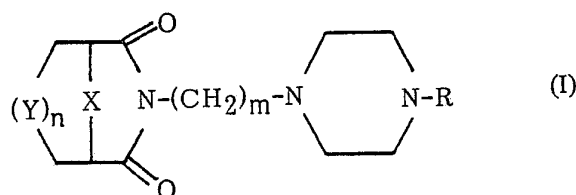




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(54) Title: PSYCHOTROPIC BICYCLIC IMIDES



(57) Abstract

Substituted imides of formula (I), are antipsychotic, anxiolytic agents with very little extrapyramidal side effects; in which X is -O-, -S-, -SO-, -SO₂-, CR₃R₄- where R₃ and R₄, independently, are hydrogen, alkyl of 1 to 4 carbon atoms or, taken together with the carbon atom to which they are attached, R₃ and R₄ form a cycloalkyl group of 3 to 5 carbon atoms; Y is alkylene of 1 to 3 carbon atoms or alkenylene of 2 to 3 carbon atoms; n is one of the integers 0 or 1; m is one of the integers 2, 3, 4 or 5; R is 2-pyrimidinyl, halopyrimidin-2-yl, 2-pyrazinyl, halopyrazin-2-yl, 2-pyridinyl, cyanopyridin-2-yl, halopyridin-2-yl, quinolyl, or haloquinolyl; or a pharmaceutically acceptable salt thereof.

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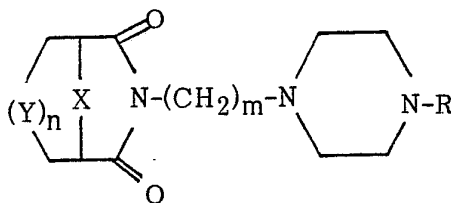
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PSYCHOTROPIC BICYCLIC IMIDESTechnical Field

This invention relates to a group of antipsychotic/anxiolytic N-(heteroaryl piperazinylalkyl) bicyclic-1,3-dicarboxylic acid imides.

Description of the Invention

In accordance with this invention there is provided a group of antipsychotic anxiolytic N-(heteroaryl piperazinylalkyl) bicyclic-1,3-dicarboxylic acid imides of the formula:



10 in which

X is -O-, -S-, -SO-, -SO₂-, -CR₃R₄- where R₃ and R₄, independently, are hydrogen, alkyl of 1 to 4 carbon atoms or, taken together with the carbon atom to which they are attached, R₃ and R₄ form a cycloalkyl group of 3 to 5 carbon atoms;

15 Y is alkylene of 1 to 3 carbon atoms or alkenylene of 2 to 3 carbon atoms;

m is one of the integers, 2, 3, 4 or 5;

n is one of the integers 0 or 1;;

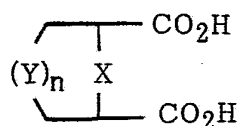
20 R is 2-pyrimidinyl, halopyrimidin-2-yl, 2-pyrazinyl, halopyrazin-2-yl, 2-pyridinyl, cyanopyridin-2-yl, halopyridin-2-yl, quinolyl, or haloquinolyl;

or a pharmaceutically acceptable salt thereof.

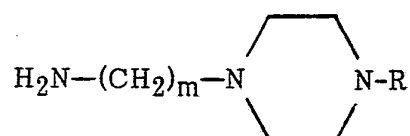
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Of the applicable halogen substituents present, including fluoro, chloro and bromo, chloro is preferred. The pharmaceutically acceptable salts are those derived from such organic and inorganic acids as: acetic, lactic, citric, tartaric, succinic, maleic, malonic, gluconic, hydrochloric, hydrobromic, phosphoric, nitric, sulfuric, methanesulfonic, and similarly known acceptable acids.

The compounds of the invention may be prepared by conventional methods. The preparation may be by (a) cyclisation of a suitable 1,3-dicarboxylic acid (II) or a reactive derivative thereof with a



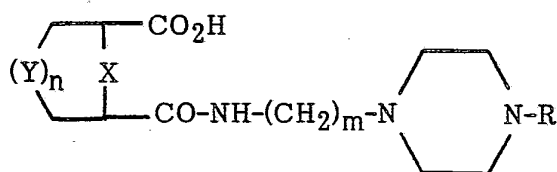
(II)



(III)

piperazinylalkyl amine (III) or a reactive derivative thereof to form an imide. The cyclisation may be carried out by combining the acid (II) or the anhydride derived from it with the amine (III) in a high boiling solvent such as toluene or xylene and refluxing for an extended period with either chemical (e.g. ethoxyacetylene) or mechanical (e.g. Dean-Stark trap) removal of water. Alternatively, the cyclisation may be carried out by reacting the anhydride derivative of the acid (II) with the isocyanate derivative of the amine (III).

The compounds of the invention may also be prepared by (b) cyclisation of an N-substituted amidic acid (IV) or a reactive

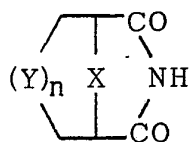


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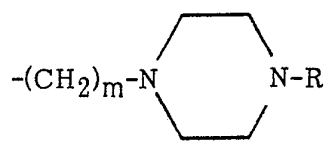
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derivative thereof. The amidic acid (IV) may be prepared by reacting the anhydride derived from the acid (II) with the amine (III) in a solvent, for instance, methylene chloride. The cyclisation of the amidic acid (IV) may be carried out by refluxing it in a high boiling solvent such as toluene or xylene with chemical or mechanical removal of water, e.g. by means of a Dean-Stark trap.

The compounds of the invention may also be prepared by (c) N-alkylation of an imide (V) or a salt thereof to introduce a

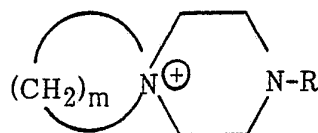


(V)



(VI)

substituted alkyl group (VI). The alkylation may be carried out by reacting the imide (V) in salt form with a compound having the formula R_1-Z where R_1 is a group having formula VI and Z is a leaving group preferably chloro or bromo. The alkylation may also be carried out by reacting the salt of V with a spirocyclic quaternary ammonium salt such as VIa.

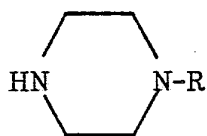
 Cl^-

(VIa)

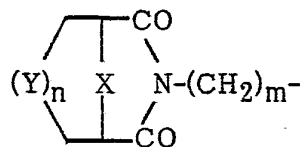
The reaction may be carried out in a solvent such as DMF. The salt form of the imide may be formed by combining the imide with a strong base such as sodium hydride. The alkylation of the imide (V) may also be carried out by reacting it with the alcohol R_1-OH by means of triphenylphosphine and diethyl azodicarboxylate.

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The compounds of the invention may also be prepared by (d) N-alkylation of a piperazine derivative (VII) to introduce a substituted

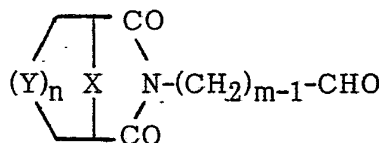


(VII)



(VIII)

alkyl group (VIII) or reductive alkylation of the piperazine derivative (VII) with an aldehyde (IX). As alkylating agents there may be used a

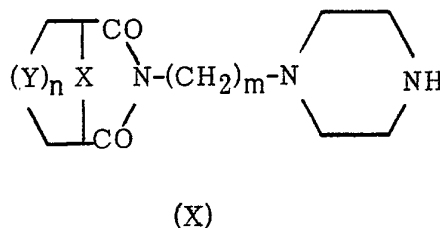


(IX)

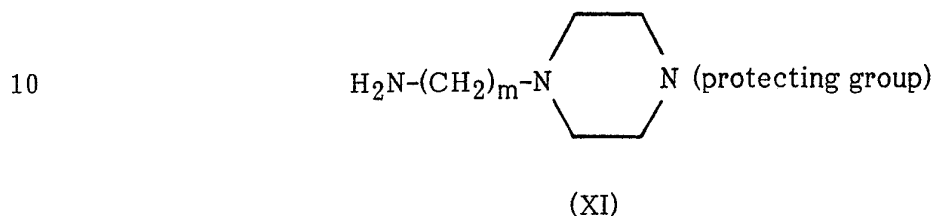
compound having the formula R_2-Z where R_2 is a group having formula VIII and Z is a leaving group preferably chloro, bromo, tosylate or mesylate. The alkylation and reductive alkylation may be carried out in known manner for the preparation of tertiary amines. The compound having the formula R_2-Z may be prepared by alkylation of an imide (V) with a suitable dihalo lower alkane $Z-(CH_2)_m-Z$ in the presence of a strong base such as sodium hydride in a solvent such as DMF. Alternatively, the compound having the formula R_2-Z may be prepared by imide formation from the anhydride of the acid (II) and an omega (trimethylsilyloxy) alkylamine, such as 4-(trimethylsilyloxy)butylamine. Removal of the trimethylsilyl protecting group can be effected with water and is followed by activation of the omega hydroxyl group, for example, with a tosyl or mesyl group. Aldehydes (IX) can be prepared from corresponding alkyl halides R_2-Z in known manner.

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The compounds of the invention may also be prepared by N-heteroarylation of a piperazine derivative (X) to introduce the group R. The reaction can be



5 carried out with a heteroaryl halide $R-Z$ where Z is chloro, bromo or fluoro, for example, 2,6-dichloropyrazine. The piperazine derivative (X) may be prepared by modifying any of methods (a) to (d) by replacing R with an N-protecting group, e.g. by reacting the anhydride derivative of acid (II) with an amine (XI) to form the



10 imide derivative thereof or by reacting the compound R_2-Z with an N^1 -protected piperazine such as 1-benzylpiperazine. Removal of the protecting group from the product yields the piperazine derivative (X). The protecting group may be benzyl. Deprotection to remove the benzyl group may be by
15 hydrogenolysis in the presence of a noble metal catalyst such as platinum or palladium.

20 The compounds of the invention where X is $-SO-$ or $-SO_2-$ may be prepared by (f) oxidising a compound having formula I where X is $-S-$ or a salt thereof to form a sulfoxide or a sulfone or oxidation of a compound having formula I where X is $-SO-$ or a salt thereof to form a sulfone. The oxidation

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can be carried out in known manner, for example, with hydrogen peroxide and glacial acetic acid or with m-chloroperbenzoic acid.

5 The compounds having formula I may be converted into their pharmaceutically acceptable salts by addition of a suitable acid. The acid addition salts of the compounds having formula I may be converted into the compounds having formula I by neutralisation of the acid addition salt.

10 The antipsychotic properties of the compounds of this invention were established by standard pharmacologically accepted procedures involving conditioned avoidance studies in which trained male CD rats (Charles River), 400-450 g. body weight are exposed to a fifteen second warning tone (conditioned stimulus) continued for an additional fifteen seconds accompanied by electric shock. The rat can avoid the electric shock by jumping to an exposed shelf (shelf-jump response). A response during the initial warning tone is considered an avoidance response, while a response during shock delivery is considered as escape response. The shelf-jump response test procedure follows that of Herman et al., Comm. in Psychopharm., 3, pp. 165-171 (1979). The compounds of this invention were tested at a single dose (40 mg./kg. i.p.) in this procedure and were rated relative to their inhibition of conditioned avoidance responding. A similar test procedure (Discrete Trial) in which a lever press was substituted for a shelf-jump was used to establish the oral (p.o.) activity of the test compounds. Orally active compounds were tested over a full dose range and the Avoidance Block activities reported as "AB₅₀'s" (mg./kg.).

25 As a further measure of antipsychotic activity, the compounds of this invention were also studied as antagonists of apomorphine-induced stereotyped behavior and climbing wherein CF-1 mice (Charles River) receive the test compound i.p. at several dose levels (1, 10, 30 and 60 mg./kg.) (six mice per dose level) and thirty minutes later receive 1 mg./kg. apomorphine s.c. Five minutes after injection, the sniffing-licking-gnawing syndrome and climbing behavior induced by apomorphine are scored for each animal. Readings are repeated every five minutes during a thirty minute test session. An ED₅₀ value (with 95% confidence intervals) is calculated for inhibition of apomorphine-induced stereotyped behavior and climbing using a non-linear least squares calculation with inverse prediction. The ratio of the ED₅₀ for stereotyped behavior to the ED₅₀ for climbing is calculated. High ratios

30

35

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indicate antipsychotic activity with low liability for the extrapyramidal side effects which attend long term treatment with such standard antipsychotic drugs as haloperidol (ratio = 1.00), chlorpromazine (ratio = 1.51) and thioridazine (ratio = 1.83).

5 In further support of the low potential for side-effects, the compounds of this invention were found to exhibit only weak binding to the D-2 dopamine receptor when tested in accordance with a modification of the procedure of Fields et al., Brain Res., 136, pp. 578-584 (1977) and Yamamura et al., eds., Neurotransmitter Receptor Binding, Raven Press, N.Y. (1978),
10 wherein homogenized limbic brain tissue is incubated with ³H-spiroperidol and various concentrations of test compound, filtered and washed and shaken with Hydrofluor scintillation cocktail (National Diagnostics) and counted in a Packard 460CD scintillation counter. In those instances where moderate binding of the D-2 dopamine receptor occurred, the binding of those
15 compounds at the 5HT_{1A} serotonin receptor was sufficient to demonstrate useful selectivity of action of such magnitude as to relatively minimize any problem of extrapyramidal side effects. The results of this testing with compounds representative of the invention whose production is exemplified, infra, are as follows:

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Conditioned Avoidance

5	Ex.	Shelf-Jump 40 mg/kg, i.p.	Discrete Trial AB ₅₀ p.o.	<u>Apomorphine Antagonism</u>		<u>[³H] Spiro- peridol Binding Inhibition</u> Ki, nM or % at 1 μ M
				<u>Stereotypy</u>	<u>Climbing</u>	
10	1	80%	inactive	inactive		38%
	2	>20%	weak	inactive		2,614 nM
	3	80%	weak	inactive		44%
	4	>20%	inactive	inactive	53.27	12%
	5	>20%	47.31	inactive	inactive	27%
15	6	>20%	inactive	inactive	inactive	14%
	7	80%	34.10	inactive		21%
	8	80%	33.62	inactive	15.66	12%
	9	>20%	98.16	inactive	40.90	31%
	10	>20%	weak	inactive	51.65	7%
20	11	80%	86.15	inactive	0.24	17%
	12	>20%	35.62	inactive	>50	34%
	13	80%	weak	inactive	>50	21%
	14	80%	inactive	51.14	9.17	12%
	15	>20%	inactive	inactive	42.95	21%
	16	>20%	inactive	inactive	0.20	53%
	17	>20%	inactive	inactive	11.11	63%

25

From these data, the activity profile of the compounds of this invention are seen to be that of antipsychotic agents with less potential for extra pyramidal side effects such as attend the use of major tranquillizers

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(sedation, pseudoparkinsonism, ataxia, muscle relaxation, etc.). This activity profile resembles that of the anxiolytic compound, buspirone. Further evidence that the pharmacological profile of the test compounds resembles that of buspirone was obtained by measuring the compound's ability to displace [3H] 8-OH DPAT (dipropylaminotetralin) from the 5-HT_{1A} serotonin receptor by the procedure of Hall et al., J. Neurochem. 44: 1685-1696, 1985. Compounds of the invention, like buspirone, exhibited potent affinity for this serotonin receptor subtype. The anxiolytic activity of buspirone is currently believed to be due, at least in part, to this receptor (Vander Maelen et al., Eur. J. Pharmacol. 1986, 129(1-2) 123-130. The test results of this study are as follows:

Inhibition of [3H]
8-OH DPAT Binding

	<u>Example</u>	<u>Ki, nM or % at 1μM</u>
15	1	10 nM
	2	106 nM
	3	31 nM
	4	46 nM
	5	16 nM
20	6	90 nM
	7	31 nM
	8	68%
	9	60 nM
	10	54%
25	11	122 nM
	12	35.2 nM
	13	63%
	14	129 nM
	15	76%
30	16	16 nM
	17	15 nM

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Hence, the compounds of this invention are antipsychotic agents and anxiolytic agents useful in the treatment of psychoses such as paranoia and schizophrenia and in alleviating anxiety. As such, they may be administered neat or with a pharmaceutical carrier to a patient in need thereof. The pharmaceutical carrier may be solid or liquid.

A solid carrier can include one or more substances which may also act as flavoring agents, lubricants, solubilisers, suspending agents, fillers, glidants, compression aids, 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% 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.

Liquid carriers are used in preparing solutions, suspensions, emulsions, syrups, elixirs and pressurized compositions. The active ingredient 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, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilisers or osmo-regulators. Suitable examples of liquid carriers for oral and parenteral administration include water (particularly containing additives as above, e.g. cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols, e.g. glycols) and their derivatives, and oils (e.g. 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. The liquid carrier for pressurized compositions can be halogenated hydrocarbon or other pharmaceutically acceptable propellant.

Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by, for example, intramuscular, intraperitoneal or

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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, e.g. 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 compositions, for example packeted powders, vials, ampoules, prefilled syringes or sachets containing liquids. 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 dosage to be used in the treatment of a specific psychosis must be subjectively determined by the attending physician. The variables involved include the specific psychosis or state of anxiety and the size, age and response pattern of the patient.

The following examples illustrate the production of representative compounds of this invention.

Example 1

3-[4-[4-(2-Pyrimidinyl)-1-piperazinyl]butyl]-3-azabicyclo[3.3.1]nonane-2,4-dione

1,3-Cyclohexane dicarboxylic acid (4.0 g., 2.3 mmole) was converted to the anhydride by refluxing for three hours in 20 ml. of acetic anhydride. The excess acetic anhydride was removed under vacuum and the residue was extracted with hexane. Upon evaporation the hexane yielded 3.54 g. of cyclohexane-1,3-dicarboxylic anhydride. This was combined with 5.99 g. (2.5 mmole) of 1-(4-aminobutyl)-4-(2-pyrimidinyl)piperazine in 50 ml. of dichloromethane and allowed to stir at room temperature overnight. The solvent was then removed in vacuo and replaced with 75 ml. of toluene. The mixture was refluxed for 24 hours with water separation via a Dean-Stark trap. The product was concentrated under vacuum and chromatographed on 200 g. of silica gel with 5% ethanol/chloroform. Recrystallization from 100 ml. of isopropanol by addition of 4.3 ml. of 4N HCl/isopropyl alcohol gave 2.06 g. of the title compound as the dihydrochloride; m.p. 213-214.5° C..

Elemental Analysis: C₂₀H₂₉N₅O₂·2HCl

Calculated: C, 54.05; H, 7.03; N, 15.76

Found: C, 53.96; H, 6.79; N, 15.80

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Example 23-[4-[4-(2-Pyrimidinyl)-1-piperazinyl]butyl]-3-azabicyclo[3.2.1]octane-2,4-dione

1,3-Cyclopentanedicarboxylic acid (4.0 g., 25 mmole) was converted to the anhydride by refluxing for 3 hours in 20 ml. of acetic anhydride. After removal of excess acetic anhydride, extraction with hexane and evaporation of the hexane, 3.95 g. of cyclopentane-1,3-dicarboxylic anhydride was obtained. The anhydride was combined with 6.51 g. (27 mmole) of 1-(4-aminobutyl)-4-(2-pyrimidinyl)piperazine in 50 ml. of dichloromethane and stirred at room temperature overnight. The dichloromethane was removed in vacuo and replaced with 75 ml. of toluene. The mixture was refluxed for 24 hours with water separation via a Dean-Stark trap. The product was concentrated under vacuum and chromatographed on 200 g. of silica gel with 5% ethanol/chloroform. The product-containing fractions were combined and concentrated and the residue crystallized (2 crops) from isopropanol with addition of 4N HCl/isopropanol. A second recrystallization from isopropanol gave 1.1 g. of the title compound as the dihydrochloride, hemihydrate; m.p. 201-203° C.(d).

Elemental Analysis: C₁₉H₂₇N₅O₂·2HCl·1/2H₂O

Calculated: C, 51.94; H, 6.88; N, 15.94

Found: C, 51.97; H, 6.66; N, 15.93

Example 33-[4-[4-(2-Pyrimidinyl)-1-piperazinyl]butyl]-8-oxa-3-azabicyclo[3.2.1]octane-2,4-dione

Tetrahydrofuran-2,5-dicarboxylic anhydride (1.5 g., 10 mmole) was dissolved in 150 ml. of toluene in a 500 ml. round bottom flask equipped with a Dean-Stark trap and condenser. 1-(4-Aminobutyl)-4-(2-pyrimidinyl)piperazine (2.59 g., 11 mmole) was added and the mixture was refluxed for 24 hours. When the analysis failed to detect the expected product, the solvent was removed in vacuum and replaced with xylene. Reflux was continued for 48 hours. The solvent was then removed in vacuum and the residue column chromatographed on 100 g. of silica gel using a gradient elution from pure chloroform to 5% ethanol/chloroform. The relevant fractions were combined and concentrated in vacuum and the product crystallized from isopropanol

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with the addition of 4N HCl/isopropanol. 1.2 Grams of the title compound was obtained as the dihydrochloride; m.p. 221-222° C.

Elemental Analysis: $C_{18}H_{25}N_5O_3 \cdot 2 HCl$

Calculated: C, 50.00; H, 6.29; N, 16.20

5 Found: C, 49.85; H, 6.01; N, 16.07

Example 4

3-[4-[4-(2-Pyrimidinyl)-1-piperazinyl]butyl]-8-thia-3-azabicyclo[3.2.1]octane-2,4-dione

10 Tetrahydrothiophene-2,5-dicarboxylic acid (3.0 g., 17 mmole) was added to 200 ml. of benzene containing 1.5 g. (19 mmole) of acetyl chloride. The solution was refluxed for 4 hours and allowed to cool overnight. The solvent was then removed in vacuum and replaced with 250 ml. of xylene. 1-(4-Aminobutyl)-4-(2-pyrimidinyl)piperazine (4.4 g., 19 mmole) was added and the mixture refluxed for 48 hours. The solvent was again removed in vacuum
15 and the residue was dissolved in chloroform and filtered through 75 g. of silica gel. After concentration in vacuum, the product was recrystallized from 25 ml. of isopropanol with addition of 4 ml. of 4N HCl/isopropanol. 1.1 Grams of the title compound was obtained as the hydrochloride, hemihydrate; m.p. 239-241° C. (d).

20 Elemental Analysis: $C_{18}H_{25}N_5O_2S \cdot HCl \cdot 1/2 H_2O$

Calculated: C, 51.35; H, 6.46; N, 16.44

Found: C, 51.01; H, 6.17; N, 16.41

Example 5

3-[4-[4-(2-Pyrimidinyl)-1-piperazinyl]butyl]-9-thia-3-azabicyclo[3.3.1]nonane-2,4-dione

25 Tetrahydrothiopyran-2,6-dicarboxylic anhydride (2.4 g., 14 mmole) and 1-(4-aminobutyl)-4-(2-pyrimidinyl)piperazine (3.5 g., 15 mmole) were dissolved in 250 ml. of toluene and refluxed for 48 hours with water removal via a Dean-Stark trap. The solvent was removed in vacuum and replaced with
30 chloroform. The mixture was filtered through 75 g. of silica gel and concentrated in vacuum and the residue was crystallized from isopropanol with addition of 4N isopropanolic HCl. A second crystallization from isopropanol gave 1. g. of the title compound as the monohydrochloride; m.p. 238-241° C. (d).

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Elemental Analysis: $C_{19}H_{27}N_5O_2S \cdot HCl$

Calculated: C, 53.57; H, 6.63; N, 16.44

Found: C, 53.42; H, 6.49; N, 16.40

Example 6

5 3-[4-[4-(2-Pyrimidinyl)-1-piperazinyl]butyl]-9-thia-3-aza-
 bicyclo[3.3.1]nonane-2,4-dione-9-oxide

 3-[4-[4-(2-Pyrimidinyl)-1-piperazinyl]butyl]-9-thia-3-aza-bicyclo[3.3.1]
nonane-2,4-dione hydrochloride (3.2 g., 8 mmole) prepared by the method of
Example 5 was dissolved in 80 ml. of glacial acetic acid and 2.4 ml. of 30%
10 hydrogen peroxide added. The mixture was stirred at room temperature
overnight. It was then heated on the steam bath for 6 hours and again allowed
to stand at room temperature overnight. The solvent was removed in vacuo
and the residue filtered through silica gel in chloroform. After evaporation of
the solvent and recrystallization from isopropanol with the addition of 4 N
15 HCl/isopropyl alcohol, 0.82 g. of the title compound was obtained as the
hydrochloride; m.p. 254-257° C.

Elemental Analysis: $C_{19}H_{27}N_5O_3S \cdot HCl$

Calcd.: C, 51.63; H, 6.38; N, 15.85

Found: C, 51.35; H, 6.29; N, 15.43

20

Example 7

2-[4-[4-(6-Chloro-2-pyrazinyl)-1-piperazinyl]butyl]-
 3-azabicyclo[3.3.1]nonane-2,4-dione

 Cyclohexane-1,3-dicarboxylic anhydride (2.3 g., 15 mmole) and 1-
(4-aminobutyl)-4-(6-chloro-2-pyrazinyl)piperazine (4.0 g., 15 mmole) were
25 combined in 300 ml. of xylene and refluxed for 48 hours with water separation
via a Dean-Stark trap. The reaction was cooled and filtered through 75 g. of
silica gel using 2% ethanol/ $CHCl_3$ to rinse the column. The solvent was
removed in vacuum and the residue recrystallized from isopropanol with
addition of 4N isopropanolic HCl to give 2.3 g. of the title compound as the
30 monohydrochloride; m.p. 238-239° C.

Elemental Analysis: $C_{20}H_{28}N_2O_2Cl \cdot HCl$

Calculated: C, 54.30; H, 6.61; N, 15.83

Found: C, 54.13; H, 6.30; N, 15.69

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Example 83-[4-[4-(6-Chloro-2-pyrazinyl)-1-piperazinyl]butyl]-3-azabicyclo[3.2.1]octane-2,4-dione

1,3-Cyclopentane dicarboxylic acid (8.0 g., 51 mmole) was converted to the anhydride by refluxing for 3 hours in 100 ml. of acetic anhydride. The excess solvent was removed under vacuum and the residue was stored in vacuum for 18 hours. The crude anhydride thus obtained was combined with 14 g. (50 mmole) of 1-(4-aminobutyl)-4-benzylpiperazine hydrochloride and 5.0 g. (50 mmole) of triethylamine in 500 ml. of xylene. The mixture was refluxed for 48 hours with water separation via a Dean-Stark trap. The product was concentrated under vacuum and chromatographed on 200 g. of silica gel with 2% ethanol/chloroform. The product was crystallized from ethanol by addition of 4N HCl/isopropyl alcohol to obtain cyclopentane-1,3-dicarboxylic-N-[4-(4-benzyl-1-piperazinyl)butyl]imide dihydrochloride; m.p. 273-275° C.

5.6 Grams (13 mmole) of the benzyl protected intermediate prepared in the preceding paragraph was dissolved in 100 ml. of acetic acid and 1.0 g. of 10% palladium on carbon added. The mixture was hydrogenated at 60 psi (about 4.14 bars) for 24 hours, filtered through celite, concentrated in vacuum, and crystallized from ethanol. 4.9 Grams of the product, cyclopentane-1,3-dicarboxylic-N-[4-(1-piperazinyl)butyl]imide was recovered as the dihydrochloride, hemihydrate; m.p. 240-241° C.

To 1.05 g. (3.0 mmole) of the deprotected intermediate prepared in the preceding paragraph was added 0.60 g. (4.0 mmole) of 2,6-dichloropyrazine, 1.0 g. (10 mmole) of triethylamine and 50 ml. of dimethylformamide. The mixture was heated at 60° C. for 16 hours. The solvent was removed in vacuum and replaced with 250 ml. of dichloromethane. The solution was washed with saturated bicarbonate solution, saturated brine and dried over sodium sulfate. Concentration in vacuum and crystallization from isopropanol with the addition of 4N HCl/isopropyl alcohol gave 0.54 g. of the title compound as the hydrochloride, hemihydrate; m.p. 220-221° C.

Elemental Analysis: C₁₉H₂₆N₅O₂Cl·HCl·1/2H₂O

Calc'd.: C, 52.17; H, 6.45; N, 16.01

Found: C, 52.15; H, 6.14; N, 16.45

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Example 93-[4-[4-(2-Quinolyl)-1-piperazinyl]butyl]-3-aza-
bicyclo[3.2.1]octane-2,4-dione

1,3-Cyclopentane dicarboxylic acid (1.6 g., 10 mmole) and 1-(4-aminobutyl)-4-(2-quinolyl)piperazine (2.8 g., 10 mmole) were combined in 200 ml. of xylene and refluxed for 24 hours with water removal via a Dean-Stark trap. The solvent was then removed in vacuum and the residue redissolved in chloroform and filtered through 75 g. of silica gel. The column was rinsed with 5% ethanol/chloroform and the product-containing fractions were combined and evaporated. The residue was recrystallized from isopropanol with the addition of 4N isopropanolic HCl to give 820 mg. of the title compound as the dihydrochloride hemihydrate; m.p. 240-242° C.

Elemental Analysis: C₂₄H₃₀N₄O₂·2 HCl·1/2 H₂O

Calculated: C, 59.02; H, 6.81; N, 11.47

Found: C, 58.93; H, 6.59; N, 11.35

Example 103-[4-[4-(6-Chloro-2-pyrazinyl)-1-piperazinyl]butyl]-
8-oxa-3-azabicyclo[3.2.1]octane-2,4-dione

Tetrahydrofuran-2,5-dicarboxylic anhydride (1.26 g., 8.8 mmole) and 1-(4-aminobutyl)-4-(6-chloro-2-pyrazinyl)piperazine (2.37 g., 8.8 mmole) were combined and stirred for 30 minutes in 200 ml. of methylene chloride. The solvent was removed in vacuum and replaced with 300 ml. of xylene. The mixture was refluxed for 48 hours with water removal via a Dean-Stark trap. After cooling, the mixture was filtered through 75 g. of silica gel and the column rinsed with 5% ethanol/chloroform. The product was concentrated in vacuum and recrystallized from isopropanol with addition of 4N isopropanolic HCl. 0.60 Grams of the title compound was obtained as the monohydrochloride; m.p. 233-235° C. (d).

Elemental Analysis: C₁₈H₂₄N₅O₃Cl·HCl

Calculated: C, 50.24; H, 5.85; N, 16.28

Found: C, 49.89; H, 5.83; N, 16.06

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Example 113-[4-[4-(2-Pyrimidinyl)-1-piperazinyl]butyl]-9-oxa-3-azabicyclo[3.3.1]nonane-2,4-dione

5 Tetrahydropyran-2,6-dicarboxylic anhydride (3.0 g., 19 mmole) and 1-(4-aminobutyl)-4-(2-pyrimidinyl)piperazine (4.98 g., 21 mmole) were combined and stirred for 30 minutes in 200 ml. of methylene chloride. The solvent was removed in vacuum and replaced with 300 ml. of xylene. The mixture was refluxed for 48 hours with water removal via a Dean-Stark trap. The solvent was again removed in vacuum and the residue was column chromatographed on 100 g. of silica with a gradient elution beginning with chloroform and ending with 5% ethanol in chloroform. The relevant fractions were combined and evaporated and the product crystallized from isopropanol with the addition of 4N isopropanolic HCl and ether. A second crystallization from isopropanol gave 1.9 g. of the title compound as the dihydrochloride, hemihydrate; m.p. 232-233° C. (d).

15 Elemental Analysis: C₁₉H₂₇N₅O₃·2HCl·1/2 H₂O

Calculated: C, 50.11; H, 6.64; N, 15.38

Found: C, 50.41; H, 6.76; N, 15.07

Example 123-[4-[4-(6-Chloro-2-pyrazinyl)-1-piperazinyl]butyl]-9-thia-3-azabicyclo[3.3.1]nonane-2,4-dione

20 Tetrahydrothiopyran-2,6-dicarboxylic anhydride (3.7 g., 21 mmole) and 1-(4-aminobutyl)-4-(6-chloro-2-pyrazinyl)piperazine (5.63 g., 21 mmole) were combined in 200 ml. of methylene chloride and stirred for 30 minutes at room temperature. The solvent was removed in vacuum and 200 ml. of toluene added. The mixture was refluxed for 48 hours with water removal via a Dean-Stark trap. Upon cooling, the reaction was concentrated to an oil and this was dissolved in 2% ethanol/chloroform and filtered through silica gel. The fractions which contained the product were concentrated in vacuum and the resulting residue was recrystallized from isopropyl alcohol with the addition of 4N isopropanolic HCl. 0.6 Grams of the title compound was obtained as the hydrochloride, hydrate; m.p. 248-250° C.

30 Elemental Analysis: C₁₉H₂₆N₅O₂Cl·HCl·H₂O

Calculated: C, 47.69; H, 6.11; N, 14.64

35 Found: C, 47.59; H, 5.78; N, 14.64

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Example 133-[4-[4-(6-Chloro-2-pyrazinyl)-1-piperazinyl]butyl]-
9-oxa-3-azabicyclo[3.3.1]nonane-2,4-dione

5 Tetrahydropyran-2,6-dicarboxylic anhydride (3.12 g., 20 mmole)
and 1-(4-aminobutyl)-4-(6-chloro-2-pyrazinyl)piperazine (5.94 g., 22 mmole)
were combined in 200 ml. of methylene chloride and stirred for 30 minutes at
room temperature. The solvent was removed in vacuum and replaced with 350
ml. of xylene. The mixture was refluxed for 50 hours with water removal via a
Dean-Stark trap. The xylene was evaporated and the residue was filtered
10 through 75 g. of silica gel with 2% ethanol/chloroform. The product was
concentrated in vacuum and crystallized from isopropanol with the addition of
4N isopropanolic HCl. A second recrystallization from methanol gave 4.18 g.
of the title compound as the monohydrochloride; m.p. 252-253° C.

Elemental Analysis: $C_{19}H_{26}N_5O_3Cl \cdot HCl$

15 Calculated: C, 51.35; H, 6.12; N, 15.76

Found: C, 51.21; H, 6.02; N, 15.56

Example 143-[4-[4-(2-Pyrazinyl)-1-piperazinyl]butyl]-3-azabicyclo-
[3.3.1]nonane-2,4-dione

20 1,3-Cyclohexane dicarboxylic acid (1.65 g., 9.6 mmole) was dis-
solved in 75 ml. of acetic anhydride and refluxed for 3 hours under N_2 . The
solvent was removed in vacuum and replaced with 250 ml. of methylene
chloride. 1-(4-Aminobutyl)-4-(2-pyrazinyl)piperazine (2.35 g., 10 mmole) was
added and the mixture was stirred for 30 minutes at room temperature. The
25 solvent was then replaced with 200 ml. xylene and the mixture was refluxed
for 24 hours with water removal via a Dean-Stark trap. The product was
concentrated to an oil in vacuum and column chromatographed in 100 g. silica
gel with a gradient elution proceeding from methylene chloride to 5% isopro-
panol/methylene chloride. Evaporation of the relevant fractions gave 1.4 g. of
30 the title compound, which was recrystallized from isopropanol with the
addition of 4N isopropanolic HCl to give 900 mg. of monohydrochloride
monohydrate; m.p. 226-229° C.

Elemental Analysis: $C_{20}H_{29}N_5O_2 \cdot HCl \cdot H_2O$

Calculated: C, 56.39; H, 7.57; N, 16.44

35 Found: C, 56.57; H, 7.12; N, 16.86

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Example 153-[4-[4-(6-Chloro-2-pyrazinyl)-1-piperazinyl]butyl]-
8,8-dimethyl-3-azabicyclo[3.2.1]octane-2,4-dione

2,2-Dimethylcyclopentane-1,3-dicarboxylic anhydride (1.68 g., 10 mmole) and 1-(4-aminobutyl)-4-(6-chloro-2-pyrazinyl)piperazine (2.97 g., 11 mmole) were combined in 500 ml. of xylene and refluxed for 48 hours with Dean-Stark water removal. Concentration in vacuum, column chromatography on 100 g. of silica gel with chloroform, and recrystallization from 50 ml. of isopropanol with addition of 4N isopropanolic HCl gave 0.55 g. of the title compound as the monohydrochloride; m.p. 210° C. (d).

Elemental Analysis: C₂₁H₃₀N₅O₂Cl·HCl

Calculated: C, 55.26; H, 6.85; N, 15.34

Found: C, 55.30; H, 6.84; N, 14.95

Example 163-[4-[4-(2-Pyrimidinyl)-1-piperazinyl]butyl]-
8,8-dimethyl-3-azabicyclo[3.2.1]octane-2,4-dione

2,2-Dimethylcyclopentane-1,3-dicarboxylic anhydride (1.68 g., 10 mmole) and 1-(4-aminobutyl)-4-(2-pyrimidinyl)piperazine (2.55 g., 11 mmole) were combined in 500 ml. of xylene and refluxed for 48 hours with water removal via a Dean-Stark trap. The solvent was removed in vacuo and the residue column chromatographed on 100 g. of silica gel using a gradient elution from straight chloroform to 5% ethanol/chloroform. Concentration of the product in vacuum and recrystallization from isopropanol with addition of 4N isopropanolic HCl and acetone gave 600 mg. of the title compound as the dihydrochloride, monohydrate; m.p. 227-229° C. (d).

Elemental Analysis: C₂₁H₃₁N₅O₂·2HCl·H₂O

Calculated: C, 52.93; H, 7.40; N, 14.70

Found: C, 52.96; H, 7.10; N, 15.25

Example 178-[4-[4-(2-Pyrimidinyl)-1-piperazinyl]butyl]-8-
azabicyclo[4.3.1]dec-3-ene-7,9-dione

5-Cycloheptene-1,3-dicarboxylic anhydride (2.1 g., 13 mmole) and 1-(4-aminobutyl)-4-(2-pyrimidinyl)piperazine (3.27 g., 14 mmole) were combin-

- 20 -

ed in 500 ml. of xylene and refluxed for 48 hours with Dean-Stark water removal. The solvent was removed in vacuum and the residue column chromatographed on 100 g. of silica gel with chloroform. After concentration in vacuum, the residue was recrystallized from isopropanol with the addition of 4N isopropanolic HCl to give 0.6 g. of the title compound as the dihydrochloride, quarter hydrate; m.p. 236-238° C. (d).

Elemental Analysis: $C_{21}H_{29}N_5O_2 \cdot 2HCl \cdot 1/4 H_2O$

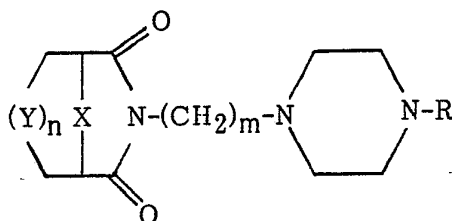
Calculated: C, 54.72; H, 6.89; N, 15.19

Found: C, 54.60; H, 6.70; N, 15.43

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What is Claimed is:

1. A compound of the formula:



in which

- 5 X is -O-, -S-, -SO-, -SO₂-, CR₃R₄- where R₃ and R₄, independently, are hydrogen, alkyl of 1 to 4 carbon atoms or, taken together with the carbon atom to which they are attached, R₃ and R₄ form a cycloalkyl group of 3 to 5 carbon atoms;

- 10 Y is alkylene of 1 to 3 carbon atoms or alkenylene of 2 to 3 carbon atoms;

m is one of the integers, 2, 3, 4, or 5;

n is one of the integers 0 or 1;

and

- 15 R is 2-pyrimidinyl, halopyrimidin-2-yl, 2-pyrazinyl, halopyrazin-2-yl, 2-pyridinyl, cyanopyridin-2-yl, halopyridin-2-yl, quinolyl, or haloquinolyl;

or a pharmaceutically acceptable salt thereof.

- 20 2. A compound of Claim 1 which is 3-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-3-azabicyclo[3.3.1]nonane-2,4-dione, or a pharmaceutically acceptable salt thereof.

3. A compound of Claim 1 which is 3-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-3-azabicyclo[3.2.1]octane-2,4-dione, or a pharmaceutically acceptable salt thereof.

- 25 4. A compound of Claim 1 which is 3-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-8-oxa-3-azabicyclo[3.2.1]octane-2,4-dione, or a pharmaceutically acceptable salt thereof.

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5. A compound of Claim 1 which is 3-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-8-thia-3-azabicyclo[3.2.1]octane-2,4-dione, or a pharmaceutically acceptable salt thereof.

6. A compound of Claim 1 which is 3-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-9-thia-3-azabicyclo[3.3.1]nonane-2,4-dione, or a pharmaceutically acceptable salt thereof.

7. A compound of Claim 1 which is 3-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-9-thia-3-azabicyclo[3.3.1]nonane-2,4-dione-9-oxide, or a pharmaceutically acceptable salt thereof.

8. A compound of Claim 1 which is 2-[4-[4-(6-chloro-2-pyrazinyl)-1-piperazinyl]butyl]-3-azabicyclo[3.3.1]nonane-2,4-dione, or a pharmaceutically acceptable salt thereof.

9. A compound of Claim 1 which is 3-[4-[4-(6-chloro-2-pyrazinyl)-1-piperazinyl]butyl]-3-azabicyclo[3.2.1]octane-2,4-dione, or a pharmaceutically acceptable salt thereof.

10. A compound of Claim 1 which is 3-[4-[4-(2-quinolyl)-1-piperazinyl]butyl]-3-azabicyclo[3.2.1]octane-2,4-dione, or a pharmaceutically acceptable salt thereof.

11. A compound of Claim 1 which is 3-[4-[4-(6-chloro-2-pyrazinyl)-1-piperazinyl]butyl]-8-oxa-3-azabicyclo[3.2.1]octane-2,4-dione, or a pharmaceutically acceptable salt thereof.

12. A compound of Claim 1 which is 3-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-9-oxa-3-azabicyclo[3.3.1]nonane-2,4-dione, or a pharmaceutically acceptable salt thereof.

13. A compound of Claim 1 which is 3-[4-[4-(6-chloro-2-pyrazinyl)-1-piperazinyl]butyl]-9-thia-3-azabicyclo[3.3.1]nonane-2,4-dione, or a pharmaceutically acceptable salt thereof.

14. A compound of Claim 1 which is 3-[4-[4-(6-chloro-2-pyrazinyl)-1-piperazinyl]butyl]-9-oxa-3-azabicyclo[3.3.1]nonane-2,4-dione, or a pharmaceutically acceptable salt thereof.

15. A compound of Claim 1 which is 3-[4-[4-(2-pyrazinyl)-1-piperazinyl]butyl]-3-azabicyclo[3.3.1]nonane-2,4-dione, or a pharmaceutically acceptable salt thereof.

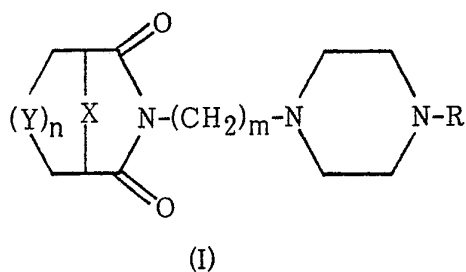
16. A compound of Claim 1 which is 3-[4-[4-(6-chloro-2-pyrazinyl)-1-piperazinyl]butyl]-8,8-dimethyl-3-azabicyclo[3.2.1]octane-2,4-dione, or a pharmaceutically acceptable salt thereof.

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17. A compound of Claim 1 which is 3-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-8,8-dimethyl-3-azabicyclo[3.2.1]octane-2,4-dione, or a pharmaceutically acceptable salt thereof.

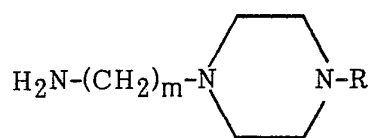
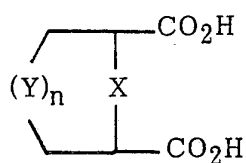
18. A compound of Claim 1 which is 8-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-8-azabicyclo[4.3.1]dec-3-ene-7,9-dione, or a pharmaceutically acceptable salt thereof.

19. A process for the preparation of a compound having the formula I



10 in which X, Y, R, m and n are defined in Claim 1 or a pharmaceutically acceptable salt thereof, in which

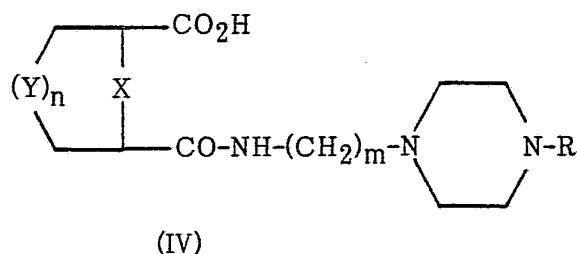
(a) a 1,3-dicarboxylic acid having the formula II, in which Y, X and



15 n are as defined above, or a reactive derivative thereof is cyclised with a piperazinylalkyl amine having the formula III, in which R and m are as defined above, or a reactive derivative to form an imide, or

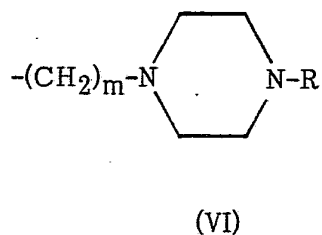
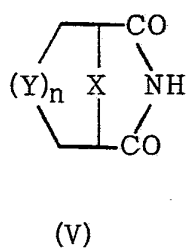
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(b) an N-substituted amidic acid having the formula IV, in which



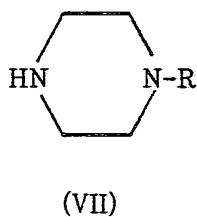
X , Y , R , n and m are as defined above, or a reactive derivative thereof is cyclised to form an imide; or

5 (c) an imide having the formula V in which X , Y and n are as defined above



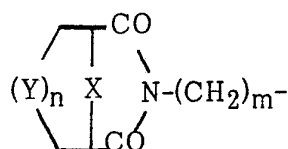
or a salt thereof is N-alkylated to introduce a substituted alkyl group having formula VI, in which R and m are as defined above; or

10 (d) a piperazine derivative having the formula VII, in which R is as defined above

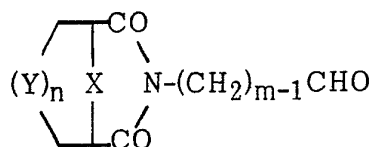


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is N-alkylated to introduce a substituted alkyl group



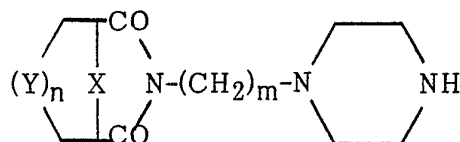
(VIII)



(IX)

having the formula VIII where X, Y, m and n are as defined above or is reductively alkylated with an aldehyde having the formula IX where X, Y, m and n are as defined above; or

(e) a piperazine derivative having the formula X, in which



(X)

X, Y, m and n are as defined above, is N-heteroarylated to introduce the group R as defined above; or

(f) a compound having formula I as shown above, where X is -S- or -SO- and Y, R, m and n are as defined above, or a salt thereof is oxidised to form a sulfoxide or sulfone from a sulfide or a sulfone from a sulfoxide; and, if desired, a compound having formula I is converted into a pharmaceutically acceptable salt thereof by addition of an acid or an acid addition salt of a compound having formula I is neutralised to form a compound having formula I.

20. A pharmaceutical composition comprising a compound as claimed in any one of Claims 1 to 18 in association or combination with a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

PCT/US 88/00974

International Application No

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶ According to International Patent Classification (IPC) or to both National Classification and IPC IPC ⁴ : C 07 D 401/12; 491/08; 495/08																	
II. FIELDS SEARCHED Minimum Documentation Searched ⁷ <table style="width: 100%; border: none;"> <tr> <td style="width: 20%; border: none;">Classification System</td> <td style="border: none;">Classification Symbols</td> </tr> <tr> <td style="border: none;">IPC⁴</td> <td style="border: none;">C 07 D 401/00; 491/00; 495/00</td> </tr> </table> Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸			Classification System	Classification Symbols	IPC ⁴	C 07 D 401/00; 491/00; 495/00											
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IPC ⁴	C 07 D 401/00; 491/00; 495/00																
III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹ <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 10%;">Category ¹⁰</th> <th style="width: 60%;">Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²</th> <th style="width: 30%;">Relevant to Claim No. ¹³</th> </tr> </thead> <tbody> <tr> <td style="text-align: center; vertical-align: top;">A</td> <td>FR, A, 2540499 (BRISTOL-MYERS) 10 August 1984 see pages 1-4,14,15 --</td> <td style="text-align: center; vertical-align: top;">1,19,20</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">A</td> <td>US, A, 4305944 (DAVIS L. TEMPLE Jr. et al.) 15 December 1981 see columns 1-10 --</td> <td style="text-align: center; vertical-align: top;">1,19,20</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">A</td> <td>Journal of Medicinal Chemistry, vol. 15, no. 5, 1972 (Washington, US) Yao-Hua Wu: "Psychosedative agents. 2.8-(4-substituted 1-piperazinylalkyl)-8-azaspiro [4.5]decane-7,9-diones " pages 477-479 --</td> <td style="text-align: center; vertical-align: top;">1,19,20</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">A</td> <td>Chemical Abstracts, vol. 103, no. 25, 23 December 1985 (Columbus, Ohio, US) see page 880, abstract no. 215155k, & JP, A, 6087262 (SUMITOMO) 16 May 1985 -----</td> <td style="text-align: center; vertical-align: top;">1,20</td> </tr> </tbody> </table>			Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³	A	FR, A, 2540499 (BRISTOL-MYERS) 10 August 1984 see pages 1-4,14,15 --	1,19,20	A	US, A, 4305944 (DAVIS L. TEMPLE Jr. et al.) 15 December 1981 see columns 1-10 --	1,19,20	A	Journal of Medicinal Chemistry, vol. 15, no. 5, 1972 (Washington, US) Yao-Hua Wu: "Psychosedative agents. 2.8-(4-substituted 1-piperazinylalkyl)-8-azaspiro [4.5]decane-7,9-diones " pages 477-479 --	1,19,20	A	Chemical Abstracts, vol. 103, no. 25, 23 December 1985 (Columbus, Ohio, US) see page 880, abstract no. 215155k, & JP, A, 6087262 (SUMITOMO) 16 May 1985 -----	1,20
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³															
A	FR, A, 2540499 (BRISTOL-MYERS) 10 August 1984 see pages 1-4,14,15 --	1,19,20															
A	US, A, 4305944 (DAVIS L. TEMPLE Jr. et al.) 15 December 1981 see columns 1-10 --	1,19,20															
A	Journal of Medicinal Chemistry, vol. 15, no. 5, 1972 (Washington, US) Yao-Hua Wu: "Psychosedative agents. 2.8-(4-substituted 1-piperazinylalkyl)-8-azaspiro [4.5]decane-7,9-diones " pages 477-479 --	1,19,20															
A	Chemical Abstracts, vol. 103, no. 25, 23 December 1985 (Columbus, Ohio, US) see page 880, abstract no. 215155k, & JP, A, 6087262 (SUMITOMO) 16 May 1985 -----	1,20															
¹⁴ Special categories of cited documents: ¹⁰ "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family																	
IV. CERTIFICATION <table style="width: 100%; border: none;"> <tr> <td style="width: 50%; border: none; vertical-align: top;"> Date of the Actual Completion of the International Search 18th July 1988 </td> <td style="width: 50%; border: none; vertical-align: top;"> Date of Mailing of this International Search Report 9 AUG 1988 </td> </tr> <tr> <td style="width: 50%; border: none; vertical-align: top;"> International Searching Authority EUROPEAN PATENT OFFICE </td> <td style="width: 50%; border: none; vertical-align: top;"> Signature of Authorized Officer M. VAN MOL </td> </tr> </table>			Date of the Actual Completion of the International Search 18th July 1988	Date of Mailing of this International Search Report 9 AUG 1988	International Searching Authority EUROPEAN PATENT OFFICE	Signature of Authorized Officer M. VAN MOL											
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ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

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