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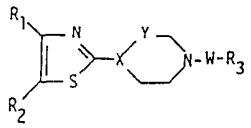
271 280 282 28X 30Y 311 313 31Y 321 32Y 338 342
34Y 351 352 357 364 365 36Y 385 386 43X 510 51X
51Y 535 579 601 603 620 623 624 625 62X 634 635 644
660 662 694 699 761 762 763 766 768 802 80Y AA KF
KG KH KP SF TM TP TT TW TX
U1S 2418 C2C

(56) Documents cited
Arzneim-Forsch 1974 24(12)1964–70

(58) Field of search
C2C

(54) Thiazole derivatives

(57) Thiazoles or pharmaceutically acceptable acid addition salt thereof and useful as *anxiolytic, psychogeriatric, antidepressant* and *antischizophrenic* agents. The compounds have the formula:—



I

wherein

R_1 and R_2 independently are hydrogen, (C_{1-6})alkyl, (C_{3-6})cycloalkyl, (C_{3-6})cycloalkyl(C_{1-3})alkyl, phenyl(C_{1-3})alkyl or

R_a and R_2 signify together trimethylene, tetramethylene or pentamethylene, optionally substituted at the same or different carbon atoms by 1 or 2 methyl groups, or

R_1 and R_2 signify together $-(CH_3)_2C-O-C(CH_3)_2-$,

R_1 may additionally signify trifluoromethyl,

W is alkylene of 2 to 6 carbon atoms, or alkenylene or alkinylene of 4 to 6 carbon atoms, whereby the unsaturation is not adjacent to the nitrogen atoms,

X–Y is $N-CH_2$, $C=CH$ or $CH-CH_2$ and

R_3 is one of a number of defined groups linked via nitrogen.

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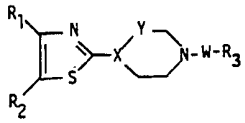
SPECIFICATION

Thiazoles, their production and pharmaceutical compositions containing them

The present invention relates to novel thiazoles, processes for their production, pharmaceutical compositions containing them and their use as pharmaceuticals.

More particularly the present invention relates to compounds of formula I,



I

wherein

R_1 and R_2 independently are hydrogen, (C_{1-6})alkyl, (C_{3-6})cycloalkyl, (C_{3-6})cycloalkyl (C_{1-3})alkyl, phenyl, phenyl(C_{1-3})alkyl or

R_1 and R_2 signify together trimethylene, tetramethylene or pentamethylene, optionally substituted at the same or different carbon atoms by 1 or 2 methyl groups, or

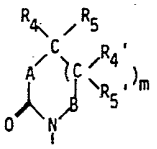
R_1 and R_2 signify together $-(CH_3)_2C-O-C(CH_3)_2-$,

R_1 may additionally signify trifluoromethyl,

W is alkylene of 2 to 6 carbon atoms, or alkenylene or alkinylene of 4 to 6 carbon atoms, whereby the unsaturation is not adjacent to the nitrogen atoms,

X–Y is $N-CH_2$, $C=CH$ or $CH-CH_2$ and

R_3 is a group of formula a)–n)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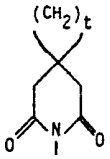
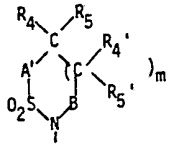

b)


c)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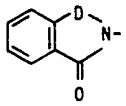
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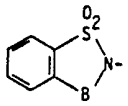
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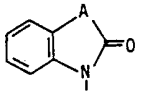
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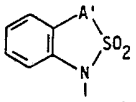
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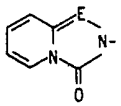
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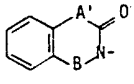
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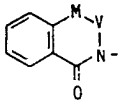
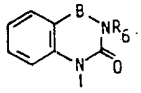
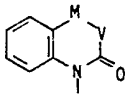
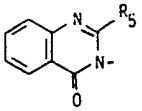
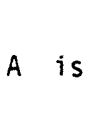

k)

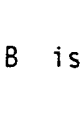

l)


m)


n)

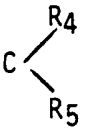
in which

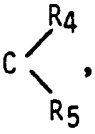
A is  , NR_6, O or S,

B is  or CO,

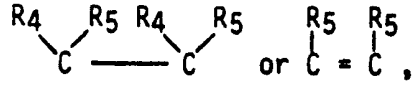
m is 0 or 1,
R_4 and R_4' independently are hydrogen or (C_{1-4})alkyl,
R_5 and R_5' independently are hydrogen, (C_{1-4})alkyl, phenyl or phenyl(C_{1-4})alkyl,
t is 4 or 5,

R_6 is hydrogen or (CR_{1-3})alkyl,
R_7 is hydrogen, (C_{1-3})alkyl, phenyl(C_{1-3})alkyl or phenoxy(C_{1-3})alkyl,
U=L is $N=CR_5$ or $CR_5=N$,

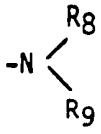
A' is  or NR_6,

D is  , CO, NR_6, S or O,

E is N or CH,

M - V is  ,

and when X–Y is N–CH2, R_3 may also be a group of formula o)

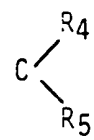


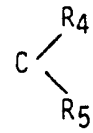
o)

wherein
R_8 is hydrogen or $(C_{1\ 3})$alkyl,
R_9 is $-COR_{10}$, $-CON(R_{11})R_{12}$, $-SO_2R_{10}$ or $-SO_2N(R_{11})R_{12}$, wherein R_{10} is $(C_{1\ 6})$alkyl, $(C_{3\ 6})$cycloalkyl, phenyl or phenyl$(C_{1\ 3})$alkyl, wherein each phenyl is optionally mono- or independently di- or trisubstituted by $(C_{1\ 3})$alkyl, hydroxy, methoxy, methylendioxy, amino, halogen or trifluoromethyl,
R_{11} and R_{12} are each, independently, hydrogen or $(C_{1\ 3})$alkyl or
R_{11} and R_{12} together signify tetramethylene or pentamethylene, provided that when W is dimethylene and R_9 is $-COR_{10}$, wherein R_{10} is 4-aminophenyl, at least one of R_1, R_2 and R_8 is other than hydrogen, and acid addition salts thereof.

Compounds of formula I, wherein W is alkenylene, can occur as cis/trans isomers. These isomers are also included within the scope of the present invention.

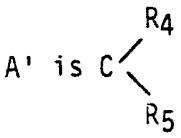
In one group of compounds of formula I R_1 and R_2 are independently hydrogen, $(C_{1\ 6})$alkyl, $(C_{3\ 6})$cycloalkyl, $(C_{3\ 6})$cycloalkyl$(C_{1\ 3})$alkyl, phenyl, phenyl$(C_{1\ 3})$alkyl or R_1 and R_2 signify together trimethylene, tetramethylene or penta-methylene, optionally substituted at the same or different carbon atoms by 1 or 2 methyl groups,
R_1 may additionally signify trifluoromethyl,
W is alkylene of 2 to 6 carbon atoms,
X–Y is $N–CH_2$ and R_3 is a group of formula a)–n), in which

A is  , NR_6, O or S,

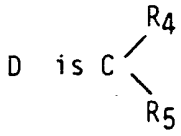
B is  or CO,

m is 0 or 1,
R_4 and R_4' independently are hydrogen or (C_{1-4})alkyl,
R_5 and R_5' independently are hydrogen, (C_{1-4})alkyl, phenyl or phenyl(C_{1-4})alkyl,
t is 4 or 5,
R_6 is hydrogen or (C_{1-3})alkyl,

R_7 is hydrogen, (C_{1-3})alkyl, phenyl(C_{1-3})alkyl or phenoxy(C_{1-3})alkyl,
U=L is $N=CR_5$ or $CR_5=N$,

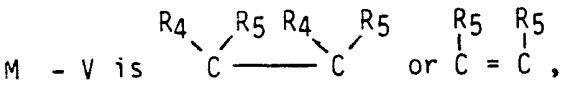


A' is C or NR_6,



D is C, CO, NR_6, S or O,

E is N or CH,



M - V is $-C-C-$ or $C=C$,

and acid addition salts thereof.

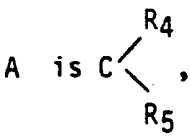
In another group of compounds of formula I X–Y is $N–CH_2$ and R_3 is a group of formula a), wherein A is CH_2, B is CO, m is 1, R_4' and R_5' are each hydrogen or R_4 and R_5 are each methyl, and either W is tetramethylene and R_1 and R_2 are the same and signify hydrogen or methyl, or R_1 is methyl, trifluoromethyl, tert. butyl or cyclopentyl and R_2 is hydrogen, or R_1 is hydrogen and R_2 is 2-methylpropyl or R_1 and R_2 signify together pentamethylene, or W is dimethylene, trimethylene, pentamethylene or hexamethylene, R_1 is tert. butyl and R_2 is hydrogen and acid addition salts thereof.

In another group of compounds of formula I X–Y is $N–CH_2$ and R_3 is a group of formula f), wherein B is CO, W is tetramethylene, R_1 is tert. butyl and R_2 is hydrogen or R_1 and R_2 together signify pentamethylene and acid addition salts thereof.

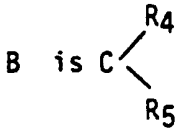
In another group of compounds X–Y is $N–CH_2$ and R_3 is a group of formula i), wherein E is N, W is trimethylene or tetramethylene, R_1 is tert. butyl and R_2 is hydrogen and acid addition salts thereof.

In one compound of formula I X–Y is $N–CH_2$ and R_3 is a group of formula b), wherein t is 4, R_1 and R_2 together signify pentamethylene and W is tetramethylene as well as acid addition salts thereof. In another compound of formula I R_3 is a group of formula a), wherein A is CH_2, R_4 and R_5 are each hydrogen, m is 0, B is CH_2, W is tetramethylene, R_1 is tert. butyl and R_2 is hydrogen and acid addition salts thereof.

In another group of compounds of formula I R_1 and R_2 are independently hydrogen, (C_{1-6})alkyl, (C_{3-6})cycloalkyl, (C_{3-6})cycloalkyl(C_{1-3})alkyl, phenyl, phenyl(C_{1-3})alkyl, or R_1 and R_2 signify together trimethylene, tetramethylene or pentamethylene, W is alkylene of 2 to 6 carbon atoms, X–Y is C=CH or $CH–CH_2$, and R_3 is a group of formula a)–n), in which



A is C, NR_6, O or S,



B is C or CO,

m is 0 or 1,
R_4 and R_4' independently are hydrogen or (C_{1-4})alkyl,
R_5 and R_5' independently are hydrogen, (C_{1-4})alkyl, phenyl or phenyl(C_{1-4})alkyl,
t is 4 or 5,
R_6 is hydrogen or (C_{1-3})alkyl,
R_7 is hydrogen, (C_{1-3})alkyl, phenyl(C_{1-3})alkyl or phenoxy(C_{1-3})alkyl,

U=L is $N=CR_5$ or $CR_5=N$,

A' is $C\begin{smallmatrix}R_4\\R_5\end{smallmatrix}$ or NR_6,

D is $C\begin{smallmatrix}R_4\\R_5\end{smallmatrix}$, CO, NR_6, S or O,

E is N or CH, and

M - V is $\begin{smallmatrix}R_4 & R_5 & R_4 & R_5\\ & C & - & C\end{smallmatrix}$ or $\begin{smallmatrix}R_5 & R_5\\ C & = & C\end{smallmatrix}$,

and acid addition salts thereof.

In still another group of compounds of formula I R_1 and R_2 independently are hydrogen, (C_{1-6})alkyl, (C_{3-6})cycloalkyl, (C_{3-6})cycloalkyl(C_{1-3})alkyl, phenyl, phenyl(C_{1-3})alkyl, or R_1 and R_2 signify together trimethylene, tetramethylene or pentamethylene optionally substituted at the same or different carbon atoms by 1 or 2 methyl groups,

R_1 may additionally signify trifluoromethyl,

W is alkylene of 2 to 6 carbon atoms,

X–Y is N–CH_2 and R_3 is a group of formula o), wherein R_8 is hydrogen or (C_{1-3})alkyl, R_9 is $-COR_{10}$, $-CON(R_{11})R_{12}$, $-SO_2R_{10}$ or $-SO_2N(R_{11})R_{12}$, wherein R_{10} is (C_{1-6})alkyl, (C_{3-6})cycloalkyl, phenyl or phenyl(C_{1-3})alkyl, wherein each phenyl is optionally mono- or independently di- or trisubstituted by (C_{1-3})alkyl, hydroxy, methoxy, methylendioxy, amino, halogen or trifluoromethyl,

R_{11} and R_{12} are each, independently, hydrogen or (C_{1-3})alkyl or

R_{11} and R_{12} together signify tetramethylene or pentamethylene, provided that when W is dimethylene and R_9 is $-COR_{10}$, wherein R_{10} is 4-aminophenyl, at least one of R_1, R_2 and R_8 is other than hydrogen,

and acid addition salts thereof.

Any alkyl radical of 1 to 6 carbon atoms is preferably of 1 to 4 carbon atoms. Cycloalkyl or the cycloalkyl moiety of cycloalkylalkyl is conveniently cyclopentyl, cyclobutyl or cyclopropyl. Halogen is preferably chlorine or fluorine and especially chlorine.

For the above formula I, the following significances, as well as combinations thereof are preferred:

R_1 is preferably alkyl, especially tert. butyl or trifluoromethyl.

R_2 is preferably hydrogen.

W is preferably alkylene, especially dimethylene, trimethylene or tetramethylene.

X–Y is preferably N–CH_2 or C=CH.

R_3 is preferably a group of formula a), b), f), g), i), j) or o).

In a preferred group of formula a) A is CH_2, B is CO, m is 1, R_4' and R_5' are each hydrogen, R_4 and R_5 are each methyl. In another preferred group of formula a) A is CH_2, B is CH_2, m is O, and R_4 and R_5 are each hydrogen.

In the preferred group of formula b) t is 4.

In preferred group of formula f) B is CO. Preferably in group g) A is NH.

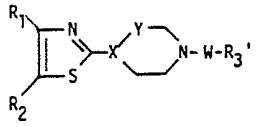
In preferred group of formula i) E is N.

The preferred group j) is the group wherein A' is CH_2 and B is CO.

In group o) R_8 is preferably hydrogen. R_9 is preferably $-COR_{10}$ or $-SO_2R_{10}$. R_{10} is preferably phenyl, optionally mono- or independently di- or trisubstituted by methoxy or chlorine.

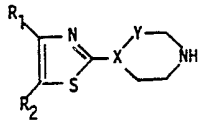
The present invention in another aspect provides a process for the production of a compound of formula I which comprises

a) producing a compound of formula Ia



Ia

wherein R_1, R_2, W and X–Y are as defined above, and R_3' is a group of formula a)–n), or an acid addition salt thereof, by reacting a compound of formula II



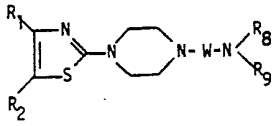
II

wherein R_1, R_2 and X–Y are as defined above, with a compound of formula III

$Q–W–R_3'$ III

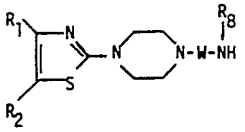
wherein W and R_3' are as defined above, and Q is a leaving group, or

b) producing a compound of formula Ib,



Ib

wherein R_1, R_2, W, R_8 and R_9 are as defined above or an acid addition salt thereof, by reacting a compound of formula IV,



IV

wherein R_1, R_2, W and R_8 are as defined above, with a compound of formula V,

$Z–R_9$ V

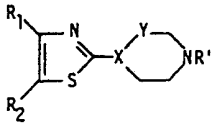
wherein R_9 is as defined above and Z is a leaving group,

and recovering the compound of formula I in free base form or acid addition salt form.

Process a) may be effected in conventional manner. The reaction is conveniently carried out in an organic solvent. Suitable solvents include dimethylformamide, dioxane or acetonitrile. Conveniently an acid binding agent, e.g. potassium carbonate, is present. In compounds of formula III the leaving group Q is for example halogen, e.g. chlorine or bromine, or $–O–SO_2–R_{13}$, wherein R_{13} is $(C_{1\text{-}4})$alkyl, phenyl or 4-tolyl.

Process b) may be effected in conventional manner for analogous reactions. In compounds of formula V is Z for example chlorine, bromine, $–OCOOC_2H_5$, $–OCOOCH=CH_2$ or $–O–(C_{1\text{-}4})$alkoxy. The process is conveniently carried out in an inert organic solvent such as tetrahydrofuran. Conveniently an acid-binding agent, e.g. triethylamine, is present. The presence of an acid binding agent is not necessary when compounds of formula V, wherein Z is $O–(C_{1\text{-}4})$alkoxy, are utilised.

Compounds of formula II can be prepared by dealkylating or debenzylating a compound of formula VI,

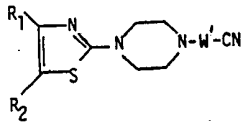


VI

wherein R_1, R_2 and X–Y are as defined above, and R' is $(C_{1\text{-}6})$alkyl or benzyl, or an acid addition salt thereof.

The dealkylation or debenzylation can be carried out in conventional manner, e.g. with haloformic acid esters, such as chloroformic acid ester, e.g. alkyl or vinyl ester or with bromocyanide.

Compounds of formula IV, wherein R_8 is hydrogen, can be prepared by reducing a compound of formula IX,



IX

wherein R_1 and R_2 are as defined above and W' is alkylene of 1 to 5 carbon atoms, or alkenylene or alkinylene of 3 to 5 carbon atoms, whereby the unsaturation is not adjacent to the nitrogen atom. The reduction may be effected with lithium aluminium hydride, diborane or with sodium borohydride in the presence of a transition metal salt, e.g. cobaltous chloride. Alkylation of the resulting compound leeds to compounds of formula IV wherein R_8 is alkyl.

Compounds of formula IX can be prepared by e.g. reacting a compound of formula II, wherein X–Y is N–CH_2 and R_1 and R_2 are as defined above, with an ω-halogeno-alkyl-, alkenyl- or -alkinyl-nitrile.

Insofar as the production of starting materials is not particularly described these compounds are known or may be produced in analogous manner to known compounds or to processes described herein.

A cis/trans mixture can be separated in known manner into the corresponding cis and trans components.

The compounds of formula I may be converted into acid addition salts thereof in conventional manner and vice versa. Suitable acids include for example, hydrochloric acid, hydrobromic acid, methanesulfonic acid, maleic acid or fumaric acid.

In the following examples all temperatures are given in degrees centigrade and are uncorrected.

In the Tables the following abbreviations are used:

1) hydrochloride
2) maleinate
3) methanesulfonate
4) hydrogenmaleinate
5) dihydrochloride

Example 1: 2-(4-(4-(4-(1,1-Dimethylethyl)-2-thiazolyl)-1-(1,2,3,6-tetrahydropyridinyl))butyl)-1,2-benzisothiazol-3-(2H)one-1,1-dioxide [compound of formula Ia]

3 g 2-(4-Bromobutyl)-1,2-benzisothiazol-3-(2H)one-1,1-dioxide, 2.1 g 4-(4-(1,1-dimethylethyl)-2-thiazolyl)-1,2,3,6-tetrahydropyridine, 1.4 g K_2CO_3, 40 ml dimethylformamide and 5 ml water are stirred at room temperature for about 15 hours. The reaction mixture is diluted with water, extracted twice with ethyl ether, the combined ether extracts are washed with water, dried (Na_2SO_4) and evaporated. The oily residue is dissolved in ethanol and treated with maleic acid to give the hydrogenmaleinate of the title compound (1:1), m.p. 176–177° (ethyl acetate/ethanol).

The starting material may be obtained as follows:

a) *4-(4-(1,1-Dimethylethyl)-2-thiazolyl)-4-oxy-1-phenylmethyl-piperidine*

6.7 g 1-Phenylmethyl-piperidin-4-one in 20 ml of abs. tetrahydrofuran are added dropwise under argon at −60° to −50° to a stirred suspension of 5 g 2-(4-(1,1-dimethylethyl)-thiazolyl)-lithium in 50 ml of abs. tetrahydrofuran. The mixture is stirred at slowly increasing temperature for 15 hours. Moisture containing tetrahydrofuran is added and the mixture evaporated. The residue is partitioned between water and ethyl ether, the ether phase dried (Na_2SO_4) and evaporated. The residue is chromatographed on silica gel (ethyl acetate) to give the heading compound as a light yellow oil. M.p. of the methanesulfonate 184–185°.

b) *4-(4-(1,1-Dimethylethyl)-2-thiazolyl)-1-phenylmethyl-1,2,3,6-tetrahydropyridine*

8 g (4-(4-(1,1-dimethyl-ethyl)-2-thiazolyl)-4-oxy-1-phenylmethylpiperidine and 100 g polyphosphoric acid are heated at 130° for 6 hours. The mixture is carefully treated with ice at 80°, diluted with ice-water, made alkaline with aqueous NaOH solution and extracted 3 times with ethyl ether. The combined extracts are washed with saturated brine solution, filtered and dried (Na_2SO_4). Upon addition of ethanolic maleic acid the hydrogenmaleinate of the heading compound, m.p. 182–183° (ethyl acetate/hexane) is obtained.

c) *4-(4-(1,1-Dimethylethyl)-2-thiazolyl)-1,2,3,6-tetrahydropyridine*

5.5 g 4-(4-(1,1-dimethylethyl)-2-thiazolyl)-1-phenylmethyl-1,2,3,6-tetrahydropyridine, 2.5 g K_2CO_3 and 50 ml 1,2-dichloroethane are treated dropwise at −10° to −7° under stirring with 3.75 ml chloroformic acid vinyl ester. The mixture is stirred at −10° to −7° for 3 hours. The solvent is evaporated, the residue partitioned between water and hexane, the water phase extracted with hexane. The combined organic layers are washed with saturated brine solution, filtered and dried (Na_2SO_4). The solvent is evaporated and the oily residue is added under ice-

cooling to 20% aqueous hydrochloric acid. The mixture is heated on a steam bath for 4 hours, then cooled to room temperature and extracted once with dichloromethane. The aqueous acidic solution is filtered, made alkaline with aqueous NaOH and extracted with ethyl ether. After evaporation of ether the heading compound is obtained as oily residue. M.p. of the hydrogenmaleinate 170–171°.

Example 2: 4,4-Dimethyl-1-(4-(4-((1,1-dimethylethyl)-2-thiazolyl)-1-piperidinyl)-butyl)-2,6-piperidin-dione [compound of formula Ia]

To a stirred mixture of 1.1 g 4-(4-(1,1-dimethylethyl)-2-thiazolyl)-piperidine, 0.7 g K_2CO_3, 15 ml dimethylformamide and 7 ml water are added 1.35 g 1-(4-bromobutyl)-4,4-dimethyl-2,6-piperidindione in 10 ml dimethylformamide. The mixture is stirred at 40° for 15 hours. The solvent is evaporated and the residue partitioned between ethyl ether and water. The ether phase is dried and evaporated. The oily-residue is treated with ethanolic maleic acid whereby the hydrogenmaleinate of the title compound, m.p. 184–186° (ethanol/ether) is obtained.

The starting material may be obtained as follows:

a) *4-(4-(1,1-Dimethylethyl)-2-thiazolyl)-1-phenylmethyl-piperidine*

3 g of the Example 1b) compound in 70 ml ethanol are hydrogenated in the presence of 1 g 5% palladium on charcoal at room temperature and normal pressure. The mixture is filtered and evaporated, whereby the title compound crystallizes out, m.p. 56°, m.p. of the hydrogenmaleinate 170°.

b) *4-(4-(1,1-Dimethylethyl)-2-thiazolyl)-piperidine*

4.8 g 4-(4-(1,1-Dimethylethyl)-2-thiazolyl)-1-phenylmethyl-piperidine, 2 g K_2CO_3 and 50 ml 1,2-dichloroethane are treated dropwise at −5° under stirring with 3.2 g chloroformic acid vinyl ester. The mixture is stirred 2 hours at room temperature and evaporated. The residue is partitioned between ethyl ether and water. The ether phase is evaporated and the residue dissolved in 30 ml methanol and 30 ml 20% aqueous hydrochloric acid. The mixture is heated 1 hour at 60° and evaporated. The residue is partitioned between aqueous NaOH and ether. The either phase is treated with maleic acid to yield the hydrogenmaleinate of the title compound, m.p. 141–142° (ethanol/ether).

Example 3: 2-(4-(4-((1,1-dimethylethyl)-2-thiazolyl)-1-piperidinyl)butyl)-1,2-benzisothiazol-3-(2H)-one-1,1-dioxide [compound of formula Ia]

In manner analogous to that described in Example 2 the title compound is produced, m.p. of the hydrogenmaleinate 187–189°.

Example 4: 4,4-Dimethyl-1-(4-(4-(4-(1,1-dimethylethyl)-2-thiazolyl)-1-piperazinyl)butyl)-2,6-piperidine-dione [compound of formula Ia]

4 g 1-(4-Bromobutyl)-4,4-dimethyl-2,6-piperidin-dione, 3.15 g 1-(4-(1,1-dimethylethyl)-2-thiazolyl)-piperazine, 2.7 g K_2CO_3, 70 ml dimethylformamide and 20 ml water are stirred at room temperature for about 35 hours. The mixture is diluted with water, extracted twice with ether, the combined extracts are washed with water, dried (Na_2SO_4) and evaporated. The residue is recristallized from hexane/ethyl acetate, whereby the title compound is obtained, m.p. 93–94°. M.p. of the hydrochloride 199–201° (ethanol/ether).

Example 5: 4,4-Dimethyl-1-(4-(4-(4-trifluoromethyl-2-thiazolyl)-1-piperazinyl)butyl)-2,6-piperidin-dione [compound of formula Ia]

6.2 g 1-(4-Bromobutyl)-4,4-dimethyl-2,6-piperidin-dione, 4.7 g 1-(4-trifluoromethyl-2-thiazolyl)-piperazine, 2.8 g K_2CO_3 and 200 ml acetonitrile are stirred at 60–70° for 24 hours. The mixture is filtered, evaporated and the residue partitioned between ether and aqueous NaOH. The ether phase is washed with water, dried and evaporated. Upon addition of ethanolic maleic acid the maleinate of the title compound is obtained, m.p. 159–161°.

The starting material may be obtained as follows:—

a) *4-Methyl-1-(4-trifluoromethyl-2-thiazolyl)-piperazine*

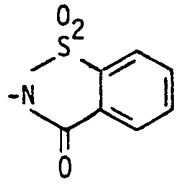
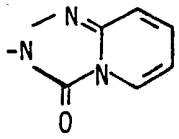
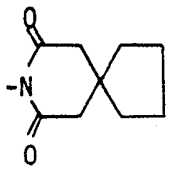
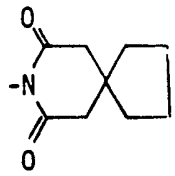
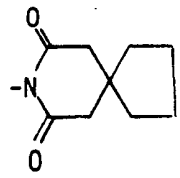
To a solution of 33.9 g 1-bromo-3,3,3-trifluoro-2-propanone in 300 ml of absolute ethanol are added 28.6 g 4-methyl-1-piperazinyl-thiocarboxamide. The mixture is refluxed for 4 hours, evaporated to dryness and the residue partitioned between ethyl ether and aqueous NaOH. The ether phase is washed, dried and evaporated, whereby the title compound is obtained, m.p. 62° (ethyl acetate/hexane).

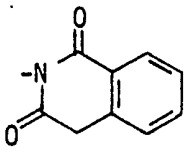
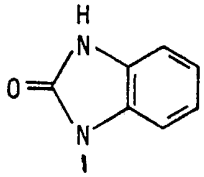
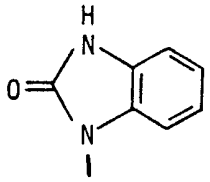
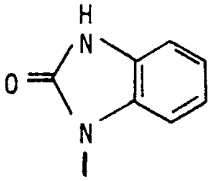
b) *1-(4-Trifluoromethyl-2-thiazolyl)-piperazine*

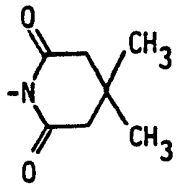
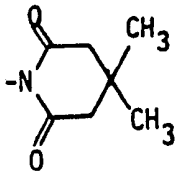
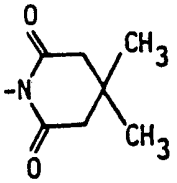
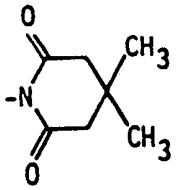
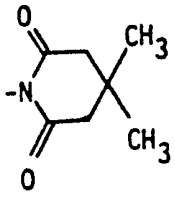
In manner analogous to that described in Example 1c) the title compound is obtained, m.p. of the maleinate 162°.

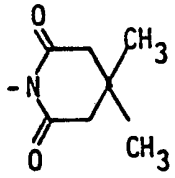
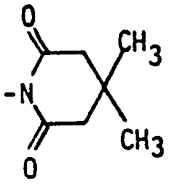
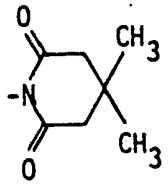
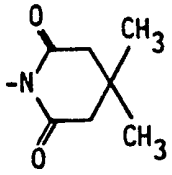
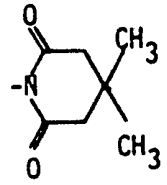
Example 6:

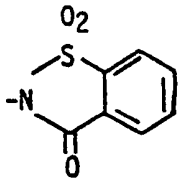
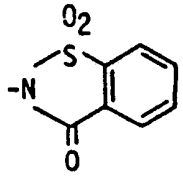
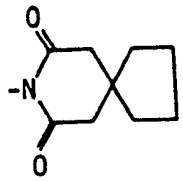
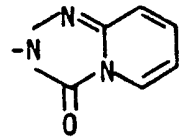
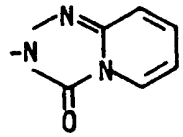
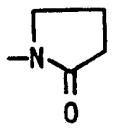
In manner analogous to that described in Example 4 the following compounds of formula Ia are obtained, wherein X–Y is N–CH_2 and W is $-(CH_2)_n-$:

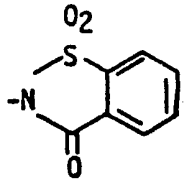
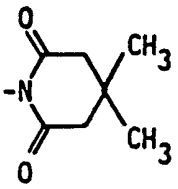
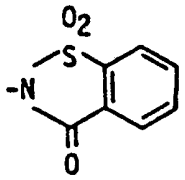
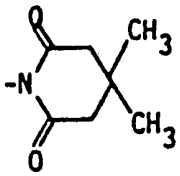
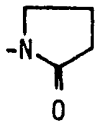
Ex.	R_1	R_2	n	R_3	m.p.
a	$C(CH_3)_3$	H	4		150-151° [2]
b	$C(CH_3)_3$	H	2		128-130°
c	$C(CH_3)_3$	H	2		99°
d	$C(CH_3)_3$	H	4		179-180° [3]
e	$C(CH_3)_3$	H	3		138-140° [2]

Ex.	R_1	R_2	n	R_3	m.p.
f	$C(CH_3)_3$	H	2		160° 2)
g	$C(CH_3)_3$	H	2		94-95°
h	$C(CH_3)_3$	H	3		118-119°
i	$C(CH_3)_3$	H	4		184-185° 2)

Ex.	R_1	R_2	n	R_3	m.p.
j	CH_3	H	4		105-106°
k	$C(CH_3)_3$	H	6		173-175° 1)
l	$C(CH_3)_3$	H	5		198-199° 1)
m	$C(CH_3)_3$	H	3		230-233° 1)
n	$C(CH_3)_3$	H	2		185° 2)

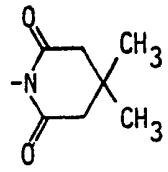
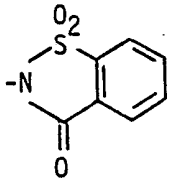
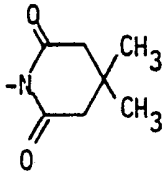
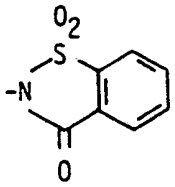
Ex.	R_1	R_2	n	R_3	m.p.
o		$-(CH_2)_5-$	4		121-122°
p	H	H	4		179-180° 2)
q	CH_3	CH_3	4		143-144° 2)
r		H	4		180° 2)
s	H	$CH_2CH(CH_3)_2$	4		167-168° 2)

Ex.	R_1	R_2	n	R_3	m.p.
t	$-(CH_2)_5-$		4		176-177° 2)
u	CH_3	H	4		160-161° 2)
v	$-(CH_2)_5-$		4		120-121°
w	$C(CH_3)_3$	H	3		166-167° 2)
x	$C(CH_3)_3$	H	4		93-95° 2)
y	$C(CH_3)_3$	H	4		179-181° 1)

Ex.	R_1	R_2	n	R_3	m.p.
z	H	H	4		133-134°
ab	CH_3	H	2		121-122°
ac	CF_3	H	4		197-198°[2)] 106-107
ad	$-(CH_3)_2C-O-C(CH_3)_2-$		4		87°[2)]
ae	CF_3	H	4		98-100°[2)]

Example 7

In manner analogous to that described in Example 4 the following compounds of formula Ia are obtained, wherein X–Y is N–CH_2:

Ex.	R_1	R_2	W	R_3	m.p.
a	$C(CH_3)_3$	H	CH_2-CH=$CHCH_2$		158-160° 2)*
b	$C(CH_3)_3$	H	$CH_2C{\equiv}CCH_2$		225-230° 1)
c	$C(CH_3)_3$	H	$CH_2C{\equiv}CCH_2$		108°
d	$C(CH_3)_3$	H	CH_2CH=$CHCH_2$		97-98°*

* trans

Example 8: 5-Chloro-2-methoxy-N-(2-(4-(4-(1,1-dimethylethyl)-2-thiazolyl)-1-piperazinyl)ethyl)-benzamide [compound of formula Ib]

To a stirred solution of 2.4 g 5-chloro-2-methoxy-benzoic acid and 1.43 g triethylamine in 50 ml tetrahydrofuran are added at −10° dropwise 1.53 g chloroformic acid ethyl ester. The reaction mixture is stirred at −10° for 1 hour and then treated dropwise with a solution of 3.45 g 4-(4-(1,1-dimethylethyl-2-thiazolyl))-1-piperazin-ethanamine in 25 ml tetrahydrofuran. The reaction mixture is stirred at room temperature for 6–8 hours and then evaporated. The residue is partitioned between CH_2Cl_2 and 4N NaOH. The organic layer is washed with saturated brine solution, dried and evaporated to give the title compound, which recrystallized from hexane/ethyl acetate has a m.p. of 97–98°. M.p. of the maleinate 173°.

The starting material may be obtained as follows:

a) *4-(4-(1,1-Dimethylethyl-2-thiazolyl))-1-piperazine-acetonitril*

A mixture of 19.1 g 4-(4-(1,1-dimethylethyl-2-thiazolyl))-1-piperazine, 13.8 g K_2CO_3, 80 ml dimethylformamide and 25 ml water is treated with 7.55 g chloro-acetonitrile and the resulting mixture stirred for 12 hours at room temperature. The reaction mixture is evaporated under vacuum to dryness and the residue partitioned between water and CH_2Cl_2. The organic layer is washed with water, dried and evaporated to give the heading compound, m.p. 99–100° (from ethanol).

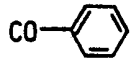
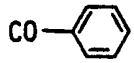
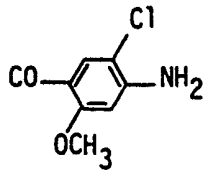
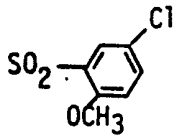
b) *4-(4-(1,1-Dimethylethyl-2-thiazolyl))-1-piperazin-ethanamine*

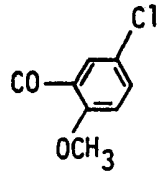
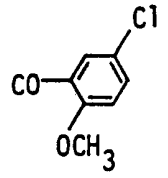
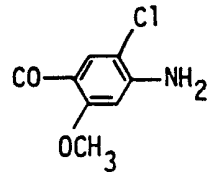
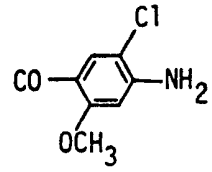
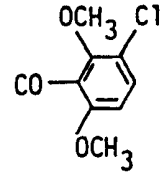
To a stirred suspension of 3.7 g lithium aluminium hydride in 250 ml abs. diethyl ether is added dropwise at 0° a solution of 17 g 4-(4-(1,1-dimethylethyl-2-thiazolyl))-1-piperazin-acetoni-

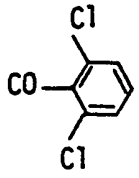
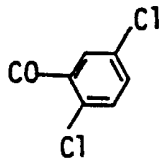
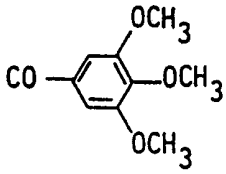
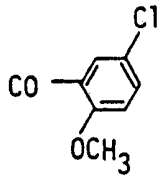
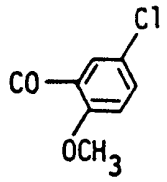
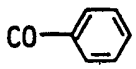
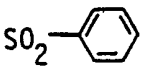
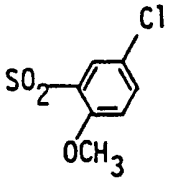
trile in 250 abs. diethyl ether, with the mixture maintained at −5° to +5° during the addition period. After the addition is completed, the reaction mixture is stirred for 12 hours at room temperature. The mixture is cooled to −10° and treated in portions with 400 ml 30% NaOH. The ether layer is separated, washed, dried and evaporated to give the heading compound as an oil.

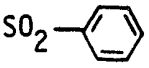
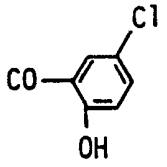
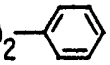
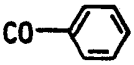
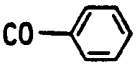
Example 9:

In manner analogous to that described in Example 8 the following compounds of formula Ib are obtained wherein W is $-(CH_2)_n-$:

Ex.	R_1	R_2	R_8	R_9	n	m.p.
a	$C(CH_3)_3$	H	H		2	192-194°[2)]
b	$C(CH_3)_3$	H	CH_3		2	145°
c	$C(CH_3)_3$	H	H		2	186-188°
d	$C(CH_3)_3$	H	H		2	179-180°[2)]

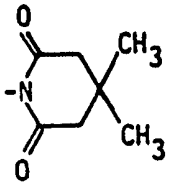
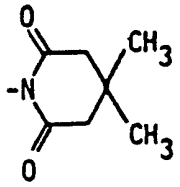
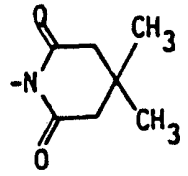
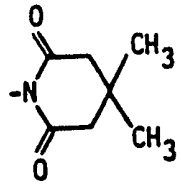
Ex.	R_1	R_2	R_8	R_9	n	m.p.
e	$C(CH_3)_3$	H	H		3	118-122 °2)
f	$C(CH_3)_3$	H	H		4	113-114°
g	$C(CH_3)_3$	H	H		3	100-103°
h	$C(CH_3)_3$	H	H		4	120°
i	$C(CH_3)_3$	H	H		2	163-165° 2)

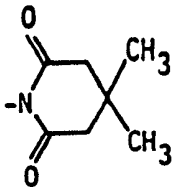
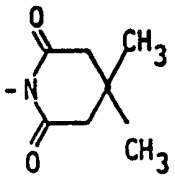
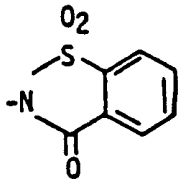
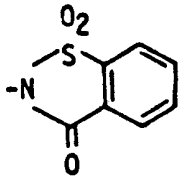
Ex.	R_1	R_2	R_8	R_9	n	m.p.
j	$C(CH_3)_3$	H	H		2	167°
k	$C(CH_3)_3$	H	H		2	120-122°
l	$C(CH_3)_3$	H	H		2	151-152°
m		H	H		2	155-156°
n	CH_3	CH_3	H		2	123-125°
o	$C(CH_3)_3$	H	H		4	119-120°
p	$C(CH_3)_3$	H	H		4	139-140° 2)
q	$C(CH_3)_3$	H	CH_3		4	89-91°

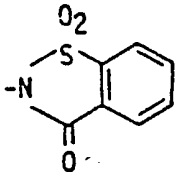
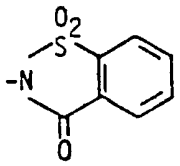
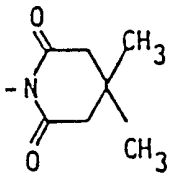
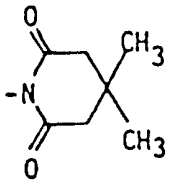
Ex.	R_1	R_2	R_8	R_9	n	m.p.
r	$C(CH_3)_3$	H	H	SO_2– 	2	220-223° [1]
s	$C(CH_3)_3$	H	H		2	164-165°
t	$C(CH_3)_3$	H	CH_3	SO_2– 	4	120-122° [1]
u	CH_3	H	H	CO– 	4	200-204° [5]
v	H	H	H	CO– 	4	114°
w	CH_3	H	H	$COC(CH_3)_3$	4	150-151 [2]
x	$C(CH_3)_3$	H	H	$COC(CH_3)_3$	4	165-165 [2]

Example 10:

In manner analogous to that described in Example 4 the following compounds of formula Ia are obtained, wherein X–Y is N–CH_2 and W is $-(CH_2)_n-$:

Ex.	R_1	R_2	n	R_3	m.p.
a	C_2H_5	H	4		73-74
b	$CH(CH_3)_2$	H	4		164-165°[2)]
c	$n\text{-}C_4H_9$	H	4		
d		H	4		128-131°[2)]

Ex.	R_1	R_2	n	R_3	m.p.
e		H	4		169-170°[2)]
f	$CH_2C_6H_5$	H	4		149-150°[2)]
g	C_2H_5	H	4		
h	$CH(CH_3)_2$	H	4		138°[2)]

Ex.	R_1	R_2	n	R_3	.m.p.
i		H	4		138-140[3)]
j		H	4		135-136°[2)]
k	$HC(CH_3)C_2H_5$	H	4		
l	$CH_2-CH(CH_3)_2$	H	4		

Example 11: 4.4-Dimethyl-1-(4-(4-(4-(1,1-dimethylethyl)-2-thiazolyl)-1-(1,2,3,6-tetrahydropyridinyl))-butyl)-2,6-piperidin-dione [compound of formula Ia]

In manner analogous to that described in Example 1 the title compound is produced, m.p. of the hydrogenmaleinate 180–181°.

The compounds of formula I and their pharmaceutically acceptable acid addition salts exhibit pharmacological activity and are therefore indicated for use as pharmaceuticals. The compounds of formula I promote social interactions are acute and chronic administration of 0.3 to 10 mg/kg p.o. in male mice in aggression-evoking social encounters [A.K. Dixon, Triangle 21 (1982) 95–105; M. Krsiak, Brit. J. Pharmacol. 55 (1975) 141–150]. Furthermore the compounds of formula I show conflict reducing activity as can be shown after administration of 0.1 to 10 mg/kg p.o. of the compounds to male intruder mice [A.K. Dixon, M. Krsiak as above]. In both the aggression as well as the intruder tests the compounds of formula I improve social interactions.

The compounds of formula I further stimulate the vigilance of test animals as can be shown in the increased spontaneous activity after administration of 0.5 to 10 mg/kg p.o. to mice according to Caviezel and Baillod [Pharm. Acta Helv. 33 (1958) 469].

Further the compounds of formula I modify the sleep phases in the sleep/wake cycle in the rat after administration of 3 to 30 mg/kg p.o. [H. Kleinlogel, EEG in Drug Research, Ed. H. Hermann, Gustav Fischer Verlag, Stuttgart, New York, 75–88 (1982)].

In the 8th-EEG the slow wave phase (SWS) is increased, the spindle phase and the paradoxical sleep phase (PS) are reduced. In Hjorth parameters are the mean EEG amplitude (CA) and the complexity (CCF) increased. Furthermore atypical dozing is observed in the rat 8h sleep-EEG after administration of 3 to 30 mg/kg p.o.

Further the compounds of formula I exhibit a strong affinity to 5HT-1A-binding sites in the pig cortex characterised by binding ^{3}H-8-hydroxy-2-(di-n-propylamino)-tetraline (^{3}H-PAT) [H. Gozlan et al., Nature *305*, 140 (1983); modified by A. Pazos, D. Hoyer, J.M. Palacios, Eur.J.Pharmacol. 106, 531, 539 (1985)].

In view of their social interaction improving activity, their conflict reducing activity and their affinity for 5HT-1A-binding sites the compounds of formula I are useful as anxiolytic agents, e.g. in the treatment of conditions or disorders characterised by deficits in approach-oriented beahaviour and/or by anxiety.

In view of their social interaction improving activity and their vigilance increasing activity the compounds of formula I are useful as psychogeriatric agents, e.g. in the treatment of geriatric disorders characterised by social withdrawal and reduced drive.

In view of their social interaction improving activity, their conflict reducing activity, their vigilance increasing activity, their ability to decrease the paradoxical sleep phase and their affinity for 5HT-1A-binding sites compounds of formula I are indicated for use as antidepressant agents, e.g. in the treatment of depressions.

In view of their social interaction improving activity, their conflict reducing activity, their vigilance increasing activity and their ability to induce atypical dozing compounds of formula I are indicated for use a antischizophrenic agents, e.g. in the treatment of schizophrenia.

For the above uses an indicated daily dosage is in the range from about 1 to about 500 mg of the compound of formula I for anxiolytic and psychogeriatric activity or from about 25 to about 500 mg for antidepressant and antischizophrenic activity respectively, conveniently administered in divided doses 2 to 4x/day in unit dosage form or in sustained release form. Suitable unit dosage forms accordingly comprise from about 0.25 to about 250 mg and from about 5 to about 250 mg; (according to intended utility) of the compound of formula I together with a pharmaceutically acceptable diluent or carrier.

The compounds of formula I may be administered in free base forms or in pharmaceutically acceptable acid addition salt form. Such salts may be prepared in conventional manner and exhibit the same order of activity as the free base form. The present invention also provides a pharmaceutical composition comprising a compound of formula I in free form or in salt form in association with a pharmaceutically acceptable diluent or carrier. Such compositions may be formulated in conventional manner. The compounds may be administered by any conventional route in particular enterally preferably orally e.g. in the form of tablet or capsules, or parenterally e.g. in form of injectable solutions or suspensions.

In accordance with the foregoing the present invention also provides a compound of formula I as hereinbefore defined for use as a pharmaceutical, i.e. for use in therapy, for example: for use as an anxiolytic or psychogeriatric; for use as an antidepressant or for use as an antischizophrenic; and especially for use in any of the specific indications hereinbefore recited in relation to such use; as well as a method of

1) effecting anxiolytic or psychogeriatric treatment or
2) effecting antidepressant or antischizophrenic treatment

e.g. for treating any of specific conditions hereinbefore recited in relation to such treatment, in a subject in need of such treatment, which method comprises administering to said subject an

effective amount of a compound of formula I as hereinbefore defined, or a pharmaceutically acceptable acid addition salt thereof.

In a preferred group of compounds of formula I,

R_1 and R_2 independently are hydrogen, (C_{1-6})alkyl, (C_{3-6})cycloalkyl, (C_{3-6})cycloalkyl(C_{1-3})alkyl, phenyl, phenyl(C_{1-3})alkyl or

R_1 and R_2 signify together pentamethylene, or

R_2 and R_2 signify together $-(CH_3)_2C-O-C(CH_3)_2-$,

R_1 is additionally trifluoromethyl,

W is alkylene of 2 to 6 carbon atoms, or alkenylene or alkinylene of 4 to 6 carbon atoms, whereby the unsaturation is not adjacent to the nitrogen atoms,

X–Y is $N-CH_2$, C=CH or $CH-CH_2$,

R_3 is a group of formula a), wherein A is CH_2, B is CO, m is 1, R_4' and R_5' are each hydrogen, R_4 and R_5 are each methyl or wherein A is CH_2, B is CH_2, m is O, and R_4 and R_5 are each hydrogen; or

R_3 is a group of formula b), wherein t is 4; or

R_3 is a group of formula f), wherein B is CO; or

R_3 is a group of formula g), wherein A is NH; or

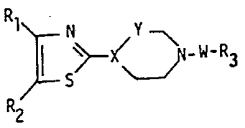
R_3 is a group of formula i), wherein E is N; or

R_3 is a group j), wherein A' is CH_2 and B is CO;

and when X–Y is $N-CH_2$, R_3 is also a group of formula o), wherein R_8 is hydrogen or (C_{1-3})alkyl, R_9 is $-COR_{10}$ or $-SO_2R_{10}$, wherein R_{10} is (C_{1-6})alkyl or phenyl, wherein phenyl is optionally mono- or indepedently di- or trisubstituted by hydroxy, methoxy, amino or halogen, provided that when W is dimethylene and R_9 is $-COR_{10}$, wherein R_{10} is 4-aminophenyl, at least one of R_1, R_2 and R_8 is other than hydrogen, and acid addition salts thereof.

CLAIMS

1. A process for the production of a compound of formula I,



I

wherein

R_1 and R_2 indepedently are hydrogen, (C_{1-6})alkyl, (C_{3-6})cycloalkyl, (C_{3-6})cycloalkyl(C_{1-3})alkyl, phenyl, phenyl(C_{1-3})alkyl or

R_1 and R_2 signify together trimethylene, tetramethylene or pentamethylene, optionally substituted at the same or different carbon atoms by 1 or 2 methyl groups, or

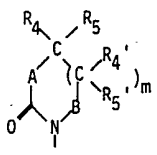
R_1 and R_2 signify together $-(CH_3)_2C-O-C(CH_3)_2-$,

R_1 may additionally signify trifluoromethyl,

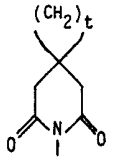
W is alkylene of 2 to 6 carbon atoms, or alkenylene or alkinylene of 4 to 6 carbon atoms, whereby the unsaturation is not adjacent to the nitrogen atoms,

X–Y is $N-CH_2$, C=CH or $CH-CH_2$ and

R_3 is a group of formula a)–n)

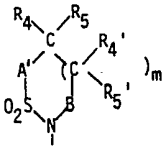


a)

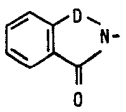


b)

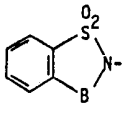
c)



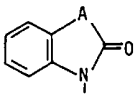
d)



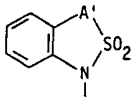
e)



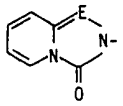
f)



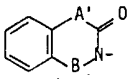
g)



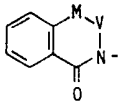
h)



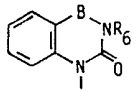
i)



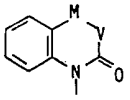
j)



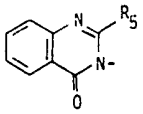
k)



l)

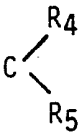


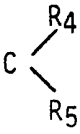
m)



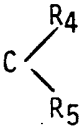
n)

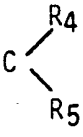
in which

A is  , NR_6, O or S,

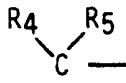
B is  or CO,

m is 0 or 1,
R_4 and R_4' independently are hydrogen or (C_{1-4})alkyl,
R_5 and R_5' independently are hydrogen, (C_{1-4})alkyl, phenyl or phenyl(C_{1-4})alkyl,
t is 4 or 5,
R_6 is hydrogen or (C_{1-3})alkyl,
R_7 is hydrogen, (C_{1-3})alkyl, phenyl(C_{1-3})alkyl or phenoxy(C_{1-3})alkyl,
U=L is $N=CR_5$ or $CR_5=N$,

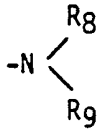
A' is  or NR_6,

D is  , CO, NR_6, S or O,

E is N or CH,

M - V is  or  ,

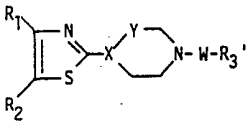
and when X–Y is N–CH_2 R_3 may also be a group of formula o)



o)

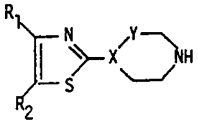
wherein
R_8 is hydrogen or (C_{1-3})alkyl,
R_9 is $-COR_{10}$, $-CON(R_{11})R_{12}$, $-SO_2R_{10}$ or $-SO_2N(R_{11})R_{12}$, wherein R_{10} is (C_{1-6})alkyl, (C_{3-6})cycloalkyl, phenyl or phenyl(C_{1-3})alkyl, wherein each phenyl is optionally mono- or independently di- or trisubstituted by (C_{1-3})alkyl, hydroxy, methoxy, methylendioxy, amino, halogen or trifluoromethyl,
R_{11} and R_{12} are each, independently, hydrogen or (C_{1-3})alkyl or
R_{11} and R_{12} together signify tetramethylene or pentamethylene, provided that when W is dimethylene and R_9 is $-COR_{10}$, wherein R_{10} is 4-aminophenyl, at least one of R_1, R_2 and R_8 is other than hydrogen, or an acid addition salt thereof, which comprises

a) producing a compound of formula Ia



Ia

wherein R_1, R_2, W and X–Y are as defined above, and R_3' is a group of formula a)–n), or an acid addition salt thereof, by reacting a compound of formula II



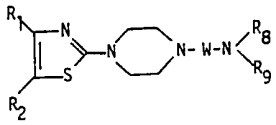
II

wherein R_1, R_2 and X–Y are as defined above, with a compound of formula III

$$Q\text{–}W\text{–}R_3' \qquad III$$

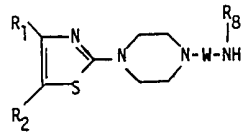
wherein W and R_3' are as defined above, and Q is a leaving group, or

b) producing a compound of formula Ib,



Ib

wherein R_1, R_2, W, R_8 and R_9 are as defined above or an acid addition salt thereof, by reacting a compound of formula IV,



IV

wherein R_1, R_2, W and R_8 are as defined above, with a compound of formula V

$$Z\text{–}R_9 \qquad V$$

wherein R_9 is as defined above and Z is a leaving group, and recovering the compound of formula I in free base form or acid addition salt form.

2. A process for the production of a compound of formula I or an acid addition salt thereof as hereinbefore described with reference to any of the Examples.

3. A compound of formula I or an acid addition salt thereof whenever produced by a process according to claim 1 or 2.

4. A compound of formula I or an acid addition salt thereof.

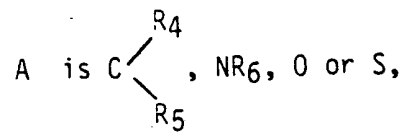
5. A compound of claim 4, wherein R_1 and R_2 are independently hydrogen, (C_{1-6})alkyl, (C_{3-6})cycloalkyl, (C_{3-6})cycloalkyl(C_{1-3})alkyl, phenyl, phenyl(C_{1-3})alkyl or

R_1 and R_2 signify together trimethylene, tetramethylene or pentamethylene, optionally substituted at the same or different carbon atoms by 1 or 2 methyl groups,

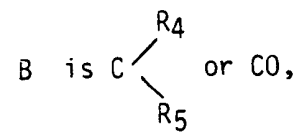
R_1 may additionally signify trifluoromethyl,

W is alkylene of 2 to 6 carbon atoms,

X–Y is N–CH_2 and R_3 is a group of formula a)–n), in which

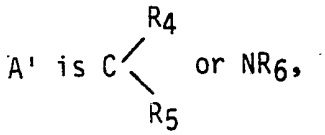


A is C(R_4)(R_5), NR_6, O or S,

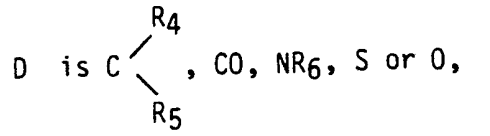


B is C(R_4)(R_5) or CO,

m is 0 or 1,
R_4 and R_4' independently are hydrogen or (C_{1-4})alkyl,
R_5 and R_5' independently are hydrogen, (C_{1-4})alkyl, phenyl or phenyl(C_{1-4})alkyl,
t is 4 or 5,
R_6 is hydrogen or (C_{1-3})alkyl,
R_7 is hydrogen, (C_{1-3})alkyl, phenyl(C_{1-3})alkyl or phenoxy(C_{1-3})alkyl,
U=L is $N=CR_5$ or $CR_5=N$,

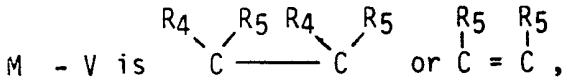


A' is $C(R_4)(R_5)$ or NR_6,



D is $C(R_4)(R_5)$, CO, NR_6, S or O,

E is N or CH,



M - V is $-C(R_4)(R_5)-C(R_4)(R_5)-$ or $-C(R_5)=C(R_5)-$,

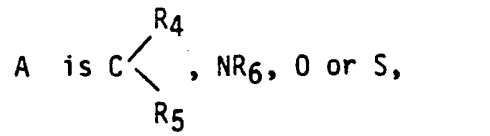
or an acid addition salt thereof.

6. A compound of claim 4, wherein X–Y is N–CH_2 and R_3 is a group of formula a), wherein A is CH_2, B is CO, m is 1, R_4' and R_5' are each hydrogen, R_4 and R_5 are each methyl, and either W is tetramethylene, R_1 and R_2 are the same and signify hydrogen or methyl, or R_1 is methyl, trifluoromethyl, tert.butyl or cyclopentyl and R_2 is hydrogen, or R_1 is hydrogen and R_2 is 2-methylpropyl or R_1 and R_2 signify together pentmethylene, or W is dimethylene, trimethylene, pentamethylene or hexamethylene, R_1 is tert.butyl and R_2 is hydrogen or an acid addition salt thereof.

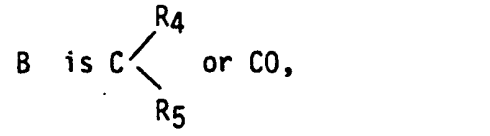
7. A compound of claim 4, wherein X–Y is N–CH_2 and R_3 is a group of formula f) wherein B is CO, W is tetramethylene and either R_1 is tert. butyl and R_2 is hydrogen or R_1 and R_2 together signify pentamethylene or an acid addition salt thereof.

8. A compound of claim 4, wherein X–Y is N–CH_2 and R_3 is a group of formula i), wherein E is N, W is trimethylene or tetramethylene, R_1 is tert.butyl and R_2 is hydrogen or an acid addition salt thereof.

9. A compound of claim 4, wherein R_1 and R_2 are independently hydrogen, (C_{1-6})alkyl, (C_{3-6})cycloalkyl, (C_{3-6})cycloalkyl(C_{1-3})alkyl, phenyl, phenyl(C_{1-3})alkyl, or R_1 and R_2 signify together trimethylene, tetramethylene or pentamethylene, W is alkylene of 2 to 6 carbon atoms,
X–Y is C=CH or CH–CH_2, and R_3 is a group of formula a)–n), in which



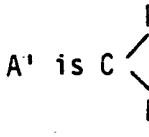
A is $C(R_4)(R_5)$, NR_6, O or S,

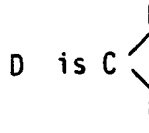


B is $C(R_4)(R_5)$ or CO,

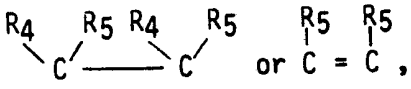
m is 0 or 1,
R_4 and R_4' independently are hydrogen or (C_{1-4})alkyl,
R_5 and R_5' independently are hydrogen, (C_{1-4})alkyl, phenyl or phenyl(C_{1-4})alkyl,
t is 4 or 5,
R_6 is hydrogen or (C_{1-3})alkyl,
R_7 is hydrogen, (C_{1-3})alkyl, phenyl(C_{1-3})alkyl or phenoxy(C_{1-3})alkyl,

U=L is $N=CR_5$ or $CR_5=N$,

A' is  or NR_6,

D is  , CO, NR_6, S or O,

E is N or CH, and

M - V is  ,

or an acid addition salt thereof.

10. A compound of claim 4, wherein R_1, R_2 independently are hydrogen, (C_{1-6})alkyl, (C_{3-6})cycloalkyl, $(C_{3\ 6})$cycloalkyl$(C_{1\ 3})$alkyl, phenyl, phenyl$(C_{1\ 3})$alkyl, or R_1 and R_2 signify together trimethylene, tetramethylene or pentamethylene optionally substituted at the same or different carbon atoms by 1 or 2 methyl groups,

R_1 may additionally signify trifluoromethyl,

X–Y is $N–CH_2$ and R_3 is a group of formula o), wherein R_8 is hydrogen or (C_{1-3})alkyl,

R_9 is $–COR_{10}$, $–CON(R_{11})R_{12}$, $–SO_2R_{10}$ or $–SO_2N(R_{11})R_{12}$, wherein

R_{10} is $(C_{1\ 6})$alkyl, $(C_{3\ 6})$cycloalkyl, phenyl or phenyl$(C_{1\ 3})$alkyl, wherein each phenyl is optionally mono- or independently di- or trisubstituted by $(C_{1\ 3})$alkyl, hydroxy, methoxy, methylendioxy, amino, halogen or trifluoromethyl,

R_{11} and R_{12} are each, independently, hydrogen or $(C_{1\ 3})$alkyl or

R_{11} and R_{12} together signify tetramethylene or pentamethylene, provided that when W is dimethylene and R_9 is $–COR_{10}$, wherein R_{10} is 4-aminophenyl, at least one of R_1, R_2 and R_8 is other than hydrogen,

or an acid addition salt thereof.

11. A compound of claim 4, wherein

R_1 and R_2 independently are hydrogen, $(C_{1\ 6})$alkyl, $(C_{3\ 6})$cycloalkyl, $(C_{3\ 6})$cycloalkyl(C_{1-3})alkyl, phenyl, phenyl$(C_{1\ 3})$alkyl or

R_1 and R_2 signify together pentamethylene, or

R_1 and R_2 signify together $–(CH3)_2C–O–C(CH_3)_2–$,

R_1 is additionally trifluoromethyl,

W is alkylene of 2 to 6 carbon atoms, or alkenylene or alkinylene of 4 to 6 carbon atoms, whereby the unsaturation is not adjacent to the nitrogen atoms,

X–Y is $N–CH_2$, C=CH or $CH–CH_2$,

R_3 is a group of formula a), wherein A is CH_2, B is CO, m is 1, R_4' and R_5' are each hydrogen, R_4 and R_5 are each methyl or wherein A is CH_2, B is CH_2, m is 0, and R_4 and R_5 are each hydrogen; or

R_3 is a group of formula b), wherein t is 4; or

R_3 is a group of formula f), wherein B is CO; or

R_3 is a group of formula g), wherein A is NH; or

R_3 is a group of formula i), wherein E is N; or

R_3 is a group j), wherein A' is CH_2 and B is CO;

and when X–Y is $N–CH_2$, R_3 is also a group of formula o), wherein R_8 is hydrogen or (C_{1-3})alkyl, R_9 is $–COR_{10}$ or $–SO_2R_{10}$, wherein R_{10} is (C_{1-6})alkyl or phenyl, wherein phenyl is optionally mono- or independently di- or trisubstituted by hydroxy, methoxy, amino or halogen, provided that when W is dimethylene and R_9 is $–COR_{10}$, wherein R_{10} is 4-aminophenyl, at least one of R_1, R_2 and R_8 is other than hydrogen or an acid addition salt thereof.

12. A compound of claim 4 which is 2-(4-(4-(4-(1,1-dimethylethyl)-2-thiazolyl)-1-(1,2,3,6-tetrahydropyridinyl))butyl)-1,2-benzisothiazol-3-(2H)one-1,1-dioxide or an acid addition salt thereof.

13. A compound of claim 4 which is 4,4-dimethyl-1-(4-(4-(1,1-dimethylethyl)-2-thiazolyl)-1-piperidinyl)butyl-2,6-piperidin-dione or an acid addition salt thereof.

14. A compound of claim 4 which is 2-(4-(4-((1,1-dimethylethyl)-2-thiazolyl)-1-piperidinyl)bu-

tyl)-1,2-benzisothiazol-3-(2H)-one-1,1-dioxide or an acid addition salt thereof.

15. A compound of claim 4 which is 4,4-dimethyl-1-((4-(4-(4-(1,1-dimethylethyl)-2-thiazolyl)-1-piperazinyl)butyl)-2,6-piperidindione or an acid addition salt thereof.

16. A compound of claim 4 which is 4,4-dimethyl-1-(4-(4-(4-trifluoromethyl-2-thiazolyl)-1-piperazinyl)butyl)-2,6-piperidindione or an acid addition salt thereof.

17. A compound of claim 4 which is 2-(4-(4-(4-(1,1-dimethylethyl)-2-thiazolyl)-1-piperazinyl)butyl)-1,2-benzisothiazol-3-(2H)on-1,1-dioxide or an acid addition salt thereof.

18. A compound of claim 4 which is 2-(2-(4-(4-(1,1-dimethylethyl)-2-thiazolyl)-1-piperazinyl)ethyl)-s-triazolo[4,3-a]pyridin-3-(2H)one or an acid addition salt thereof.

19. A compound of claim 4 which is 8-(2-(4-(4-(1,1-dimethylethyl)-2-thiazolyl)-1-piperazinyl)ethyl)-8-azaspiro[4,5]decan-7,9-dione or an acid addition salt thereof.

20. A compound of claim 4 which is 8-(4-(4-(4-(1,1-dimethylethyl)-2-thiazolyl)-1-piperazinyl)butyl)-8-azaspiro[4,5]decan-7,9-dione or an acid addition salt thereof.

21. A compound of claim 4 which is 8-(3-(4-(4-(1,1-dimethyl-ethyl)-thiazol-2-yl)-1-piperazinyl)-propyl)-8-azaspiro[4,5]decan-7,9-dione or an acid addition salt thereof.

22. A compound of claim 4 which is 2-(2-(4-(4-(1,1-dimethylethyl)-2-thiazolyl)-1-piperazinyl)ethyl)-1,3-(2H,4H)-isochinolindione or an acid addition salt thereof.

23. A compound of claim 4 which is N-(2-(4-(1,1-dimethylethyl-2-thiazolyl)-1-piperazinyl)ethyl)-benzimidazolone or an acid addition salt thereof.

24. A compound of claim 4 which is N-(3-(4-(1,1-dimethylethyl-2-thiazolyl)-1-piperazinyl)propyl)-benzimidazolone or an acid addition salt thereof.

25. A compound of claim 4 which is N-(4-(4-(1,1-dimethylethyl-2-thiazolyl)-1-piperazinyl)butyl)-benzimidazolone or an acid addition salt thereof.

26. A compound of claim 4 which is 4,4-dimethyl-1-(4-(4-(4-methyl-2-thiazolyl)-1-piperazinyl)-butyl)-2,6-piperidin-dione or an acid addition salt thereof.

27. A compound of claim 4 which is 4,4-dimethyl-1-(6-(4-(4-(1,1-dimethylethyl)-2-thiazolyl)-1-piperazinyl)hexyl)-2,6-piperidindione or an acid addition salt thereof.

28. A compound of claim 4 which is 4,4-dimethyl-1-(5-(4-(4-(1,1-dimethylethyl)-2-thiazolyl)-1-piperazinyl)pentyl)-2,6-piperidin-dione or an acid addition salt thereof.

29. A compound of claim 4 which is 4,4-dimethyl-1-(3-(4-(4-(1,1-dimethylethyl)-2-thiazolyl)-1-piperazinyl)propyl)-2,6-piperidin-dione or an acid addition salt thereof.

30. A compound of claim 4 which is 4,4-dimethyl-1-(2-(4-(4-(1,1-dimethylethyl)-2-thiazolyl)-1-piperazinyl)ethyl)-2,6-piperidin-dione or an acid addition salt thereof.

31. A compound of claim 4 which is 4,4-dimethyl-1-(4-(4-(4H-5,6,7,8-tetrahydro-2-cycloheptathiazolyl)-1-piperazinyl)butyl)-2,6-piperidin-dione or an acid addition salt thereof.

32. A compound of claim 4 which is 4,4-dimethyl-1-(4-(4-(2-thiazolyl)-1-piperazinyl)butyl)-2,6-piperidin-dione or an acid addition salt thereof.

33. A compound of claim 4 which is 4,4-dimethyl-1-(4-(4-(4,5-dimethyl-2-thiazolyl)-1-piperazinyl)butyl)-2,6-piperidindione or an acid addition salt thereof.

34. A compound of claim 4 which is 4,4-dimethyl-1-(4-(4-(4-cyclopentyl-2-thiazolyl)-1-piperazinyl)butyl)-2,6-piperidindione or an acid addition salt thereof.

35. A compound of claim 4 which is 4,4-dimethyl-1-(4-(4-(5-(2-methylpropyl)-2-thiazolyl)-1-piperazinyl)butyl)-2,6-piperidin-dione or an acid addition salt thereof.

36. A compound of claim 4 which is 2-(4-(4-(4H-5,6,7,8-tetrahydro-2-cycloheptathiazolyl)-1-piperazinyl) butyl)-1,2-benzisothiazol-3-(2H)-on-1,1-dioxide or an acid addition salt thereof.

37. A compound of claim 4 which is 2-(4-(4-(4-methyl-2-thiazolyl)-1-piperazinyl)butyl)-1,2-benzisothiazol-3-(2H)on-1,1-dioxide or an acid addition salt thereof.

38. A compound of claim 4 which is 8-(4-(4-(4H-5,6,7,8-tetrahydro-2-cycloheptathiazolyl)-piperazinyl)butyl)-8-azaspiro[4,5]decan-7,9-dione or an acid addition salt thereof.

39. A compound of claim 4 which is 2-(3-(4-(4-(1,1-dimethylethyl)-2-thiazolyl)-1-piperazinyl)-propyl)-s-triazolo[4,3-a] pyridin-3-(2H)one or an acid addition salt thereof.

40. A compound of claim 4 which is 2-(4-(4-(4-(1,1-dimethylethyl)-2-thiazolyl)-1-piperazinyl) butyl)-s-triazolo[4,3-a] pyridin-3-(2H)one or an acid addition salt thereof.

41. A compound of claim 4 which is 1-(4-(4-(4-(1,1-dimethylethyl)-2-thiazolyl)-1-piperazinyl)butyl)-pyrrolidin-2-one or an acid addition salt thereof.

42. A compound of claim 4 which is 2-(4-(4-(2-thiazolyl)-1-piperazinyl)butyl)-1,2-benzisothiazol-3-(2H)on-1,1-dioxide or an acid addition salt thereof.

43. A compound of claim 4 which is 4,4-dimethyl-1-(2-(4-(4-methyl-2-thiazolyl)-1-piperazinyl)ethyl)-2,6-piperidin-dione or an acid addition salt thereof.

44. A compound of claim 4 which is 2-(4-(4-(4-trifluoromethyl-2-thiazolyl)-1-piperazinyl)butyl)-1,2-benzisothiazol-3-(2H)-on-1,1-dioxide or an acid addition salt thereof.

45. A compound of claim 4 which is 1-(4-(4-(4,6-dihydro-4,4,6,6-tetramethylfuro[3,4-d]thiazol-2-yl)-1-piperazinyl) butyl)-4,4-dimethyl-2,6-piperidin-dione or an acid addition salt thereof.

46. A compound of claims 4 which is E-4,4-dimethyl-1-(4-(4-(4-(1,1-dimethylethyl)-2-thiazolyl)-1-piperazinyl)-2-butenyl)-2,6-piperidin-dione or an acid addition salt thereof.

47. A compound of claim 4 which is 2-(4-(4-(4-(1,1-dimethylethyl)-2-thiazoly)-1-piperazinyl)-2-butinyl)-1,2-benzisothiazol-3-(2H)on-1,1-dioxide or an acid addition salt thereof.

48. A compound of claim 4 which is 4,4-dimethyl-1-(4-(4-(4-(1,1-dimethylethyl)-2-thiazolyl)-1-piperazinyl)-2-butinyl)-2,6-piperidin-dione or an acid addition salt thereof.

49. A compound of claim 4 which is E-2-(4-(4-(4-(1,1-dimethylethyl)-2-thiazolyl)-1-piperazinyl)-2-butenyl)-1,2-benzisothiazol-3-(2H)on-1,1-dioxide or an acid addition salt thereof.

50. A compound of claim 4 which is 5-chloro-2-methoxy-N-(2-(4-(4-(1,1-dimethylethyl-2-thiazolyl)-1-piperazinyl)ethyl)-benzamide or an acid addition salt thereof.

51. A compound of claim 4 which is N-(2-(4-(4-(1,1-dimethylethyl-2-thiazolyl)-1-piperazinyl) ethyl)-benzamide or an acid addition salt thereof.

52. A compound of claim 4 which is N-methyl-N-(2-(4-(4-(1,1-dimethylethyl-2-thiazolyl))-1-piperazinyl)ethyl-benzamide or an acid addition salt thereof.

53. A compound of claim 4 which is 4-amino-5-chloro-2-methoxy-N-(2-(4-(4-(1,1-dimethylethyl)-2-thiazolyl)-1-piperazinyl)ethyl)benzamide or an acid addition salt thereof.

54. A compound of claim 4 which is N-5-chloro-2-methoxy-(2-(4-(4-(1,(1-dimethylethyl-2-thiazolyl))-1-piperazinyl)-ethyl)benzenesulfonamide or an acid addition salt thereof.

55. A compound of claim 4 which is 5-chloro-2-methoxy-N-(3-(4-(4-(1,1-dimethylethyl-2-thiazolyl))-1-piperazinyl)-propyl)-benzamide or an acid addition salt thereof.

56. A compound of claim 4 which is 5-chloro-2-methoxy-N-(4-(4-(4-(1,1-dimethylethyl-2-thiazolyl))-1-piperazinyl)butyl)-benzamide or an acid addition salt thereof.

57. A compound of claim 4 which is 4-amino-5-chloro-2-methoxy-N-(3-(4-(4-(1,1-dimethylethyl-2-thiazolyl))-1-piperazinyl)-propyl)-benzamide or an acid addition salt thereof.

58. A compound of claim 4 which is 4-amino-5-chloro-2-methoxy-N-(4-(4-(4-(1,1-dimethylethyl-2-thiazolyl))-1-piperazinyl)butyl)-benzamide or an acid addition salt thereof.

59. A compound of claim 4 which is 3-chloro-2,6-dimethoxy-N-(2-(4-(4-(1,1-dimethylethyl-2-thiazolyl))-1-piperazinyl)-ethyl)-benzamide or an acid addition salt thereof.

60. A compound of claim 4 which is 2,6-dichloro-N-(2-(4-(4-(1,1-dimethylethyl)-2-thiazolyl)-1-piperazinyl)ethyl)-benzamide or an acid addition salt thereof.

61. A compound of claim 4 which is 2,5-dichloro-N-(2-(4-(4-(1,1-dimethylethyl)-2-thiazolyl)-1-piperazinyl)ethyl-benzamide or an acid addition salt thereof.

62. A compound of claim 4 which is 3,4,5-trimethoxy-N-(2-(4-(4-(1,1-dimethylethyl)-2-thiazolyl)-1-piperazinyl)ethyl-benzamide or an acid addition salt thereof.

63. A compound of claim 4 which is 5-chloro-2-methoxy-N-(2-(4-(4-phenyl-2-thiazolyl)-1-piperazinyl)ethyl)-benzamide or an acid addition salt thereof.

64. A compound of claims 4 which is 5-chloro-2-methoxy-N-(2-(4-(4,5-dimethyl-2-thiazolyl)-1-piperazinyl)ethyl)-benzamide or an acid addition salt thereof.

65. A compound of claim 4 which is N-(4-(4-(4-(1,1-dimethylethyl)-2-thiazolyl)-1-piperazinyl)butyl)-benzamide or an acid addition salt thereof.

66. A compound of claim 4 which is N-(4-(4-(4-(1,1-dimethylethyl)-2-thiazolyl)-1-piperazinyl) butyl)-benzenesulfonamide or an acid addition salt thereof.

67. A compound of claim 4 which is N-methyl-N-5-chloro-2-methoxy-(4-(4-(4-(1,1-dimethylethyl)-2-thiazolyl)-1-piperazinyl) butyl)-benzenesulfonamide or an acid addition salt thereof.

68. A compound of claim 4 which is N-(2-(4-(4-(1,1-dimethylethyl)-2-thiazolyl)-1-piperazinyl)ethyl)-benzenesulfonamide or an acid addition salt thereof.

69. A compound of claim 4 which is 5-chloro-2-hydroxy-N-(2-(4-(4-(1,1-dimethylethyl)-2-thiazolyl)-1-piperazinyl) ethyl)-benzamide or an acid addition salt thereof.

70. A compound of claim 4 which is N-Methyl-N-(4-(4-(4-(1,1-dimethylethyl)-2-thiazolyl)-1-piperazinyl)butyl)-benzenesulfonamide or an acid addition salt thereof.

71. A compound of claim 4 which is N-(4-(4-(4-methyl-2-thiazolyl)-1-piperazinyl)butyl)-benzamide or an acid addition salt thereof.

72. A compound of claim 4 which is N-(4-(4-(2-thiazolyl)-1-piperazinyl)butyl)-benzamide or an acid addition salt thereof.

73. A compound of claim 4 which is N-(4-(4-(4-methyl-2-thiazolyl)-1-piperazinyl)butyl)-2,2-dimethylpropionamide or an acid addition salt thereof.

74. A compound of claim 4 which is N-(4-(4-(4-(1,1-dimethylethyl)-2-thiazolyl)-1-piperazinyl)butyl)-2,2-dimethylpropionamide or an acid addition salt thereof.

75. A compound of claim 4 which is 4,4-dimethyl-1-(4-(4-(4-ethyl-2-thiazolyl)-1-piperazinyl)butyl)-2,6-piperidin-dione or an acid addition salt thereof.

76. A compound of claim 4 is 4,4-dimethyl-1-(4-(4-(4-isopropyl-2-thiazolyl)-1-piperazinyl)butyl)-2,6-piperidin-dione or an acid addition salt thereof.

77. A compound of claim 4 which is 4,4-dimethyl-1-(4-(4-(4-n-butyl-2-thiazolyl)-1-piperazinyl)-butyl)-2,6-piperidin-dione or an acid addition salt thereof.

78. A compound of claim 4 which is 4,4-dimethyl-1-(4-(4-(4-cyclopropl-2-thiazolyl)-1-piperazinyl)butyl)-2,6-piperidin-dione or an acid addition salt thereof.

79. A compound of claim 4 which is 4,4-dimethyl-1-(4-(4-(4-cyclobutyl-2-thiazolyl-1-piperazi-

nyl)butyl-2,6-piperidin-dione or an acid addition salt thereof.

80. A compound of claim 4 which is 4,4-dimethyl-1-(4-(4-(4-benzyl-2-thiazolyl)-1-piperazinyl)-butyl)-2,6-piperidin-dione or an acid addition salt thereof.

81. A compound of claim 4 which is 2-(4-(4-(4-ethyl-2-thiazolyl)-1-piperazinyl)butyl)-1,2-benzisothiazol-3-(2H)-on-1,1-dioxide or an acid addition salt thereof.

82. A compound of claim 4 which is 2-(4-(4-(4-isopropyl-2-thiazolyl)-1-piperazinyl)butyl)-1,2-benzisothiazol-3-(2H)on-1,1-dioxide or an acid addition salt thereof.

83. A compound of claim 4 which is 2-(4-(4-(4-cyclopentyl-2-thiazolyl)-1-piperazinyl)butyl)-1,2-benzisothiazol-3-(2H)on-1,1-dioxide or an acid addition salt thereof.

84. A compound of claim 4 which is 2-(4-(4-(4-cyclobutyl-2-thiazolyl)-1-piperazinyl)butyl)-1,2-benzisothiazol-3-(2H)on-1,1-dioxide or an acid addition salt thereof.

85. A compound of claim 4 which is 1-(4-(4-(4-trifluoromethyl-2-thiazolyl)-1-piperazinyl)butyl)-pyrrolidin-2-one or an acid addition salt thereof.

86. A compound of claim 4 which is 4,4-dimethyl-1-(4-(4-(4-(1-methylpropyl)-2-thiazolyl)-1-piperazinyl)butyl-2,6-piperidin-dione or an acid addition salt thereof.

87. A compound of claim 4 which is 4,4-dimethyl-1-(4-(4-(4-isobutyl-2-thiazolyl)-1-piperazinyl)-butyl-2,6-piperidin-dione or an acid addition salt thereof.

88. A compound of claim 4 which is 4,4-dimethyl-1-(4-(4-(4-(1,1-dimethylethyl)-2-thiazolyl)-1-(1,2,3,6-tetrahydropyridinyl))butyl)-2,6-piperidin-dione or an acid addition salt thereof.

89. A compound according to any one of claims 4 to 88 or a pharmaceutically acceptable acid addition salt thereof for use as a pharmaceutical.

90. A compound according to any one of claims 4 to 88 or a pharmaceutically acceptable acid addition salt thereof for use as an anxiolytic or psychogeriatric.

91. A compound to any one of claims 4 to 88 or a pharmaceutically acceptable acid addition salt thereof for use as an antidepressant or antischizophrenic.

92. A pharmaceutical composition which comprises a compound of any one of claims 4 to 88 or a pharmaceutically acceptable acid addition salt thereof in association with a pharmaceutical carrier or diluent.

93. A method of effecting anxiolytic or psychogeriatric treatment which comprises administering a therapeutically effective amount of a compound of any one of claims 4 to 88 or a pharmaceutically acceptable acid addition salt thereof to a subject in need of such treatment.

94. A method of effecting antidepressant or antischizophrenic treatment which method comprises administering a therapeutically effective amount of a compound of any one of claims 4 to 88 or a pharmaceutically acceptable acid addition salt thereof to a subject in need of such treatment.

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