile liquid form compositions for parenteral administration.

Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by, for example, intramuscular, intraperitoneal or subcutaneous injection. Sterile solutions can also be administered intravenously. When the compound is orally active it can be administered orally either in liquid or solid composition form.

Preferably the pharmaceutical composition is in unit dosage form, eg as tablets or capsules. In such form, the composition is sub-divided in unit dose containing appropriate quantities of the active ingredient; the unit dosage forms can be packaged composition, for example packeted powders, vials, ampoules, prefilled syringes or sachets containing liquid. The unit dosage form can be, for example, a capsule or tablet itself, or it can be the appropriate number of any such

compositions in package form. The quantity of the active ingredient in unit dose of composition may be varied or adjusted from 0.5 mg or less to 750 mg or more, according to the particular need and the activity of the active ingredient.

The following Examples 5 to 58 illustrate the invention. Examples 1 to 4 illustrate the preparation of intermediates which may be used in the preparation of the compounds of the invention.

EXAMPLE 1 α -{1-[4-(2-Methoxyphenyl)piperazinyl]methyl}benzene-
acetic acid

1-(2-Methoxyphenyl)piperazine (22.6 g, 0.118 mol) and
atropic acid (174 g, 0.118 mol) in ethanol (300 ml)
were heated under reflux for 18 hours, cooled to room
temperature, and evaporated in vacuo. The solid was
trituated with acetone (3 x 100 ml) to give a first
crop of product (13.8 g) as white crystals. The
filtrate was evaporated in vacuo to give an oil which
slowly crystallised over 1 month. The solid was
trituated with acetone (200 ml) to give a second crop
of the hemihydrate of the product (9.01 g) as white
crystals, m.p. 160-163°.

(Found: C, 68.4; H, 7.2; N, 7.9.

$C_{20}H_{24}N_2O_3 \cdot 0.5H_2O$ requires C, 68.8; H, 7.2; N, 8.0%.)

EXAMPLE 22-{1-[4-(2-Methoxyphenyl)piperazinyl]methyl}-3-benzene-
propanoic acid

2-(Phenylmethyl)propenoic acid (Mannich and Ganz,
Chem. Ber., 1922, 55, 3486) (2.00 g, 12.35 mmol) and
1-(2-methoxyphenyl)piperazine (2.37 g, 12.35 mmol) in
propanol (25 ml) were heated under reflux for 18 hours,
cooled to room temperature, and evaporated in vacuo.

The residue was trituated with acetone and ether to
give the product (0.80 g) as a colourless powder, m.p.
155-158°.

(Found: C, 71.6; H, 7.4; N, 7.6.

$C_{21}H_{26}N_2O_3$ requires C, 71.2; H, 7.3; N, 7.9%.)

EXAMPLE 32-Phenyl-N-(phenylmethyl)propenamide

A stirred solution of atropic acid (10.3 g, 69.5 mmol) in dry tetrahydrofuran (100 ml) was treated under nitrogen with N-methylmorpholine (7.7 ml, 70.0 mmol), cooled to -10°, treated dropwise with iso-butylchloroformate (9 ml, 69.4 mmol), treated dropwise with benzylamine (7.6 ml, 69.6 mmol), warmed to room temperature over 1 hour, filtered and evaporated in vacuo to give a yellow oil which was dissolved in ether (100 ml). The solution was washed with 0.1N-HCl (200 ml), brine (100 ml), 0.1N-NaOH (100 ml) and brine (100 ml), dried (MgSO₄), and evaporated in vacuo to give a yellow liquid. Purification by chromatography (silica; di-iso-propyl ether) gave the product as white crystals (7.3g), m.p. 84-86° (from di-iso-propyl ether).

(Found: C, 80.8; H, 6.3; N, 5.7.

C₁₆H₁₅NO requires C, 81.0; H, 6.4; N, 5.9%.)

EXAMPLE 4N-Cyclohexyl-2-phenylpropenamide

This compound was made from atropic acid (10.48 g, 70.8 mmol), N-methylmorpholine (7.8 ml, 70.9 mmol), iso-butyl chloroformate (9.2 ml, 70.9 mmol), and cyclohexylamine (8.1 ml, 70.7 mmol) using the procedure described in Example 3. The crude product was purified by recrystallisation from cyclohexane to give the product (4.69 g), as white crystals, m.p. 131-133°.

(Found: C, 78.7; H, 8.8; N, 5.95. C₁₅H₁₉NO requires C, 78.6; H, 8.35; N, 6.1%.)

EXAMPLE 5Propyl 3-[1-[4-(2-methoxyphenyl)piperazinyl]]-2-phenylpropanoate

5 A stirred solution of atropic acid (2.11 g, 14.3 mmol) and cyclohexanol (1.51 ml, 14.2 mmol) in ethyl acetate (40 ml) at 2-5° was treated dropwise with N,N'-dicyclohexylcarbodiimide (3.27 g, 15.8 mmol), warmed to room temperature, filtered and evaporated in vacuo to give a yellow oil.

10 A solution of the oil in propanol (20 ml) was heated under reflux for 1 day, cooled to room temperature, evaporated in vacuo, and the residue purified by chromatography [silica; ether-hexane (1:3) and silica; di-iso-propyl ether] to give the free base as an oil
15 (1.1 g).

Formation of the salt in the usual manner gave the hydrochloride (0.95 g), m.p. 200-204°.
(Found: C, 60.9; H, 7.25; N, 6.3. $C_{23}H_{30}N_2O_3 \cdot 2HCl$ requires C, 60.7; H, 7.1; N, 6.15%.)

EXAMPLE 63-[1-[4-(2-Methoxyphenyl)piperazinyl]]-2-phenyl-N-phenylpropanamide

25 A solution of the product of Example 1 (1.102 g, 3.2 mmol) in dichloromethane (50 ml) was treated with 1,1'-carbonyldiimidazole (0.58 g, 3.6 mmol), stirred for 1 hour, treated with aniline (0.4 ml, 4.4 mmol), stirred for 18h, evaporated in vacuo, and the residue purified by chromatography (silica; di-iso-propyl ether --> ether). The foam was dissolved in hot propan-2-ol
30 (10 ml) and the solution acidified with ethereal hydrogen chloride. Evaporation in vacuo gave a glass

which crystallised upon trituration with ether as the dihydrochloride quarter hydrate salt of the product (0.897 g), m.p. 250-255° (dec.).

(Found: C, 63.4; H, 6.8; N, 8.5.

5 $C_{26}H_{29}N_3O_2 \cdot 2HCl \cdot \frac{1}{4}H_2O$ requires C, 63.35; H, 6.4; N, 8.5%.)

EXAMPLES 7-21

10 The following 3-[1-[4-(2-methoxyphenyl)piperazinyl]]-2-phenylpropanamides were prepared following the procedure of Example 6 but using the indicated amine reactant instead of aniline.

3-[1-4-(2-Methoxyphenyl)piperazinyl]-2-phenylpropanamides

Example	Amine Reactant	Amide Product	Formula	Found % (Required)			m.p. (°C)
				C	H	N	
7	NH ₃ -THF	amide	C ₂₀ H ₂₅ N ₃ O ₂ ·2HCl	58.05 (58.25)	6.7 (6.6)	10.2 (10.2)	194-195
8	MeNH ₂ -EtOH (33% w/w)	methylamide	C ₂₁ H ₂₇ N ₃ O ₂ ·2HCl $\frac{1}{2}$ H ₂ O	57.6 (57.3)	7.15 (7.0)	9.2 (9.55)	203-205
9	EtNH ₂ -EtOH (33% w/w)	ethylamide	C ₂₂ H ₂₉ N ₃ O ₂ ·2HCl $\frac{1}{2}$ H ₂ O	59.4 (59.4)	7.2 (7.1)	9.5 (9.4)	204-206
10	PrNH ₂	propylamide	C ₂₃ H ₃₁ N ₃ O ₂ ·2HCl	60.6 (60.8)	7.6 (7.3)	9.7 (9.25)	213-215
11	BuNH ₂	butylamide	C ₂₄ H ₃₃ N ₃ O ₂ ·2HCl	61.6 (61.5)	7.8 (7.5)	9.2 (9.0)	199-200
12	<u>iso</u> -PrNH ₂	<u>iso</u> -propylamide	C ₂₃ H ₃₁ N ₃ O ₂ ·2HCl	60.55 (60.8)	7.6 (7.3)	9.6 (9.25)	221-224
13	<u>iso</u> -BuNH ₂	<u>iso</u> -butylamide	C ₂₄ H ₃₃ N ₃ O ₂ ·2HCl	61.4 (61.5)	7.7 (7.5)	9.0 (9.0)	202-203

14	$C_3H_5CH_2NH_2$	cyclopropyl- methyleamide	$C_{24}H_{31}N_3O_2 \cdot 2HCl$	61.9 (61.8)	7.0 (7.1)	8.7 (9.0)	200-202
15	$t-BuCH_2NH_2$	neopentylamide	$C_{25}H_{35}N_3O_2 \cdot 2HCl$	61.9 (62.2)	7.6 (7.7)	8.7 (8.7)	200-203
16	$C_6H_{13}NH_2$	hexylamide	$C_{26}H_{37}N_3O_2 \cdot 2HCl$	62.5 (62.9)	7.9 (7.5)	8.4 (8.5)	189-190
17	$C_6H_{11}CH_2NH_2$	cyclohexyl- methyleamide	$C_{27}H_{37}N_3O_2 \cdot 2HCl$	63.5 (63.8)	8.0 (7.7)	8.4 (8.3)	205-207
18	$C_5H_9NH_2$	cyclopentylamide	$C_{25}H_{33}N_3O_2 \cdot 2HCl \cdot \frac{1}{2}H_2O$	62.0 (62.0)	7.3 (7.4)	8.9 (8.7)	213-214
19	$C_6H_{11}NH_2$	cyclohexylamide	$C_{26}H_{35}N_3O_2 \cdot 2HCl$	63.0 (63.15)	7.8 (7.5)	8.1 (8.5)	216-219
20	$C_7H_{13}NH_2$	cycloheptylamide	$C_{27}H_{37}N_3O_2 \cdot 2HCl$	63.6 (63.8)	7.9 (7.7)	8.0 (8.3)	206-208
21	$C_{11}H_{18}N_2O_2$ ^a	^b	$C_{31}H_{40}N_4O_4 \cdot 2HCl$	61.4 (61.5)	7.3 (7.0)	9.2 (9.25)	148-152

^a 8-(Aminoethyl)-8-azaspiro[4.5]deca-7,9-dione

^b The product was 8-{ α -[1-[4-(2-methoxyphenyl)piperazinyl]methyl]phenylacetamidoethyl}-8-azaspiro[4.5]deca-7,9-dione

EXAMPLE 22N,N-Dimethyl-3-[1-[4-(2-methoxyphenyl)piperazinyl]]-2-phenylpropanamide

5 A stirred solution of the product of Example 1
(1.786 g, 5.2 mmol) and N-methylmorpholine (0.65 ml,
5.9 mmol) in dichloromethane (20 ml) at -30° was
treated with diphenylphosphinyl chloride (1.1 ml, 5.8
mmol) under an atmosphere of nitrogen. After 1 hour,
25-30% w/v dimethylamine in water (1.2 ml, ca. 7.5
10 mmol) was added and the solution warmed to room
temperature over 3 hours. Evaporation in vacuo and
chromatography (silica, ethyl acetate) gave the free
base (0.532 g.)

15 The solid was dissolved in hot methanol (5 ml) and the
solution acidified with ethereal hydrogen chloride and
evaporated in vacuo to give the dihydrochloride
three-quarter hydrate salt of the product (0.581 g) as
colourless crystals, mp. 236-238° (dec.).
(Found: C, 58.1; H, 7.4; N, 9.1.
20 $C_{22}H_{29}N_3O_2 \cdot 2HCl \cdot \frac{3}{4}H_2O$ requires C, 58.2; H, 7.2;
N, 9.3%.)

EXAMPLE 233-[1-[4-(2-Methoxyphenyl)piperazinyl]]-2-phenyl-N-(phenylmethyl)propanamide

25 A solution of the product of Example 3 (1.25 g,
5.3 mmol), 1-(2-methoxyphenyl)piperazine (1.00 g,
5.2 mmol), and acetic acid (3 drops) was heated under
reflux under an atmosphere of nitrogen for 40 hours,
cooled to room temperature, and evaporated in vacuo to
30 give an oil which crystallised from ethyl acetate. A

suspension of the crystals in hot propan-2-ol was acidified with ethereal hydrogen chloride. The hot solution was cooled to room temperature and the precipitate filtered and washed with propan-2-ol and ether to give the product (1.94 g), m.p. 211-214°. (Found: C, 64.5; H, 7.1; N, 7.9. $C_{27}H_{31}N_3O_2 \cdot 2HCl$ requires C, 64.5; H, 6.6; N, 8.4%.)

EXAMPLE 24

N-Cyclohexyl-2-phenyl-3-[1-[4-(2-pyrimidinyl)-piperazinyl]]propanamide

A solution of the product of Example 4 (0.90 g, 3.9 mmol) and N-(2-pyrimidyl)piperazine dihydrochloride (0.95 g, 4.0 mmol) in 1 N-NaOH (8.0 ml), propanol (10 ml), and acetic acid (8 drops) was heated under reflux for 48 hours, cooled to room temperature, and concentrated in vacuo. The aqueous residue was diluted with water (50 ml) and extracted with dichloromethane (50 ml). The extracts were washed with water (50 ml), dried ($MgSO_4$), and evaporated in vacuo to give an oil. Purification by column chromatography (alumina; ether) gave the product free base (0.63 g) as colourless crystals.

The crystals were dissolved in hot propan-2-ol (20 ml), acidified with ethereal hydrogen chloride, and evaporated in vacuo to give a foam which crystallised upon trituration with ether as the dihydrochloride three-quarter hydrate salt of the product (0.67g) m.p. 165-175°.

(Found: C, 62.5; H, 7.6; N, 15.6.

$C_{23}H_{31}N_5O \cdot HCl \cdot \frac{3}{4}H_2O$ requires C, 62.3; H, 7.6; N, 15.8%.)

EXAMPLE 253,N-Bis[1-[4-(2-methoxyphenyl)piperazinyl]]-2-phenyl-
propanamide

This compound was isolated as a side-product from the
5 reaction following the procedure of Example 6 but
substituting t-butylamine for aniline. The
dihydrochloride trihydrate of the product was produced
by standard methods as colourless crystals, m.p.
180-190° (dec.)

10 (Found: C, 57.9; H, 7.3; N, 8.3.

$C_{31}H_{38}N_4O_3 \cdot 2HCl \cdot 3H_2O$ requires C, 58.0; H, 7.2;
N, 8.7%.)

EXAMPLE 262-Methylpropyl 3-[1-[4-(2-methoxyphenyl)piperazinyl]]-
15 2-phenylpropanoateStep 1: 2-Methylpropyl 2-phenylpropenoate

This compound was isolated as a side-product from the
reaction described in Example 3 as a colourless oil
(1.03 g) and was used without further purification in
20 Step 2.

Step 2: 2-Methylpropyl 3-[1-[4-(2-methoxy-
phenyl)piperazinyl]]-2-phenylpropanoate

A solution of the product of Step 1 (0.97 g, 4.7 mmol)
and 1-(2-methoxyphenyl)piperazine (0.91 g, 4.7 mmol) in
25 propanol (10 ml) was maintained at room temperature for
90 hours and evaporated in vacuo. The residue was
purified by chromatography (silica; di-iso-propyl
ether) to give an oil. The oil was dissolved in

propan-2-ol (10 ml) and the solution acidified with ethereal hydrogen chloride and evaporated in vacuo. The solid was triturated with ether to give the dihydrochloride salt of the product (1.173 g) m.p. 208-212°.

(Found: C, 61.6; H 7.6; N, 5.8.

$C_{24}H_{32}N_2O_3 \cdot 2HCl$ requires C, 61.4; H, 7.3; N, 6.0%.)

EXAMPLE 27

Ethyl 3-{1-[4-(2-methoxyphenyl)piperazinyl]}-2-phenylpropanoate

This compound was isolated as a side-product from the reaction described in Example 9. The dihydrochloride salt of the product, mp. 220-222° was produced in the conventional manner.

(Found: C, 59.5; H, 6.9; N, 6.5.

$C_{22}H_{28}N_2O_3 \cdot 2HCl$ requires C, 59.9; H, 6.85; N, 6.35%).

EXAMPLE 28

2-{1-[4-(2-Methoxyphenyl)piperazinyl]methyl}-N-methyl-3-phenylpropanamide

This compound was prepared from the acid of Example 2 (2.00 g, 5.65 mmol) 1,1'-carbonyldiimidazole (0.92 g, 5.65 mmol), and methylamine solution, approx 33% w/w in industrial methylated spirit (0.58 g, ca 6.2 mmol) using the processes outlined in Example 6. The hydrochloride hydrate salt of the product was isolated as crystals (0.73 g), m.p. 186.5-188.5° (from methyl acetate-ether).

(Found: C, 62.8; H, 7.6; N, 10.0.

$C_{22}H_{29}N_3O_2 \cdot HCl \cdot H_2O$ requires C, 62.6; H, 7.9; N, 10.0%.)

EXAMPLE 29Ethyl 2-[1-[4-(2-methoxyphenyl)piperazinyl]methyl]-
3-phenylpropanoate

5 This compound was prepared from the acid of Example 2
(2.00 g, 5.65 mmol) by a method analogous to that
described in Example 28 with the exception that excess
ethanol was used in place of methylamine. The
dihydrochloride quarter hydrate salt of the salt
(1.20 g) was isolated as crystals, m.p. 197-201°.
10 (Found: C, 60.2; H, 7.3; N, 6.0.
 $C_{23}H_{30}N_2O_3 \cdot 2HCl \cdot \frac{1}{4}H_2O$ requires C, 60.1; H, 7.1;
N, 6.1%.)

EXAMPLES 30-36

15 The following 3-[1-[4(2-methoxyphenyl)piperazinyl]]-2-
phenylpropanamides were prepared following the
procedure of Example 6, but using the indicated amine
reactant instead of aniline.

3-[1-[4-(2-Methoxyphenyl)piperazinyl]-2-phenylpropanamides

Example	Amine Reactant	Amide Product	Formula	Found % (Required)			m.p. (°C)
				C	H	N	
30	3,3-dimethyl-butylamine	(3,3-dimethyl)-butylamide	$C_{26}H_{37}N_3O_2 \cdot 2HCl$	62.6 (62.9)	8.0 (7.9)	8.5 (8.5)	187-193
31	cyclopropylamine	cyclopropylamide	$C_{23}H_{29}N_3O_2 \cdot 2HCl$	60.7 (60.5)	7.2 (7.0)	9.2 (9.2)	193-195
32	pyrrolidine	c	$C_{24}H_{31}N_3O_2 \cdot 2HCl \cdot 0.25H_2O$	61.4 (61.3)	7.4 (7.2)	9.0 (8.9)	212-213
33	piperidine	d	$C_{25}H_{33}N_3O_2 \cdot 1.75HCl$	63.7 (63.7)	7.5 (7.4)	8.8 (8.9)	191-194
34	hexamethyleneimine	e	$C_{26}H_{35}N_3O_2 \cdot 1.5HCl$	65.75 (65.6)	7.9 (7.9)	8.8 (8.8)	203-204
35	cyclooctylamine	cyclooctylamide	$C_{28}H_{39}N_3O_2 \cdot 2HCl$	64.3 (64.3)	7.9 (7.9)	8.0 (8.0)	204-206
36	cyclododecylamine	cyclododecylamide	$C_{32}H_{47}N_3O_2 \cdot 2HCl \cdot 0.25H_2O$	66.0 (65.9)	8.5 (8.6)	7.2 (7.2)	184-188

c 1-{3-[1-[4-(2-methoxyphenyl)piperazinyl]-2-phenylpropionyl]pyrrolidine

d 1-{3-[1-[4-(2-methoxyphenyl)piperazinyl]-2-phenylpropionyl]piperidine

e 2,3,4,5,6,7-hexahydro-1-[3-[1-[4-(2-methoxyphenyl)piperazinyl]-2-phenylpropionyl]-1H-azepine

EXAMPLE 37(S)-N-[2-[1-[4-(2-Methoxyphenyl)piperazinyl]]-1-phenylethyl]cyclohexanecarboxylic acid amide

5 A solution of (S)-2-[1-[4-(2-methoxyphenyl)piperazinyl]]-1-phenylethylamine (1.03 g, 3.3 mmol) in dichloromethane (50 ml) was treated with cyclohexanecarboxylic acid chloride (0.5 ml, 3.7 mmol), after 40 minutes washed with 0.1 N-NaOH (100 ml), dried (MgSO₄), evaporated in vacuo, and the residual oil
10 purified by column chromatography [silica; di-isopropyl ether --> ether] to give the product free base (0.83 g) as white crystals.

The crystals were dissolved in hot propan-2-ol, acidified with ethereal hydrogen chloride, evaporated
15 in vacuo, and the resulting pink crystals dried in vacuo at 70° for 24 hours to give the title compound as the hydrochloride hydrate, m.p. 141-143°.

(Found: C, 65.7; H, 8.0; N, 9.2.

20 C₂₆H₃₅N₃O₂.HCl.H₂O requires C, 65.6; H, 8.05; N, 8.8%.)

EXAMPLE 38O-[2-[1-(4-(2-Methoxyphenyl)piperazinyl)]-1-phenylethyl]-N-cyclohexylcarbamate

25 Tributyltin methoxide (0.05 ml) was added to a solution of 2-[1-(4-(2-methoxyphenyl)piperazinyl)]-1-phenylethanol (1.00 g, 3.2 mmol) and cyclohexylisocyanate (0.44 g, 3.5 mmol) in dry toluene (10.0 ml). The reaction mixture was stirred at room temperature overnight and the suspension was treated

with dichloromethane to afford a solution which was chromatographed on silica gel, gradient eluting with hexane ethyl acetate (2:1 to 1:2) to afford a white solid. The solid was dissolved in ethyl acetate and the solution acidified with ethereal hydrogen chloride to afford the title compound as the dihydrochloride semihydrate (1.3 g), m.p. 182.4-186.3°.

(Found: C, 60.4; H, 7.2; N, 8.0.

$C_{26}H_{35}N_3O_3 \cdot 2HCl \cdot \frac{1}{2}H_2O$ requires C, 60.1; H, 7.4; N, 8.1%.)

EXAMPLE 39

O-[2-[1-[4-(2-Methoxyphenyl)piperazinyl]]-1-phenylethyl]-N-phenylcarbamate

The above compound was prepared following the procedure of Example 38 but substituting phenylisocyanate for cyclohexylisocyanate. The product was obtained as the dihydrochloride, m.p. 189.4-191.7°.

EXAMPLE 40

2-[1-[4-(2-Methoxyphenyl)piperazinyl]]-1-phenylethyl cyclohexanecarboxylate

2-[1-(4-(2-Methoxyphenyl)piperazinyl)]-1-phenyl ethanol dihydrochloride (1.50 g, 3.9 mmol) was treated with cyclohexanecarbonyl chloride prepared from the corresponding acid (1.0 g, 7.8 mmol) by reaction with thionyl chloride in chloroform and diisopropylethylamine (2.26 g, 17.5 mmol) in chloroform (15 ml). The crude product was chromatographed and the oil obtained was dissolved in acetonitrile and acidified with ethereal hydrogen chloride to afford the title compound as the dihydrochloride, m.p. 213.2-217.4°.

(Found: C, 63.0; H, 7.3; N, 5.6.

$C_{26}H_{34}N_2O_3 \cdot 2HCl$ requires C, 63.0; H, 7.3; N, 5.7%.)

EXAMPLE 41(S)-1-[2-[4-(2-Methoxyphenyl)piperazin-1-yl]-1-phenylethyl]-3-phenylurea

Phenyl isocyanate (0.45 ml, 4.2 mmol) was added to (S)-2-[1-[4-(2-methoxyphenyl)piperazinyl]]-1-phenylethylamine in dry tetrahydrofuran (10 ml) at 0° under an atmosphere of nitrogen. The solution was warmed to room temperature and after 18 hours evaporated in vacuo. The residue was chromatographed (silica; ether), dissolved in methanol, acidified with ethereal hydrogen chloride, and evaporated in vacuo to give a foam. Crystallisation from ethyl acetate propan-2-ol gave the product as the hydrochloride (0.572 g), m.p. 165-170° (dec.).

(Found: C, 63.8; H, 7.0; N, 11.1.

$C_{26}H_{30}N_4O_2 \cdot 1\frac{1}{2}HCl$ requires C, 63.8; H, 6.5; N, 11.4%.)

EXAMPLE 42Ethyl (S)-N-[2-[1-[4-(2-methoxyphenyl)piperazin-yl]]-1-phenylethyl]carbamate

(S)-2-[1-[4-(2-methoxyphenyl)piperazinyl]]-1-phenylethylamine (0.94 g, 3.0 mmol) in dichloromethane (20 ml) was treated with ethyl chloroformate (0.4 ml, 4.2 mmol), and after 4 days evaporated in vacuo. The residue was chromatographed, dissolved in ethanol, acidified with constant boiling hydrobromic acid, and evaporated in vacuo to give an oil. Crystallisation from ethyl acetate-propan-2-ol gave the product as the dihydrobromide (0.08 g), m.p. 170-180° (dec.).

(Found: C, 48.6; H, 6.0; N, 7.4.

$C_{22}H_{29}N_3O_3 \cdot 2HBr$ requires C, 48.5; H, 5.7; N, 7.7%.)

EXAMPLE 43Methyl 3-[1-[4-(2-methoxyphenyl)piperazinyl]]-2-phenylpropionate

1,1'-Carbonyldiimidazole (1.62 g, 10.0 mmol) was added to a stirred suspension of 3-[1-[4-(2-methoxyphenyl)piperazinyl]]-2-phenylpropionic acid (3.40 g, 10.0 mmol) in dry tetrahydrofuran (40 ml). The mixture was stirred at room temperature for 1 hour and methanol (40 ml, 32 g, 990 mmol) was added. The solution was stirred at room temperature for 18 hours, and was concentrated in vacuo to give a pale yellow oil. The product was chromatographed on silica with eluant ether to give the title compound as the free base (2.37 g). A portion of the product (0.65 g) was dissolved in ethyl acetate (30 ml) and the solution was acidified with ethereal hydrogen chloride (5 ml). The mixture was concentrated in vacuo, the product was dissolved in methanol, and the solution was concentrated in vacuo. The product was triturated with acetonitrile to give the title compound as the dihydrochloride (691 mg), m.p. 211-212°.

(Found: C, 58.8; H, 6.9; N, 6.3.

$C_{21}H_{26}N_2O_3 \cdot 2HCl$ requires C, 59.0; H, 6.6; N, 6.5%.)

EXAMPLE 44N-(1-Ethylpropyl)-3-[1-[4-(2-methoxyphenyl)piperazinyl]]-2-phenylpropionamide

1,1'-Carbonyldiimidazole (649 mg, 4.0 mmol) was added to a stirred suspension of 3-[1-[4-(2-methoxyphenyl)piperazinyl]]-2-phenylpropionic acid (1.36 g, 4.0 mmol) in dry tetrahydrofuran (20 ml). The

mixture was stirred at room temperature for 1 hour, and 1-ethylpropylamine (0.6 ml, 0.45 g, 5.1 mmol) was added dropwise. The mixture was stirred at room temperature for 18 hours, and was concentrated in vacuo to give a white semi solid. The product was chromatographed on silica with eluant ethyl acetate to give the title compound as the free base (0.90 g). The product was dissolved in ethyl acetate (45 ml), and the solution was acidified to give the dihydrochloride half hydrate (0.90 g), m.p. 204-208°.

(Found: C, 61.3; H, 7.8; N, 8.5.

$C_{25}H_{35}N_3O_2 \cdot 2HCl \cdot 0.5H_2O$ requires C, 61.1; H, 7.8; N, 8.55%.)

EXAMPLE 45

4-[3-[4-(2-methoxyphenyl)piperazinyl]]-2-phenylpropionyl]morpholine

The above compound was prepared following the procedure of Example 44 substituting morpholine for 1-ethylpropylamine. The product was isolated as the dihydrochloride, m.p. 213-217°.

Example 46

1-[3-[1-[4-(2-Methoxyphenyl)piperazinyl]]-2-phenylpropionyl]azetidine

1,1-carbonyldiimidazole (1.81g, 5 mmol) was added to a stirred suspension of 3-[1-[4-(2-methoxyphenyl)piperazinyl]]-2-phenylpropionic acid (1.70g, 5mmol) in dry tetrahydrofuran (25ml). The suspension was stirred at room temperature for 1h, and azetidine (1.12g, 20mmol) was added in one portion.

After 21h the solution was concentrated in vacuo to give a solid which was purified by chromatography (silica; ethyl acetate). The free base was dissolved in methanol, the solution was acidified with ethereal hydrogen chloride and evaporated in vacuo, and the solid triturated with acetonitrile to give the product as the dihydrochloride quarter hydrate (0.25g), m.p. 181°-184° (Found: C, 60.4; H, 7.0; N, 9.3; $C_{23}H_{29}N_3O_2 \cdot 2HCl \cdot 0.25H_2O$ requires C, 60.3; H, 6.9; N, 9.2%).

Example 47

O-[2-[1-[4-(2-Methoxyphenyl)piperazinyl]]-1-phenylethyl]-N-(3-chlorophenyl)carbamate

Tributyltin methoxide (0.10ml) was added to a stirred solution of 2-[1-[4-(2-methoxyphenyl)piperazinyl]]-1-phenylethanol (1.60g, 5.1mmol) and 3-chlorophenylisocyanate (0.87g, 5.7mmol) in dichloromethane (15ml). The mixture was stirred for 70h, filtered, and the filtrate evaporated in vacuo. The residue was purified by chromatography [silica; hexane-ethyl acetate (1:1→1:2)] to afford an oil which solidified on standing. The off white solid was dissolved in acetonitrile (10ml) and acidified with ethereal hydrogen chloride to afford the product as the one and eight-tenth hydrochloride salt (1.57g), m.p. 159.2-163.0° (Found: C, 58.6; H, 5.9; N, 7.9; $C_{26}H_{28}N_3O_3Cl \cdot 1.8HCl$ requires C, 58.5; H, 5.6; N, 7.9%).

Example 48

1-Ethyl-3-[2-[1-[4-(2-methoxyphenyl)piperazinyl]]-1-phenylethyl} carbonate

Ethyl chloroformate (0.60g, 5.5 mmol) was added to a solution of 2-[1-[4-(2-methoxyphenyl)piperazinyl]]-1-phenylethanol (1.57g, 5.0mmol) and triethylamine (0.56g, 5.5mmol) in dichloromethane (15ml). The mixture was stirred for 70h, evaporated in vacuo, and the residue purified by chromatography [silica; hexane-ethyl acetate (1:1)] to afford an oil. The oil was dissolved in acetonitrile (10ml) and acidified with ethereal hydrogen chloride to afford the dihydrochloride salt of the product (0.41g), m.p. 213-215° (dec.) Found C, 57.6; H, 6.7; N, 6.1; C₂₂H₂₈N₂O₄.2HCl requires C, 57.8; H, 6.6; N, 6.1%)

Example 49

2-[1-[4-(2-Methoxyphenyl)piperazinyl]]-1-phenylethyl benzo-2,4-dioxin-2-ylcarboxylate

Benzo-2,4-dioxin-2-ylcarboxylic acid (2.10g, 11.7mmol) in thionyl chloride (10.0ml) was heated under reflux for 1h and the excess thionyl chloride removed under reduced pressure. The crude acid chloride was dissolved in dichloromethane (10.0ml) and a solution of 2-[1-[4-(2-methoxyphenyl)piperazinyl]]-1-phenylethanol dihydrochloride (1.50g, 3.9mmol) in dichloro-methane (5.0ml) added, followed by triethylamine (1.22g, 12.1mmol). The mixture was stirred for 18h, filtered and the filtrate evaporated in vacuo. The oil was purified by chromatography [silica; hexane-ethyl

acetate (2:1→2;3], dissolved in acetonitrile (10ml) and acidified with ethereal hydrogen to give the product as a dihydrochloride salt (1.37g), m.p. 202-206° (Found C, 61.5; H, 6.0; N, 5.1. $C_{28}H_{30}N_2O_5 \cdot 2HCl$ requires C, 61.4; H, 5.9; N, 5.1%)

Example 50

(S)-8-[2-[1-[4-(2-Methoxyphenyl)piperazinyl]]-1-phenylethyl]-8-azaspiro[4.5]decan-7,9-dione

A solution of (S)-2-[1-[4-(2-methoxyphenyl)piperazinyl]]-1-phenethylamine (1.0g, 3.2mmol) and 3,3-tetramethyleneglutaric anhydride (0.543g, 3.2mmol) in pyridine (10ml) was heated under reflux under an atmosphere of nitrogen for 2lh, cooled to room temperature, and evaporated in vacuo to give a brown oil. A solution of the oil in acetic anhydride (15ml) was heated under reflux for 2lh, cooled to room temperature, and evaporated in vacuo. The residue in water was basified with saturated aqueous ammonia and extracted with ethyl acetate (2 x 50ml). The extracts were washed with water (100ml), dried ($MgSO_4$), and evaporated in vacuo. The residue was purified by chromatography [silica; hexane-ethyl acetate (3:2)] to give the product free base a yellow oil (0.82g).

The oil was dissolved in methanol (5ml) and the solution acidified with ethereal hydrogen chloride, evaporated in vacuo, and the crystals triturated with ether to give the dihydrochloride salt of the product (0.63g) m.p. 203-206° (Found: C, 62.9; H, 7.0; N, 7.9; $C_{28}H_{35}N_3O_3 \cdot 2HCl$ requires C, 62.5; H, 7.1; N, 8.0%).

Example 512,3,4,5,6,7-Hexahydro-1-[2-[1-(4-(2-methoxyphenyl) piperazinyl)methyl]-3-phenylpropanoyl]-1H-azepine

This compound was prepared from the acid of Example 2 (20g, 5.65mmol), 1,1'-carbonyldiimidazole (0.92g, 5.7mmol), and hexahydro-1H-azepine (0.62g, 6.3mmol) using the method outlined in Example 6 and the crude product was purified by chromatography [silica; ethyl acetate-hexane (1:1)]. The sesquihydrochloride salt of the product was isolated as crystals (0.96g), m.p. 195-195.5° (from ethyl acetate).
(Found: C, 65.9; H, 8.0; N, 8.5).
 $C_{27}H_{37}N_3O_2 \cdot 1\frac{1}{2}HCl$ requires C, 66.1; H, 7.9; N, 8.6%)

Example 52N-Cycloheptyl-2-[1-[4-(2-methoxyphenyl) piperazinyl)methyl]-3-phenylpropanamide

This compound was prepared from the dihydrochloride salt of the acid of Example 2 (2.2g, 4.5mmol), 1,1'-carbonyldiimidazole (0.8g, 4.9mmol), and cycloheptylamine (0.56g, 4.9mmol) in the presence of triethylamine (1.18g, 11.7mmol) using the method outlined in Example 51. The dihydrochloride salt of the product was isolated as off white crystals (0.91g), m.p. 178.5 - 181.5°.
(Found: C, 64.1; H, 7.9; N, 8.0).
 $C_{28}H_{39}N_3O_2 \cdot 2HCl$ requires C, 64.4; H, 7.9; N, 8.0%).

Example 53(a) 1-[1-[4-(2-Methoxyphenyl)piperazinyl]]-3,3-dimethylbutan-2-ol

A mixture of 1-(2-methoxyphenyl)piperazine hydrochloride (34.5g, 0.16mol), 3,3-dimethyl-1,2-epoxybutane (20g, 0.2mol) triethylamine (20g), and acetonitrile (120ml) was heated at reflux for 56h. The reaction was then diluted with water (500ml) and extracted with ether (200ml). The extract was washed with water (2 x 200ml), dried (sodium sulphate), and evaporated in vacuo. The residue was dissolved in ethanol (100ml) and ether (50ml) and the solution acidified with ethanolic hydrogen chloride to precipitate the dihydrochloride salt of the product (26.1g), m.p. 243-245°.

(b) 2-[1-[1-(4-(2-Methoxyphenyl)piperazinyl]-3,3-dimethyl}butyl-4-fluorobenzoate

The dihydrochloride salt of the product of Example 53(a) (1.0g, 2.7mmol), triethylamine (0.4g, 3.8mmol), and 4-fluorobenzoyl chloride (0.6g, 3.8mmol) in dichloromethane (15ml) was stirred at room temperature for 18h and the reaction mixture concentrated in vacuo. The residue was purified by chromatography [silica; ethyl acetate-hexane (1:1)] to afford an oil which was dissolved in ethyl acetate and acidified with ethereal hydrogen chloride to afford the dihydrochloride salt of the product, m.p. 232.5 - 234°.

(Found: C, 58.9; H, 6.9; N, 5.6.

$C_{24}H_{31}FN_2O_3$ requires C 59.1; H, 6.8; N, 5.8%).

Example 54N-Cyclopropyl-2-[1-[4-(2-methoxyphenyl)
piperazinyl]methyl]-3-phenylpropanamide

This compound was prepared from the acid of Example 2 (2.5g, 7.0mmol), 1,1'-carbonyldiimidazole (1.2g, 7.4mmol) and cyclopropylamine (0.44g, 7.7mmol) using the method outlined in Example 51.. The hydrochloride quarter hydrate salt of the product was isolated as a powder (2.12g,), m.p. 169 - 170.5° (Found: C, 66.3; H 7.6; N, 9.4. $C_{24}H_{31}N_3O_2 \cdot HCl \cdot \frac{1}{4}H_2O$ requires C, 66.3; H, 7.5; N, 9.7%).

Example 55(a) α -[[1-(4-Phenylpiperazinyl)]methyl]benzeneacetic acid

1-Phenylpiperazine and atropic acid in ethanol is heated under reflux for 18h, cooled to room temperature, and evaporated in vacuo. The solid is triturated with acetone to give the title product.

(b) N-Cyclopropyl-2-phenyl-3-[1-(4-phenylpiperazinyl)]
propanamide

This compound is prepared by the reaction of the product of Example 55(a) with 1,1'-carbonyldiimidazole and cyclopropylamine following the procedure outlined in Example 6.

Example 56

N-cyclohexyl-2-phenyl-3-[1-[4-(3-trifluoromethylphenyl) piperazinyl]]propanamide

5 A solution of the product of Example 4 and N-(3-trifluoromethylphenyl)piperazine is heated in propanol in the presence of a small quantity of acetic acid as catalyst to give the title product.

Example 57

(a) 2-[1-[4-(1-Naphthyl)piperazinyl]]-1-phenylethanol

10 Styrene oxide and 1-(1-naphthyl)piperazine in acetonitrile are heated under reflux. Concentration in vacuo and purification by chromatography (silica; ethyl acetate) gives the product.

15 (b) 2-[1-[4-(1-Naphthyl)piperazinyl]]-1-phenylethyl cyclohexanecarboxylate

This compound is prepared by the reaction of the product of Example 57(a) with cyclohexanecarbonyl chloride using the method described in Example 40

Example 58

20 (a) 2-[1-[4-(3-Chlorophenyl)piperazinyl]]-1-phenyl ethanol

The reaction of styrene oxide and 1-(3-chlorophenyl)piperazine gives the title compound using the method outlined in Example 57(a).

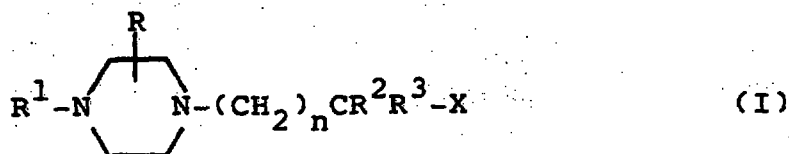
(b) 0-[2-[1-(4-(3-Chlorophenyl)piperazinyl)]-1-phenyl
ethyl]-N-phenylcarbamate

5 The above compound is prepared following the procedure
of Example 38 but substituting phenylisocyanate for
cyclohexylisocyanate and the product of Example 58 (a)
for

2-[4-(2-methoxyphenyl)piperazin-1-yl]-1-phenylethanol.

CLAIMS

1. A compound of the general formula (I)



or a pharmaceutically acceptable acid addition salt thereof wherein

n is one of the integers 1 or 2.

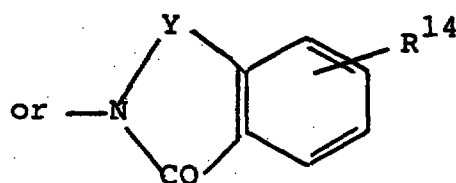
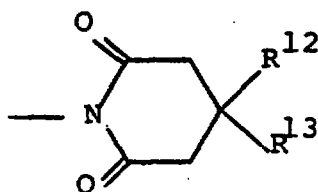
R is hydrogen or lower alkyl,

R^1 is an aryl or nitrogen containing heteroaryl radical,

R^2 is hydrogen or lower alkyl,

R^3 is an aryl radical, an alkyl radical containing 4 to 8 carbon atoms or an aryl(lower)alkyl radical,

X is $-\text{OCOR}^{10}$, $-\text{CO}_2\text{R}^6$, $-\text{CONR}^5\text{R}^9$, $-\text{OCO}_2\text{R}^6$,
 $-\text{NR}^4\text{COR}^6$,
 OCONHR^{11} , $-\text{NHCO}_2\text{R}^6$, $-\text{NR}^4\text{CONHR}^6$, $-\text{CONHNHR}^6$,
 $-\text{CONHOR}^6$,



R^4 and R^5 are each hydrogen or lower alkyl

R^6 is $-\text{CHR}^7\text{R}^8$, cycloalkyl of 3 to 12 carbon atoms



or aryl(lower)alkyl (where R^7 and R^8 are each hydrogen or lower alkyl)

R^9 is hydrogen, an alkyl group of 1 to 8 carbon atoms other than a tertiary alkyl group, cycloalkyl of 3 to 12 carbon atoms, cycloalkyl(lower)alkyl, aryl, aryl(lower)alkyl or 8-azaspiro [4.5]deca-7,9-dione-8-yl-(lower)alkyl [with the proviso that when R^3 is aryl or aralkyl, R^9 is not a phenyl group substituted in the ortho position by halogen, nitro, trifluoroalkyl, cyano, sulphonic acid, sulphonamido, carboxy, carbalkoxy, carboxylanilino or a 4-carboxylamino-benzosulphonamido group and that when R^9 is hydrogen, alkyl, aryl or aryl(lower)alkyl, R^5 is hydrogen or a primary or secondary lower alkyl group]

or R^5 and R^9 together with the nitrogen atom to which they are attached represent an azetidino, pyrrolidino, piperidino, hexahydroazepino, morpholino or piperazino ring which may be optionally substituted by lower alkyl, aryl or aryl(lower)alkyl

R^{10} is cycloalkyl of 3 to 12 carbon atoms, or 2,3-dihydro[1,4]benzodioxinyl optionally substituted by lower alkyl, lower alkoxy or halogen or, when R^3 is an alkyl radical containing 4 to 8 carbon atoms, R^{10} , can also be aryl;

R^{11} is cycloalkyl of 3 to 12 carbon atoms, aryl or aryl(lower)alkyl,

R^{12} and R^{13} are each lower alkyl or together with the carbon atom to which they are both attached represent C_{4-6} cycloalkyl,



R^{14} represents hydrogen, halogen, lower alkyl or lower alkoxy

and

Y is CO or SO₂

with the further proviso that n is 1 when X is -COOC₂H₅, -CONH₂ or -CON(CH₃)₂, R² is hydrogen and R³ is aryl.

2. A compound as claimed in claim 1 in which R¹ is a phenyl radical optionally substituted by one or more lower alkoxy, halogen, trifluoromethyl, nitro, carbalkoxy, carboxamido, cyano, amino, (lower)alkylamino or di(lower)alkylamino substituents.
3. A compound as claimed in claim 1 in which R³ is a phenyl radical optionally substituted by one or more lower alkoxy, halogen, trifluoromethyl, nitro, carbalkoxy, carboxamido, cyano, amino, (lower)alkylamino or di(lower)alkylamino substituents.
4. A compound as claimed in claim 1 in which X represents -CO₂R⁶ or -CONR⁵R⁹ where R⁶, R⁵ and R⁹ are as defined in claim 1.
5. A compound as claimed in claim 1 where X is -CONR⁵R⁹ wherein R⁵ and R⁹ together with the nitrogen atom to which they are attached represent an azetidino, pyrrolidino, piperidino, hexahydroazepino, morpholino or piperazino ring.



6. 1-{3-[1-[4-(2-Methoxyphenyl)piperazinyl] }-2-phenylpropionyl}pyrrolidine or a pharmaceutically acceptable acid addition salt thereof.

7. 1-{3-[1-[4-(2-Methoxyphenyl)piperazinyl] }-2-phenylpropionyl}piperidine or a pharmaceutically acceptable acid addition salt thereof.

8. A compound as claimed in claim 1 which is

propyl 3-[1-[4-(2-methoxyphenyl)piperazinyl] }-2-phenylpropanoate,

3-[1-[4-(2-methoxyphenyl)piperazinyl] }-2-phenyl-N-phenylpropanamide,

3-[1-[4-(2-methoxyphenyl)piperazinyl] }-2-phenylpropanamide,

N-methyl-3-[1-[4-(2-methoxyphenyl)piperazinyl] }-2-phenylpropanamide,

N-ethyl-3-[1-[4-(2-methoxyphenyl)piperazinyl] }-2-phenylpropanamide,

N-propyl-3-[1-[4-(2-methoxyphenyl)piperazinyl] }-2-phenylpropanamide,

N-butyl-3-[1-[4-(2-methoxyphenyl)piperazinyl] }-2-phenylpropanamide,

N-isobutyl-3-[1-[4-(2-methoxyphenyl)piperazinyl] }-2-phenylpropanamide,



N-cyclopropylmethyl-3-{1-[4-(2-methoxyphenyl)
piperazinyl]}-2-phenylpropanamide,

N-neopentyl-3-{1-[4-(2-methoxyphenyl)]
piperazinyl]}-2-phenylpropanamide,

N-hexyl-3-{1-[4-(2-methoxyphenyl)piperazinyl]}-2-
phenylpropanamide,

N-cyclohexylmethyl-3-{1-[4-(2-methoxyphenyl)
piperazinyl]}-2-phenylpropanamide,

8-{ α -{1-[4-(2-methoxyphenyl)piperazinyl]methyl}
phenylacetamidoethyl}-8-azaspiso[4.5]deca-7,9-
dione,

N,N-dimethyl-3-{1-[4-(2-methoxyphenyl)
piperazinyl]}-2-phenylpropanamide,

3-{1-[4-(2-methoxyphenyl)piperazinyl]}-2-phenyl
-N-(phenylmethyl)propanamide,

N-cyclohexyl-2-phenyl-3-{1-[4-(2-pyrimidinyl)-
piperazinyl]}propanamide,

3,N-bis{1-[4-(2-methoxyphenyl)piperazinyl]}
-2-phenylpropanamide,

2-methylpropyl 3-{1-[4-(2-methoxyphenyl)
piperazinyl]}-2-phenylpropanoate,

ethyl 3-{1-[4-(2-methoxyphenyl)piperazinyl]}
-2-phenylpropanoate,

2-{1-[4-(2-methoxyphenyl)piperazinyl]methyl}
-N-methyl-3-phenylpropanamide



ethyl 2-[1-[4-(2-methoxyphenyl)piperazinyl]
methyl]-3-phenylpropanoate

3-[1-[4-(2-methoxyphenyl)piperazinyl]]-N-(3,3
-dimethyl)butyl-2-phenylpropionamide

N-cyclopropyl-3-[1-[4-(2-methoxyphenyl)
piperazinyl]]-2-phenylpropanamide

1-[3-[1-[4-(2-methoxyphenyl)piperazinyl]]-2-
phenylpropionyl]pyrrolidine

N-cyclooctyl-3-[1-[4-(2-methoxyphenyl)
piperazinyl]]-2-phenylpropionamide

N-cyclododecyl-3-[1-[4-(2-methoxyphenyl)
piperazinyl]]-2-phenylpropionamide

(S)-N-[2-[1-[4-(2-Methoxyphenyl)piperazinyl]]
-1-phenylethyl]cyclohexanecarboxylic acid amide

O-[2-[1-(4-(2-Methoxyphenyl)piperazinyl)]-1-
phenylethyl]-N-cyclohexylcarbamate

O-[2-[1-[4-(2-Methoxyphenyl)piperazinyl]]-1-
phenylethyl]-N-phenylcarbamate

2-[1-[4-(2-Methoxyphenyl)piperazinyl]]-1-
phenylethyl cyclohexanecarboxylate

(S)-1-[2-[4-(2-Methoxyphenyl)piperazin-1-yl]-1-
phenylethyl]-3-phenylurea

Ethyl (S)-N-[2-[1-[4-(2-Methoxyphenyl)
piperazinyl]]-1-phenylethyl]carbamate



Methyl 3-[1-[4-(2-methoxyphenyl)piperazinyl]]
-2-phenylpropionate

N-(1-Ethylpropyl)-3-[1-4-(2-methoxyphenyl)-
piperazinyl]]-2-phenylpropionamide

4-[3-[1-[4-(2-methoxyphenyl)piperazinyl]]-2-
phenylpropionyl]morpholine

1-{3-[1-[4-(2-Methoxyphenyl)piperazinyl]]-2-
phenylpropionyl}azetidine

O-{2-[1-[4-(2-Methoxyphenyl)piperazinyl]]-1-
phenylethyl}-N-(3-chlorophenyl)carbamate

1-Ethyl-3-{2-[1-[4-(2-methoxyphenol)piperazinyl]]
-1-phenylethyl} carbonate

2-[1-[4-(2-Methoxyphenyl)piperazinyl]]-1-
phenylethyl benzo-2,4-dioxin-2-ylcarboxylate

(S)-8-{2-[1-[4-(2-Methoxyphenyl)piperazinyl]]-1-
phenylethyl}}-8-azaspiro[4.5]decan-7,9-dione

2,3,4,5,6,7-Hexahydro-1-{2-[1-(4-(2-
methoxyphenyl)piperazinyl)methyl]-3-
phenylpropanoyl}-1H-azepine

N-Cycloheptyl-2-{1-[4-(2-methoxyphenyl)
piperazinyl]methyl-3-phenylpropanamide

2-[1-[1-(4-Methoxyphenyl)piperazinyl]-3,3-
dimethyl}butyl-4-fluorobenzoate



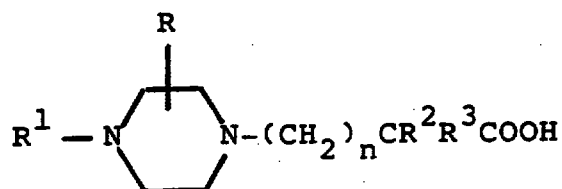
N-Cyclopropyl-2-[1-[4-(2-methoxyphenyl)
piperazinyl]methyl]-3-phenylpropanamide
or a pharmaceutically acceptable acid addition
salt thereof.

9. A process for preparing a compound claimed in
claim 1 which comprises

(a) acylating an amine of formula



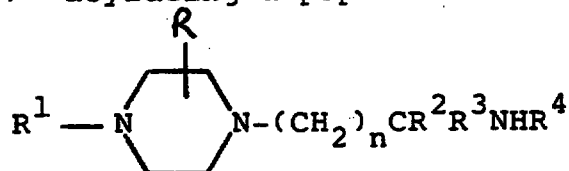
(where R^5 and R^9 are as defined in claim 1)
with an acid of formula



(III)

(where $\text{R}, \text{R}^1, \text{R}^2$ and R^3 are as defined in
claim 1) or with an acylating derivative
thereof
or

(b) acylating a piperazine alkylamine of formula



with an acid of formula

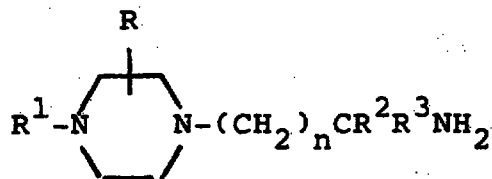


or with an acylating derivative thereof

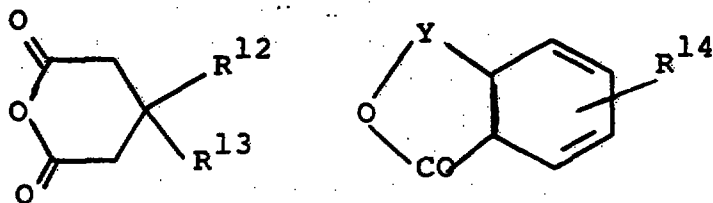


or

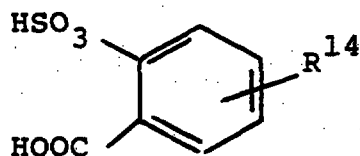
(c) reacting an amine of formula



with an anhydride of formula



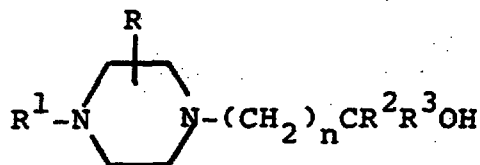
or with an acid of formula



or

(d) esterifying an acid of formula (III), as given above with an alcohol of formula R^6OH
or

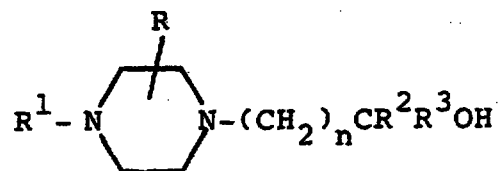
(e) esterifying a piperazine alcohol of formula



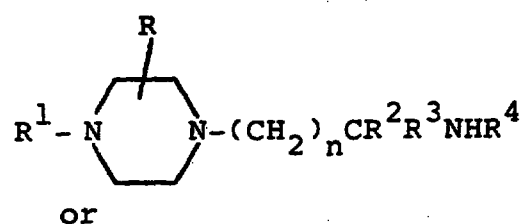
with an acid of formula R^{10}COOH
or



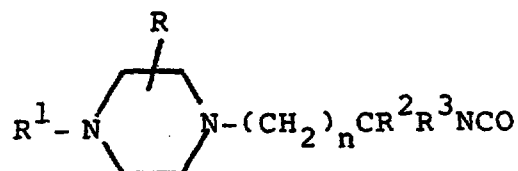
- (f) reacting an isocyanate with a piperaziny-alkanol of formula



or with a piperaziny-alkylamine of formula



- (g) reacting a piperazine isocyanate derivative of formula

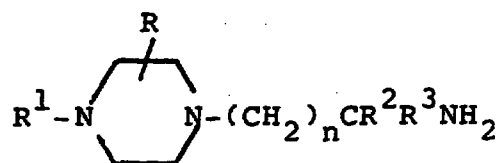


with an alcohol of formula



or

- (h) reacting an amine of formula



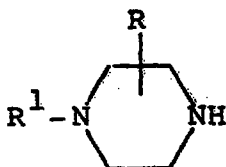
with a compound of formula $\text{R}^6 \text{OCOHal}$ (where Hal is halogen)



or

- (i) reacting an acid of formula (III) given above with a hydroxylamine of formula NH_2OR^6 or with a hydrazide of formula NH_2NHR^6 or

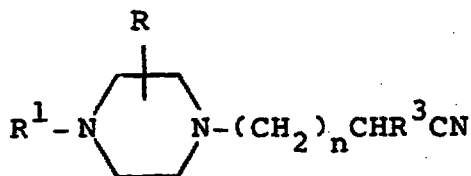
- (j) alkylating a piperazine of formula



(IV)

with an alkylating agent providing the group $-(\text{CH}_2)_n \text{CR}^2\text{R}^3\text{X}$ or

- (k) reacting a nitrile of formula (IX)

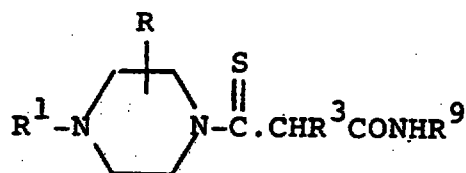


(IX)

with a secondary alcohol or subjecting the nitrile to acid hydrolysis or



- (l) desulphurising a sulphur containing compound of formula



(XI)

or

- (m) converting a free base of formula (I) into a pharmaceutically acceptable salt thereof
or

- (n) resolving a racemic compound of formula (I) to give an optically active enantiomer

10. A process for preparing a compound claimed in claim 1 substantially as hereinbefore described with reference to any one of Examples 5 to 29.
11. A process for preparing a compound claimed in claim 1 substantially as hereinbefore described with reference to any one of Examples 30 to 45.
12. A process for preparing a compound claimed in claim 1 substantially as hereinbefore described with reference to any of of Examples 46 to 54.



13. A compound as claimed in claim 1 when prepared by the process claimed in any one of claims 9 to 12.
 14. A pharmaceutical composition comprising a compound claimed in any one of claims 1 to 8 and 13 in association with a pharmaceutically acceptable carrier.
 15. A compound as claimed in any one of claims 1 to 8 and 13 for use as a pharmaceutical.
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