

PATENT SPECIFICATION

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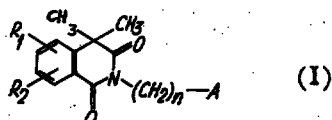
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 630 634 635 644 650 662 672 682 694 698 761
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(54) 1,3-DIKETO-1,2,3,4-TETRAHYDROISOQUINOLINES

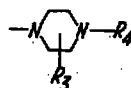
(71) We, DR. KARL THOMAE GMBH, a Body Corporate organised under the laws of the Federal Republic of Germany of Biberach Riss, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to new isoquinoline derivatives having interesting physiological properties.

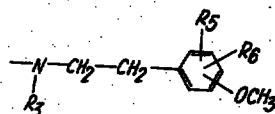
According to one feature of the present invention there are provided compounds of general formula



(wherein R₁ represents a hydrogen or halogen atom or a methoxy or a methylmercapto group, R₂ represents a hydrogen atom or a methoxy group, n represents the number 2 or 3, and A represents a group of formula



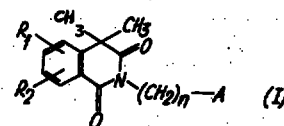
or a group of formula



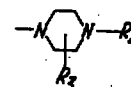
(wherein R₃ represents a hydrogen atom or a methyl group, R₄ represents a pyridyl group optionally substituted by a methyl group, or a phenyl group optionally substituted by a chlorine atom, by a trifluoromethyl group or

by one of two methyl, ethyl or methoxy groups, and R₅ and R₆, which may be the same or different, each represents a hydrogen atom or a methoxy group) and acid addition salts thereof.

According to one embodiment of the present invention there are provided compounds of general formula

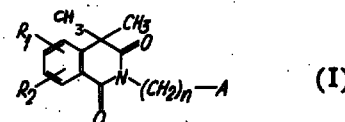


(wherein R₁ represents a hydrogen, fluorine or chlorine atom or a methoxy group, R₂ represents a hydrogen atom or a methoxy group, and A represents a group of formula



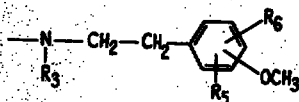
(wherein R₃ represents a hydrogen atom or a methyl group and R₄ represents a pyridyl group optionally substituted by a methyl group or a phenyl group optionally substituted by a chlorine atom, a trifluoromethyl group or by one or two methyl, ethyl or methoxy groups), and n represents the number 2 or 3) and acid addition salts thereof.

According to a further embodiment of the present invention there are provided compounds of general formula



(wherein R₁ represents a hydrogen or chlorine

atom or a methoxy or methylmercapto group, R_2 represents a hydrogen atom or a methoxy group, A represents a group of formula



(wherein R_3 represents a hydrogen atom or a methyl group, and R_5 and R_6 , which may be the same or different, each represents a hydrogen atom or a methoxy group) and n represents the number 2 or 3) and acid addition salts thereof.

In general the new compounds according to the invention possess valuable physiological properties, in particular a hypotensive activity usually accompanied by a bradycardiac, anti-arrhythmic and sedative activity.

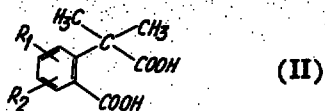
Preferred compounds of general formula I and acid addition salts thereof by virtue of their particularly favourable physiological properties include the following:—

a) 1 - [4,4 - Dimethyl - 1,3 - dioxo(2H, 4H) - isoquinolin - 2 - yl] - 2 - [4 - (2-methoxy - phenyl) - piperazin - 1 - yl] ethane and physiologically compatible acid addition salts thereof; and

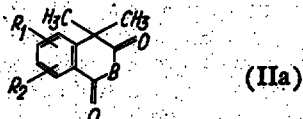
b) 1 - [4,4 - Dimethyl - 7 - methoxy - 1,3-dioxo - (2H,4H) - isoquinolin - 2 - yl] - 3 - [2 - (3,4 - dimethoxy - phenyl) - ethyl-amino] propane and physiologically compatible acid addition salts thereof.

The new compounds of general formula I as hereinbefore defined may be prepared according to any one of the following processes, which processes constitute further features of the present invention:

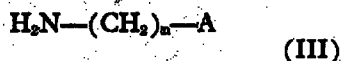
a) Reaction of a compound of formula



or a compound of formula



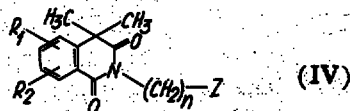
(wherein R_1 and R_2 are as hereinbefore defined and B represents an oxygen atom or an optionally substituted secondary amino group) with a compound of formula



(wherein A and n are as hereinbefore defined) or with an acid addition salt thereof.

The reaction is preferably carried out in the presence of a solvent, e.g. ethylene glycol, or in the melt at temperatures from 50 to 250°C. Advantageously the reaction is effected in the presence of a base such as potassium tert.-butoxide, especially if an acid addition salt of a compound of formula III is used.

b) Reaction of a compound of formula



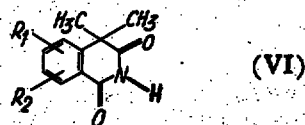
(wherein, R_1 , R_2 and n are as hereinbefore defined and Z represents a group exchangeable with the group A as hereinbefore defined, preferably a chlorine, bromine or iodine atom or an alkylsulfonyloxy or arylsulfonyloxy group e.g. a toluenesulfonyloxy group) with a compound of formula



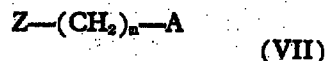
(wherein A is as hereinbefore defined).

The reaction is preferably carried out in the presence of a solvent, e.g. methanol, ether, tetrahydrofuran, methyl formamide, dimethylformamide, dimethylsulfoxide or benzene, and conveniently at temperatures from -50 to 250°C depending on the reactivity of the group Z. Advantageously the reaction is effected in the presence of an acid binding agent, for example a metal alcoholate, metal hydroxide, metal oxide or metal carbonate.

c) Reaction of a compound of formula



(wherein R_1 and R_2 are as hereinbefore defined) or a metal salt thereof, preferably an alkali metal salt, with a compound of formula



(wherein A, Z and n are as hereinbefore defined).

The reaction is preferably carried out in the presence of an acid binding agent, e.g. a metal alcoholate, metal oxide, metal hydroxide or metal carbonate, conveniently in the presence of a solvent, e.g. methanol, isopropanol, dimethylformamide or dimethylsulfoxide and preferably at temperatures from 0°C up to the boiling temperature of the solvent used.

If an alkali metal salt of the amine of formula VI is used, the reaction may be easily effected in the absence of an acid binding agent.

d) For the preparation of acid addition salts of compounds of general formula I as hereinbefore defined:

Conversion of a compound of formula I into an acid addition salt thereof, preferably a physiologically compatible acid addition salt.

Suitable acids for this purpose include mineral acids such as hydrochloric acid, hydrobromic acid, hydriodic acid, hydrofluoric acid, nitric acid, sulfuric acid and phosphoric acid and also organic acids such as acetic acid, propionic acid, butyric acid, malonic acid, succinic acid, maleic acid, fumaric acid, malic acid, tartaric acid, citric acid, benzoic acid, p-hydroxybenzoic acid, p-aminobenzoic acid, salicylic acid, acetyl-salicylic acid, phthalic acid, terephthalic acid, ascorbinic acid, methane sulfonic acid and ethane phosphonic acid.

The compounds of general formulae II to VII used as starting materials are for the most part known from the literature or they may be prepared according to methods known from the literature.

The new compounds of general formula I according to the invention and physiologically compatible acid addition salts thereof which we have tested show valuable physiological properties. For example the following compounds have been tested with regard to their hypotensive activity:

A = 1 - [4,4 - Dimethyl - 1,3 - dioxo - (2H,4H) - isoquinolin - 2 - yl] - 2 - [4 - (2 - methoxy - phenyl) - piperazin - 1 - yl]ethane dihydrochloride and

B = 1 - [4,4 - Dimethyl - 7 - methoxy - 1,3 - dioxo - (2H,4H) - isoquinolin - 2 - yl] - 3 - [2 - (3,4 - dimethoxy - phenyl) - ethyl-amino]propane hydrochloride.

The hypotensive effect was determined in 2 to 4 crossbreed dogs of male and female sex (body weight between 14 and 23 kg) in chloralose - urethane - nembutal narcosis (54 + 270 + 10 mg/kg i.v.). The compounds under test in aqueous solution were injected intravenously into the vena saphena. The arterial blood pressure was measured in the arteria femoralis by a Statham pressure transducer P 23Db and registered on a "Grass" (registered Trade Mark) polygraph.

The following Table gives the results of these tests:

Substance	Dose mg/kg i.e.	Decrease of blood-pressure		Duration of activity in minutes
		mm syst.	Hg diast.	
A	0.05	-27 /	-31	53
A	0.1	-33 /	-34	47
B	0.5	-32 /	-36	35
B	1.0	-36 /	-40	40

The acute toxicity of the compounds under test was determined in mice (observation time: 14 days) after oral application. The LD₅₀ was measured from the percentage of the animals which died within the observation time after application of various doses (see J. Pharmacol, exper. Therap. 96, 99 (1949)):

Substance	LD ₅₀ mg/kg p.o.
A	850
B	775

According to a yet further feature of the present invention there are provided pharma-

ceutical compositions comprising as active ingredient at least one compound of formula I as hereinbefore defined or a physiologically compatible acid addition salt thereof in association with a pharmaceutical carrier or excipient.

The compositions may for example be presented in a form suitable for oral, rectal or parenteral administration. Thus for example compositions for oral administration may be solid or liquid and may take the form of solutions, tablets, coated tablets, suspensions and powders, such compositions comprising carriers or excipients conventionally used in the pharmaceutical art.

For parenteral administration the carrier may be a parenterally acceptable liquid, such

as sterile water, or a parenterally acceptable oil, e.g. arachis oil, contained in ampoules. For rectal administration the compositions may take the form of suppositories, the carrier comprising a suppository base.

If desired the compositions may be formulated in combination with other active ingredients.

Advantageously the compositions may be formulated as dosage units. Each dosage unit preferably contains from 20 to 300 mg, preferably 25 to 200 mg of active ingredient.

The following Examples serve to illustrate the preparation of the new compounds according to the invention and also the preparation of pharmaceutical compositions containing the same:

Example 1.

1 - [4,4 - Dimethyl - 1,3 - dioxo - (2H,4H) - isoquinolin - 2 - yl] - 2 - (4 - phenyl - piperazin - 1 - yl) - ethane dihydrochloride.

19 g of 1,2,3,4 - tetrahydro - 4,4 - dimethyl - isochroman - 1,3 - dione and 20.5 g of 2 - (4 - phenyl - piperazin - 1 - yl) - ethylamine were refluxed in 150 ml of xylene for 12 hours using an apparatus incorporating a water separator. Subsequently, the solvent was removed. The residue was taken up in ether and the dihydrochloride was precipitated with ethereal hydrochloric acid. Recrystallization from ethanol: m.p.: 193 to 205°C (decomp.).

Example 2.

1 - [4,4 - Dimethyl - 7 - chloro - 1,3 - dioxo - (2H,4H) - isoquinolin - 2 - yl] - 2 - (4 - phenyl - piperazin - 1 - yl) - ethane dihydrochloride.

Prepared analogously to Example 1 from 1,2,3,4 - tetrahydro - 7 - chloro - 4,4 - dimethyl - isochroman - 1,3 - dione and 2 - (4 - phenyl - piperazin - 1 - yl) - ethylamine. Recrystallization from isopropanol: m.p.: 231 to 232°C.

Example 3.

1 - [4,4 - Dimethyl - 7 - methoxy - 1,3 - dioxo - (2H,4H) - isoquinolin - 2 - yl] - 2 - (4 - phenyl - piperazin - 1 - yl) - ethane dihydrochloride.

Prepared analogously to Example 1 from 1,2,3,4 - tetrahydro - 7 - methoxy - 4,4 - dimethyl - isochroman - 1,3 - dione and 2 - (4 - phenyl - piperazin - 1 - yl) - ethylamine, but using ethylene glycol as solvent. Recrystallization from isopropanol: m.p.: 215 to 218°C.

Example 4.

1 - [4,4 - Dimethyl - 7 - fluoro - 1,3 - dioxo - (2H,4H) - isoquinolin - 2 - yl] - 2 - (4 - phenyl - piperazin - 1 - yl) - ethane dihydrochloride.

Prepared analogously to Example 3 from

1,2,3,4 - tetrahydro - 7 - fluoro - 4,4 - dimethyl - isochroman - 1,3 - dione and 2 - (4 - phenyl - piperazin - 1 - yl) - ethylamine. Recrystallization from isopropanol: m.p.: 200 to 203°C.

Example 5.

1 - [4,4 - Dimethyl - 6,7 - dimethoxy - 1,3 - dioxo - (2H,4H) - isoquinolin - 2 - yl] - 2 - [4 - (2 - methoxy - phenyl) - piperazin - 1 - yl] - ethane hydrochloride.

Prepared analogously to Example 1 from 1,2,3,4 - tetrahydro - 6,7 - dimethoxy - 4,4 - dimethyl - isochroman - 1,3 - dione and 2 - [4 - (2 - methoxyphenyl) - piperazin - 1 - yl] - ethylamine.

Recrystallization from ethanol: m.p.: 264 to 265°C.

Example 6.

1 - [4,4 - Dimethyl - 1,3 - dioxo - (2H,4H) - isoquinolin - 2 - yl] - 3 - (4 - pyridyl - (2)) - piperazin - 1 - yl] - propane dihydrochloride.

Prepared analogously to Example 1 from 1,2,3,4 - tetrahydro - 4,4 - dimethyl - isochroman - 1,3 - dione and 3 - [4 - (pyridyl - (2)) - piperazin - 1 - yl] - propylamine as starting material.

Precipitation from toluene solution with ethereal hydrochloric acid and crystallization from acetone.

M.p. of the dihydrochloride: 176 to 178°C.

Example 7.

1 - [4,4 - Dimethyl - 1,3 - dioxo - (2H,4H) - isoquinolin - 2 - yl] - 2 - [4 - (2 - methoxy - phenyl) - piperazin - 1 - yl] - ethane dihydrochloride.

Prepared analogously to Example 1 from 1,2,3,4 - tetrahydro - 4,4 - dimethyl - isochroman - 1,3 - dione and 2 - [4 - (2 - methoxyphenyl) - piperazin - 1 - yl] - ethylamine as starting material.

The dihydrochloride was directly precipitated from toluene-solution with ethereal hydrochloric acid.

M.p.: 215 to 217°C.

Example 8.

1 - [4,4 - Dimethyl - 1,3 - dioxo - (2H,4H) - isoquinolin - 2 - yl] - 2 - [4 - (2 - methoxy - phenyl) - piperazin - 1 - yl] - ethane dihydrochloride.

5 g of 2 - (2 - chloroethyl) - 4,4 - dimethyl - 1,2,3,4 - tetrahydro - isoquinolin - 1,3 - dione and 5.3 g of 1 - (2 - methoxyphenyl) - piperazine dihydrochloride were heated in 50 ml of ethylene glycol together with 6.75 g of potassium tert.-butoxide at 180°C for 4 hours. Subsequently, the mixture was cooled, diluted with water and extracted with chloroform. The chloroform extracts were washed with water, dried and evaporated. The residue was purified by column chromatography on silica gel with

chloroform/methanol = 95:5 as eluant. The fraction containing the desired product was isolated and evaporated. The residue was dissolved in isopropanol and the dihydrochloride was precipitated with ethereal hydrochloric acid.

Recrystallization from isopropanol: m.p. 215 to 217°C.

Example 9.

10 1 - [4,4 - Dimethyl - 7 - methoxy - 1,3-dioxo - (2H,4H) - isoquinolin - 2 - yl] - 2 - [4 - (2 - methoxyphenyl) - piperazin - 1 - yl] - ethane dihydrochloride.

Prepared analogously to Example 8 from 15 2 - (2 - chloroethyl) - 4,4 - dimethyl - 7-methoxy - 1,2,3,4 - tetrahydro - isoquinolin - 1,3 - dione and 1 - (2 - methoxyphenyl) - piperazine dihydrochloride.

Recrystallization from isopropanol: m.p. 211 to 213°C.

Example 10.

25 1 - [4,4 - Dimethyl - 7 - methoxy - 1,3 - dioxo - (2H,4H) - isoquinolin - 2 - yl] - 3 - [4 - (2 - methoxyphenyl) - piperazin - 1 - yl] - propane dihydrochloride.

Prepared analogously to Example 8 from 30 2 - (3 - chloropropyl) - 4,4 - dimethyl - 7-methoxy - 1,2,3,4 - tetrahydro - isoquinolin - 1,3 - dione and 1 - (2 - methoxyphenyl) - piperazine dihydrochloride.

Recrystallization from ethanol: m.p.: 195 to 200°C.

Example 11.

35 1 - [4,4 - Dimethyl - 1,3 - dioxo - (2H,4H) - isoquinolin - 2 - yl] - 2 - (4 - phenyl - 3-methyl - piperazin - 1 - yl) - ethane dihydrochloride.

Prepared analogously to Example 8 from 40 2 - (2 - chloroethyl) - 4,4 - dimethyl - 1,2,3,4-tetrahydro - isoquinolin - 1,3 - dione (1,3) and 1 - phenyl - 2 - methyl - piperazine but in the absence of potassium tert. - butoxide. Recrystallization from isopropanol: m.p.: 196°C (decomp.).

Example 12.

45 1 - [4,4 - Dimethyl - 1,3 - dioxo - (2H,4H) - isoquinolin - 2 - yl] - 2 - [4 - (4 - methoxyphenyl) - piperazin - 1 - yl] - ethane dihydrochloride.

Prepared analogously to Example 8 from 50 2 - (2 - chloroethyl) - 4,4 - dimethyl - 1,2,3,4-tetrahydro - isoquinolin - 1,3 - dione and 1 - (4 - methoxyphenyl) - piperazine but in the absence of potassium tert.-butoxide.

Recrystallization from isopropanol: decomposition above 228°C.

Example 13.

60 1 - [4,4 - Dimethyl - 1,3 - dioxo - (2H,4H) - isoquinolin - 2 - yl] - 2 - [4 - (4 - chlorophenyl) - piperazin - 1 - yl] - ethane dihydrochloride.

Prepared analogously to Example 8 from

2 - (2 - chloroethyl) - 4,4 - dimethyl - 1,2,3,4-tetrahydro - isoquinolin - 1,3 - dione and 1 - (4 - chlorophenyl) - piperazine dihydrochloride. 65

Recrystallization from isopropanol: decomposition above 135°C.

Example 14.

1 - [4,4 - Dimethyl - 1,3 - dioxo - (2H,4H) - isoquinolin - 2 - yl] - 2 - [4 - (3 - trifluoromethyl - phenyl) - piperazin - 1 - yl] - ethane hydrochloride. 70

Prepared analogously to Example 8 from 75 2 - (2 - chloroethyl) - 4,4 - dimethyl - 1,2,3,4-tetrahydro - isoquinolin - 1,3 - dione and 1 - (3 - trifluoromethyl - phenyl) - piperazine with an equimolar quantity of potassium tert.-butoxide.

Recrystallization from isopropanol: m.p.: 230°C. 80

Example 15.

1 - [4,4 - Dimethyl - 1,3 - dioxo - (2H,4H) - isoquinolin - 2 - yl] - 2 - [4 - (2,6 - dimethyl - phenyl) - piperazin - 1 - yl] - ethane hydrochloride. 85

Prepared analogously to Example 8 from 90 2 - (2 - chloroethyl) - 4,4 - dimethyl - 1,2,3,4-tetrahydro - isoquinolin - 1,3 - dione and 1 - (2,6 - dimethyl - phenyl) - piperazine with an equimolar quantity of potassium tert.-butoxide.

Recrystallization from isopropanol/ether: decomposition above 230°C.

Example 16.

1 - [4,4 - Dimethyl - 1,3 - dioxo - (2H,4H) - isoquinolin - 2 - yl] - 2 - [4 - (2 - chlorophenyl) - piperazin - 1 - yl] - ethane hydrochloride. 95

Prepared analogously to Example 8 from 100 2 - (2 - chloroethyl) - 4,4 - dimethyl - 1,2,3,4-tetrahydro - isoquinolin - 1,3 - dione and 1 - (2 - chlorophenyl) - piperazine hydrochloride hydrate with 2 equivalents of potassium tert.-butoxide.

Recrystallization from isopropanol/ether: m.p.: 228°C. 105

Example 17.

1 - [4,4 - Dimethyl - 1,3 - dioxo - (2H,4H) - isoquinolin - 2 - yl] - 3 - [4 - (trifluoromethyl - phenyl) - piperazin - 1 - yl] - propane hydrochloride. 110

Prepared analogously to Example 8 from 115 2 - (3 - chloropropyl) - 4,4 - dimethyl - 1,2,3,4 - tetrahydro - isoquinolin - 1,3 - dione and 1 - (3 - trifluoromethyl - phenyl) - piperazine with one equivalent of potassium tert.-butoxide.

Crystallization from methanol/ethereal hydrochloric acid: m.p.: 215 to 220°C. 120

Example 18.

1 - [4,4 - Dimethyl - 1,3 - dioxo - (2H,4H) - isoquinolin - 2 - yl] - 2 - [4 - (3,4 - dimethoxy - phenyl) - piperazin - 1 - yl] - ethane dihydrochloride.

Prepared analogously to Example 8 from 2 - (2 - chloroethyl) - 4,4 - dimethyl - 1,2,3,4 - tetrahydro - isoquinolin - 1,3 - dione and 1 - (3,4 - dimethoxy - phenyl) - piperazine with one equivalent of potassium tert.-butoxide. Crystallization from methanol/etheral hydrochloric acid: decomposition above 158°C.

Example 19.

1 - [4,4 - Dimethyl - 1,3 - dioxo - (2H,4H) - isoquinolin - 2 - yl] - 2 - [4 - (2 - methylphenyl) - piperazin - 1 - yl] - ethane hydrochloride.

Prepared analogously to Example 8 from 2 - (2 - chloroethyl) - 4,4 - dimethyl - 1,2,3,4 - tetrahydro - isoquinolin - 1,3 - dione and 1 - (2 - methylphenyl) - piperazine dihydrochloride. Recrystallization from isopropanol/ether: decomposition above 247°C.

Example 20.

1 - [4,4 - Dimethyl - 1,3 - dioxo - (2H,4H) - isoquinolin - 2 - yl] - 2 - [4 - (2 - ethylphenyl) - piperazin - 1 - yl] - ethane dihydrochloride.

Prepared analogously to Example 8 from 2 - (2 - chloroethyl) - 4,4 - dimethyl - 1,2,3,4 - tetrahydro - isoquinolin - 1,3 - dione and 1 - (2 - ethyl - phenyl) - piperazine with an equimolar quantity of potassium tert.-butoxide. Recrystallization from methanol/ether: m.p.: 188 to 192°C.

Example 21.

1 - [4,4 - Dimethyl - 6,7 - dimethoxy - 1,3 - dioxo - (2H,4H) - isoquinolin - 2 - yl] - 3 - [4 - (2 - methoxyphenyl) - piperazin - 1 - yl] - propane hydrochloride.

Prepared analogously to Example 8 from 2 - (3 - chloropropyl) - 4,4 - dimethyl - 6,7 - dimethoxy - 1,2,3,4 - tetrahydro - isoquinolin - 1,3 - dione and 1 - (2 - methoxyphenyl) - piperazine dihydrochloride. Recrystallization from methanol/ether: m.p.: 198 to 202°C (decomp.).

Example 22.

1 - [4,4 - Dimethyl - 1,3 - dioxo - (2H,4H) - isoquinolin - 2 - yl] - 3 - [4 - (2 - methoxyphenyl) - piperazin - 1 - yl] - propane hydrochloride.

Prepared analogously to Example 8 from 2 - (3 - chloropropyl) - 4,4 - dimethyl - 1,2,3,4 - tetrahydro - isoquinolin - 1,3 - dione and 1 - (2 - methoxy - phenyl) - piperazine dihydrochloride. Recrystallization from ethanol: m.p.: 235 to 237°C.

Example 23.

1 - [4,4 - Dimethyl - 7 - methoxy - 1,3 - dioxo - (2H,4H) - isoquinolin - 2 - yl] - 3 - [4 - (pyridyl - (2)) - piperazin - 1 - yl] - propane dihydrochloride.

Prepared analogously to Example 8 from 2 - (3 - chloropropyl) - 4,4 - dimethyl - 7 - methoxy - 1,2,3,4 - tetrahydro - isoquinolin - 1,3 - dione and 1 - [pyridyl - (2)] - piperazine with an equimolar quantity of potassium tert. butoxide.

Precipitation with ethereal hydrochloric acid: m.p.: 193 to 196°C.

Example 24.

1 - [4,4 - Dimethyl - 7 - methoxy - 1,3 - dioxo - (2H,4H) - isoquinolin - 2 - yl] - 3 - [4 - (6 - methyl - pyridyl - (2)) - piperazin - 1 - yl] - propane dihydrochloride.

Prepared analogously to Example 8 from 2 - (3 - chloropropyl) - 4,4 - dimethyl - 7 - methoxy - 1,2,3,4 - tetrahydro - isoquinolin - 1,3 - dione and 1 - [6 - methyl - pyridyl - (2)] - piperazine with an equimolar quantity of potassium tert.-butoxide.

Recrystallization from ethanol/ether: m.p.: 172 to 176°C.

Example 25.

1 - [4,4 - Dimethyl - 1,3 - dioxo - (2H,4H) - isoquinolin - 2 - yl] - 3 - [4 - (6 - methylpyridyl - (2)) - piperazin - 1 - yl] - propane hydrochloride.

Prepared analogously to Example 8 from 2 - (3 - chloropropyl) - 4,4 - dimethyl - 1,2,3,4 - tetrahydro - isoquinolin - 1,3 - dione and 1 - [6 - methyl - pyridyl - (2)] - piperazine with an equimolar quantity of potassium tert.-butoxide.

Crystallization from methanol/etheral hydrochloric acid: decomposition above 88°C.

Example 26.

1 - [4,4 - Dimethyl - 1,3 - dioxo - (2H,4H) - isoquinolin - 2 - yl] - 3 - [4 - (phenyl - piperazin - 1 - yl) - propane hydrochloride.

4.9 g of 3 - (4 - phenyl - piperazin - 1 - yl) propyl chloride hydrochloride were dissolved in the minimum quantity of water and vigorously shaken with a mixture of 100 ml of saturated potassium carbonate solution and 100 ml of toluene. The toluene layer which separated was dried over magnesium sulfate. The toluene solution obtained after filtration was added dropwise to a solution of 3.8 g of 1,2,3,4 - tetrahydro - 4,4 - dimethyl - 1,3 - dioxo - (2H,4H) - isoquinoline and 2.6 g of potassium tert. - butoxide in 100 ml of dimethylformamide at 70°C within one hour. Subsequently the mixture was stirred for a further 2 hours at this temperature. After removing the solvent, the residue was mixed with water, extracted several times with ether and the ether extracts were dried over

anhydrous calcium chloride and filtered. Ethereal hydrochloric acid was added, and the precipitate was recrystallized from isopropanol. M.p.: 235 to 238°C (decomp.).

Example 27.

1 - [4,4 - Dimethyl - 7 - methoxy - 1,3 - dioxo - (2H,4H) - isoquinolin - 2 - yl] - 2 - [2 - (3,4 - dimethoxy - phenyl) - ethylamino] - ethane hydrochloride.

8.5 g of 2 - (2 - chloroethyl) - 4,4 - dimethyl - 7 - methoxy - 1,2,3,4 - tetrahydro - isoquinolin - 1,3 - dione and 13.6 g of 3,4 - dimethoxyphenylethylamine were heated for 4 hours on a bath at a temperature of 180°C. Subsequently water was added. The mixture was extracted with chloroform and the chloroform extracts were washed with water, dried and evaporated. The mixture was then purified by column chromatography (silica gel column, chloroform/methanol = 95/5). The fraction containing the desired product was isolated and the hydrochloride was precipitated with ethereal hydrochloric acid.

Recrystallization from ethanol: m.p.: 263 to 265°C.

Example 28.

1 - [4,4 - Dimethyl - 1,3 - dioxo - (2H,4H) - isoquinolin - 2 - yl] - 2 - [2 - (3,4 - dimethoxy - phenyl) - ethylamino] - ethane hydrochloride.

Prepared analogously to Example 27 from 2 - (2 - chloroethyl) - 4,4 - dimethyl - 1,2,3,4 - tetrahydro - isoquinolin - 1,3 - dione and 3,4 - dimethoxy - phenyl - ethylamine as starting materials.

Recrystallization from ethanol: m.p.: 148 to 151°C.

Example 29.

1 - [4,4 - Dimethyl - 7 - methoxy - 1,3 - dioxo - (2H,4H) - isoquinolin - 2 - yl] - 2 - [N - methyl - 2 - (3,4 - dimethoxy - phenyl) - ethylamino] - ethane hydrochloride.

Prepared analogously to Example 27 from N - methyl - 2 - (3,4 - dimethoxyphenyl) - ethylamine and 2 - (2 - chloroethyl) - 4,4 - dimethyl - 7 - methoxy - 1,2,3,4 - tetrahydro - isoquinolin - 1,3 - dione as starting materials. M.p.: 138 to 140°C.

Example 30.

1 - [4,4 - Dimethyl - 1,3 - dioxo - (2H,4H) - isoquinolin - 2 - yl] - 3 - [N - methyl - 2 - (3,4 - dimethoxy - phenyl) - ethylamino] - propane.

Prepared analogously to Example 27 from 2 - (3 - chloropropyl) - 4,4 - dimethyl - 1,2,3,4 - tetrahydro - isoquinolin - 1,3 - dione and N - methyl - 2 - (3,4 - dimethoxyphenyl) - ethylamine as starting materials. Isolation as free base: sticky oil.

Example 31.

1 - [4,4 - Dimethyl - 7 - methoxy - 1,3 - dioxo - (2H,4H) - isoquinolin - 2 - yl] - 3 - [N - methyl - 2 - (3,4 - dimethoxy - phenyl) - ethylamino] - propane.

Prepared analogously to Example 30 from 2 - (3 - chloropropyl) - 4,4 - dimethyl - 7 - methoxy - 1,2,3,4 - tetrahydro - isoquinolin - 1,3 - dione and N - methyl - 2 - (3,4 - dimethoxyphenyl) - ethylamine as starting materials. Isolation as free base: sticky oil.

Example 32.

1 - [4,4 - Dimethyl - 7 - methoxy - 1,3 - dioxo - (2H,4H) - isoquinolin - 2 - yl] - 3 - [2 - (3,4,5 - trimethoxy - phenyl) - ethylamino] - propane hydrochloride.

Prepared analogously to Example 27 from 2 - (3,4,5 - trimethoxy - phenyl) - ethylamine and 2 - (3 - chloropropyl) - 4,4 - dimethyl - 7 - methoxy - 1,2,3,4 - tetrahydro - isoquinolin - 1,3 - dione as starting materials. Recrystallization from isopropanol: m.p.: 157 to 159°C.

Example 33.

1 - [4,4 - Dimethyl - 7 - methoxy - 1,3 - dioxo - (2H,4H) - isoquinolin - 2 - yl] - 3 - [2 - (4 - methoxy - phenyl) - ethylamino] - propane hydrochloride.

Prepared analogously to Example 27 from 2 - (3 - chloropropyl) - 4,4 - dimethyl - 7 - methoxy - 1,2,3,4 - tetrahydro - isoquinolin - 1,3 - dione and 2 - (4 - methoxyphenyl) - ethylamine.

Recrystallization from isopropanol: m.p.: 175 to 176°C.

Example 34.

1 - [4,4 - Dimethyl - 1,3 - dioxo - (2H,4H) - isoquinolin - 2 - yl] - 3 - [2 - (3,4 - dimethoxyphenyl) - ethylamino] - propane hydrochloride.

Prepared analogously to Example 27 from 2 - (3 - chloropropyl) - 4,4 - dimethyl - 1,2,3,4 - tetrahydro - isoquinolin - 1,3 - dione and 2 - (3,4 - dimethoxy - phenyl) - ethylamine.

Recrystallization from isopropanol: m.p.: 162 to 165°C.

Example 35.

1 - [4,4 - Dimethyl - 7 - methoxy - 1,3 - dioxo - (2H,4H) - isoquinolin - 2 - yl] - 3 - [2 - (3,4 - dimethoxy - phenyl) - ethylamino] - propane hydrochloride.

a) 2 - [2 - (3,4 - Dimethoxy - phenyl) - ethylamine] - 1 - cyano - ethane.

54.5 g of 2 - (3,4 - dimethoxy - phenyl) - ethylamine were dissolved in 100 ml of methanol, 16.2 g of acrylonitrile dissolved in 50 ml of methanol were added dropwise at 50°C and the mixture was stirred for 1 hour at 50°C. After evaporation, the crude

16

product thus obtained was processed without further purification.

b) 1 - [2 - (3,4 - Dimethoxy - phenyl) - ethylamino] - 3 - amino - propane.

70.3 g of the crude product obtained according to Example 35a was dissolved in 1.3 l of methanolic ammonia and hydrogenated in an autoclave in the presence of Raney nickel as catalyst at 80°C and 50 atmospheres pressure.

B.p. 1 mm = 168 to 173°C.

c) 1 - [4,4 - Dimethyl - 7 - methoxy - 1,3-dioxo - (2H,4H) - isoquinolin - 2 - yl] - 3 - [2 - (3,4 - dimethoxy - phenyl) - ethylamino] - propane hydrochloride.

13.2 g of 4,4 - dimethyl - 7 - methoxy - 1,2,3,4 - tetrahydro - isochroman - 1,3-dione and 14.3 g of 1 - [2 - (3,4 - dimethoxy - phenyl) - ethylamino] - 3 - amino - propane were refluxed in 250 ml of toluene for 5 hours in an apparatus incorporating a water separator. After cooling, the hydrochloride was precipitated with ethereal hydrochloric acid, and the oily product was recrystallized from ethanol.

M.p.: 191 to 193°C.

Example 36.

1 - [4,4 - Dimethyl - 6,7 - dimethoxy - 1,3-dioxo - (2H,4H) - isoquinolin - 2 - yl] - 3 - [2 - (3,4 - dimethoxy - phenyl) - ethylamino] - propane hydrochloride.

Prepared analogously to Example 35 from 4,4 - dimethyl - 6,7 - dimethoxy - 1,2,3,4-tetrahydro - isochroman - 1,3 - dione and 1 - [2 - (3,4 - dimethoxyphenyl) - ethylamino] - 3 - amino - propane as starting materials.

Recrystallization from ethyl acetate: m.p.: 98 to 101°C.

Example 37.

1 - [4,4 - Dimethyl - 6,7 - dimethoxy - 1,3-dioxo - (2H,4H) - isoquinolin - 2 - yl] - 3 - [N - methyl - 2 - (3,4 - dimethoxyphenyl) - ethylamino] - propane hydrochloride.

Prepared analogously to Example 35 from 4,4 - dimethyl - 6,7 - dimethoxy - 1,2,3,4-tetrahydro - isochroman - 1,3 - dione and 1 - [N - methyl - 2 - (3,4 - dimethoxyphenyl) - ethylamino] - 3 - amino - propane. M.P.: 167 to 168°C.

Example 38.

1 - [4,4 - Dimethyl - 7 - methylmercapto - 1,3 - dioxo - (2H,4H) - isoquinolin - 2 - yl] - 3 - [2 - (3,4 - dimethoxy - phenyl) - ethylamino] - propane hydrochloride.

Prepared analogously to Example 35 from 4,4 - dimethyl - 7 - methylmercapto - 1,2,3,4-tetrahydro - isochroman - 1,3 - dione and 1 - [2 - (3,4 - dimethoxy - phenyl) - ethyl-

amino] - 3 - amino - propane as starting materials.

Recrystallization from ethanol: m.p.: 133 to 135°C.

Example 39.

1 - [4,4 - Dimethyl - 7 - chloro - 1,3 - dioxo - (2H,4H) - isoquinolin - 2 - yl] - 3 - [2 - (3,4 - dimethoxy - phenyl) - ethylamino] - propane hydrochloride.

Prepared analogously to Example 35 from 4,4 - dimethyl - 7 - chloro - 1,2,3,4 - tetrahydro - isochroman - 1,3 - dione and 1 - [2 - (3,4 - dimethoxy - phenyl) - ethylamino] - 3 - amino - propane as starting materials.

Recrystallization from ethanol: m.p.: 222 to 226°C.

Example 40.

Tablets containing 100 mg of 1 - [4,4 - dimethyl - 7 - methoxy - 1,3 - dioxo - (2H,4H) - isoquinolin - 2 - yl] - 3 - [2 - (3,4 - dimethoxy - phenyl) - ethylamino] - propane hydrochloride.

Composition:

Active ingredient	100.0 mg
lactose	50.0 mg
polyvinyl pyrrolidone	5.0 mg
carboxymethylcellulose	19.0 mg
magnesium stearate	1.0 mg
	175.0 mg

Method of preparation:

The active ingredient and lactose were homogeneously moistened with the aqueous PVP solution and granulated. After drying, the granulate was admixed with the remaining auxiliary products and pressed into tablets.

Example 41.

Tablets containing 100 mg of 1 - [4,4 - dimethyl - 1,3 - dioxo - (2H,4H) - isoquinolin - 2 - yl] - 2 - [4 - phenylpiperazin - 1 - yl] - ethane hydrochloride.

Composition:

Active ingredient	100.0 mg
lactose	50.0 mg
polyvinyl pyrrolidone	5.0 mg
carboxymethylcellulose	19.0 mg
magnesium stearate	1.0 mg
	175.0 mg

Method of preparation:

The active ingredient and lactose were homogeneously moistened with the aqueous PVP solution and granulated. After drying, the granulate was admixed with the remaining auxiliary products and pressed into tablets.

Example 42.

Coated tablets containing 50 mg of 1 - [4,4-dimethyl - 1,3 - dioxo - (2H,4H) - isoquinolin - 2 - yl] - 2 - [4 - (2 - chlorophenyl) - piperazin - 1 - yl] - ethane hydrochloride.

1 coated tablet core contains:

Active ingredient	50.0 mg
Dried corn starch	20.0 mg
Soluble starch	2.0 mg
Carboxymethylcellulose	7.0 mg
Magnesium stearate	1.0 mg
	80.0 mg

Method of preparation:

- 15 The coated tablet cores were prepared as described in Example 41 and coated with sugar and gum arabic.

Example 43.

- 20 Suppositories containing 150 mg of 1 - [4,4-dimethyl - 1,3 - dioxo - (2H,4H) - isoquinolin - 2 - yl] - 3 - [4 - (6 - methylpyridyl - (2)) - piperazin - 1 - yl] - propane hydrochloride.

Composition:

25 Active ingredient	150.0 mg
suppository mass	1 550.0 mg
	1 700.0 mg

Method of preparation:

- 30 The active ingredient was homogeneously dispersed in the molten suppository mass. The liquid mixture was poured into cooled suppository moulds.

Example 44.

- 35 Suspension containing 250 mg of 1 - [4,4-dimethyl - 1,3 - dioxo - (2H,4H) - isoquinolin - 2 - yl] - 2 - [4 - (2 - methylphenyl) - piperazin - 1 - yl] - ethane hydrochloride per 5 ml.

100 ml of suspension contain:

40 Active ingredient	5.0 g
carboxymethylcellulose	0.1 g
methyl p-hydroxybenzoate	0.05 g
propyl p-hydroxybenzoate	0.01 g
sugar	10.0 g
45 glycerine	5.0 g
sorbit solution 70%	20.0 g
aroma (cocoa essence)	0.3 g
distilled water	ad 100.0 ml

Method of preparation:

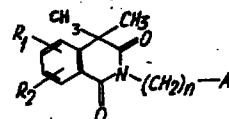
- 50 The distilled water was heated to 70°C and the methyl and propyl p-hydroxybenzoates, the glycerine and carboxymethylcellulose were dissolved therein whilst stirring. The solution was cooled to room temperature and the active ingredient was added whilst stirring. The solu-

tion was then made homogeneous. After addition of the sugar, sorbit solution and aroma, the suspension was de-aerated whilst stirring.

5 ml of the suspension contain 250 mg of 1 - [4,4 - dimethyl - 1,3 - dioxo - (2H,4H) - isoquinolin - 2 - yl] - 2 - [4 - (2 - methylphenyl) - piperazin - 1 - yl] - ethane hydrochloride.

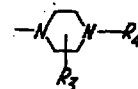
WHAT WE CLAIM IS:—

1. Compounds of general formula

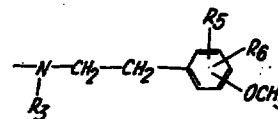


(I)

(wherein R₁ represents a hydrogen or halogen atom or a methoxy or methylmercapto group, R₂ represents a hydrogen atom or a methoxy group, n represents the number 2 or 3, and A represents a group of formula



or a group of formula



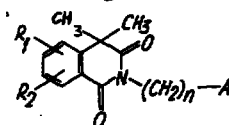
(wherein R₃ represents a hydrogen atom or a methyl group, R₄ represents a pyridyl group optionally substituted by a methyl group, or a phenyl group optionally substituted by a chlorine atom, by a trifluoromethyl group or by one or two methyl, ethyl or methoxy groups, and R₅ and R₆, which may be the same or different, each represents a hydrogen atom or a methoxy group)) and acid addition salts thereof.

2. 1 - [4,4 - Dimethyl - 1,3 - dioxo - (2H,4H) - isoquinolin - 2 - yl] - 2 - [4 - (2-methoxy - phenyl) - piperazin - 1 - yl]ethane and physiologically compatible acid addition salts thereof.

3. 1 - [4,4 - Dimethyl - 7 - methoxy - 1,3-dioxo - (2H,4H) - isoquinolin - 2 - yl] - 3 - [2 - (3,4 - dimethoxy - phenyl) - ethylamino]-propane and physiologically compatible acid addition salts thereof.

4. Compounds of general formula I as defined in claim 1 and acid addition salts thereof as herein specifically disclosed other than those claimed in claim 2 and 3.

5. Compounds of general formula



(I)

100

Example 42.

Coated tablets containing 50 mg of 1 - [4,4-dimethyl - 1,3 - dioxo - (2H,4H) - isoquinolin - 2 - yl] - 2 - [4 - (2 - chlorophenyl) - piperazin - 1 - yl] - ethane hydrochloride.

1 coated tablet core contains:	
Active ingredient	50.0 mg
Dried corn starch	20.0 mg
Soluble starch	2.0 mg
Carboxymethylcellulose	7.0 mg
Magnesium stearate	1.0 mg
	80.0 mg

Method of preparation:

- 15 The coated tablet cores were prepared as described in Example 41 and coated with sugar and gum arabic.

Example 43.

20 Suppositories containing 150 mg of 1 - [4,4-dimethyl - 1,3 - dioxo - (2H,4H) - isoquinolin - 2 - yl] - 3 - [4 - (6 - methylpyridyl - (2)) - piperazin - 1 - yl] - propane hydrochloride.

25 Composition:	
Active ingredient	150.0 mg
suppository mass	1 550.0 mg
	1 700.0 mg

Method of preparation:

- 30 The active ingredient was homogeneously dispersed in the molten suppository mass. The liquid mixture was poured into cooled suppository moulds.

Example 44.

35 Suspension containing 250 mg of 1 - [4,4-dimethyl - 1,3 - dioxo - (2H,4H) - isoquinolin - 2 - yl] - 2 - [4 - (2 - methylphenyl) - piperazin - 1 - yl] - ethane hydrochloride per 5 ml.

100 ml of suspension contain:	
Active ingredient	5.0 g
carboxymethylcellulose	0.1 g
methyl p-hydroxybenzoate	0.05 g
propyl p-hydroxybenzoate	0.01 g
sugar	10.0 g
glycerine	5.0 g
sorbit solution 70%	20.0 g
aroma (cocoa essence)	0.3 g
distilled water ad	100.0 ml

Method of preparation:

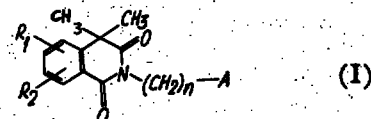
- 50 The distilled water was heated to 70°C and the methyl and propyl p-hydroxybenzoates, the glycerine and carboxymethylcellulose were dissolved therein whilst stirring. The solution was cooled to room temperature and the active ingredient was added whilst stirring. The solu-

tion was then made homogeneous. After addition of the sugar, sorbit solution and aroma, the suspension was de-aerated whilst stirring.

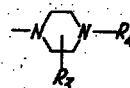
5 ml of the suspension contain 250 mg of 1 - [4,4 - dimethyl - 1,3 - dioxo - (2H,4H) - isoquinolin - 2 - yl] - 2 - [4 - (2 - methylphenyl) - piperazin - 1 - yl] - ethane hydrochloride.

WHAT WE CLAIM IS:—

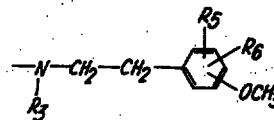
1. Compounds of general formula



(wherein R₁ represents a hydrogen or halogen atom or a methoxy or methylmercapto group, R₂ represents a hydrogen atom or a methoxy group, n represents the number 2 or 3, and A represents a group of formula



or a group of formula



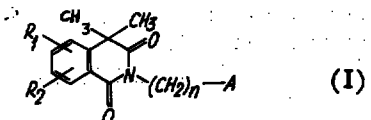
(wherein R₃ represents a hydrogen atom or a methyl group, R₄ represents a pyridyl group optionally substituted by a methyl group, or a phenyl group optionally substituted by a chlorine atom, by a trifluoromethyl group or by one or two methyl, ethyl or methoxy groups, and R₅ and R₆, which may be the same or different, each represents a hydrogen atom or a methoxy group)) and acid addition salts thereof.

2. 1 - [4,4 - Dimethyl - 1,3 - dioxo - (2H,4H) - isoquinolin - 2 - yl] - 2 - [4 - (2-methoxy - phenyl) - piperazin - 1 - yl]ethane and physiologically compatible acid addition salts thereof.

3. 1 - [4,4 - Dimethyl - 7 - methoxy - 1,3-dioxo - (2H,4H) - isoquinolin - 2 - yl] - 3 - [2 - (3,4 - dimethoxy - phenyl) - ethyl-amino]-propane and physiologically compatible acid addition salts thereof.

4. Compounds of general formula I as defined in claim 1 and acid addition salts thereof as herein specifically disclosed other than those claimed in claim 2 and 3.

5. Compounds of general formula



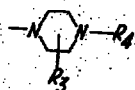
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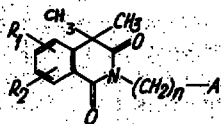
(wherein R_1 represents a hydrogen, fluorine or chlorine atom or a methoxy group, R_2 represents a hydrogen atom or a methoxy group, and A represents a group of formula



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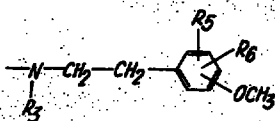
(wherein R_3 represents a hydrogen atom or a methyl group and R_4 represents a pyridyl group optionally substituted by a methyl group or a phenyl group optionally substituted by a chlorine atom, a trifluoromethyl group or by one or two methyl, ethyl or methoxy groups), and n represents the number 2 or 3) and acid addition salts thereof.

6. Compounds of general formula



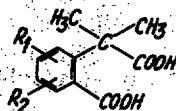
(I)

(wherein R_1 represents a hydrogen or chlorine atom or a methoxy or methylmercapto group, R_2 represents a hydrogen atom or a methoxy group, A represents a group of formula



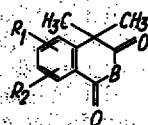
(wherein R_3 represents a hydrogen atom or a methyl group, and R_5 and R_6 , which may be the same or different, each represents a hydrogen atom or a methoxy group) and n represents the number 2 or 3) and acid addition salts thereof.

7. A process for the preparation of compounds of general formula I as defined in claim 1 which comprises reacting a compound of formula



(II)

or a compound of formula



(IIa)

(wherein R_1 and R_2 are as defined in claim 1 and B represents an oxygen atom or an optionally substituted secondary amino group) with a compound of formula



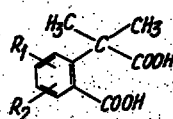
(III)

(wherein A and n are defined as in claim 1) or with an acid addition salt thereof.

8. A process as claimed in claim 7 wherein the reaction is effected in the presence of an organic solvent.

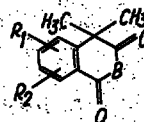
9. A process as claimed in claim 8 wherein the reaction is effected at temperatures from 0°C up to the boiling temperature of the solvent used.

10. A process for the preparation of compounds of general formula I as defined in claim 5 which comprises reacting a compound of formula



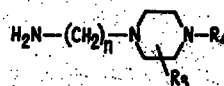
(II)

(wherein R_1 and R_2 are as defined in claim 5) or a compound of formula



(IIa)

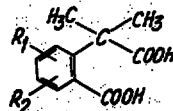
(wherein R_1 and R_2 are as defined in claim 5 and B represents an oxygen atom or an optionally substituted secondary amino group) with a compound of formula



(IIIa)

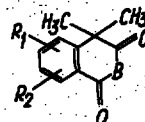
(wherein R_3 , R_4 and n are as defined in claim 5) or with an acid addition salt thereof.

11. A process for the preparation of compounds of general formula I as defined in claim 6 which comprises reacting a compound of formula



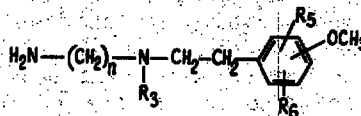
(II)

(wherein R_1 and R_2 are as defined in claim 6) or a compound of formula



(IIa)

(wherein R_1 and R_2 are as defined in claim 6 and B represents an oxygen atom or an optionally substituted secondary amino group) with a compound of formula



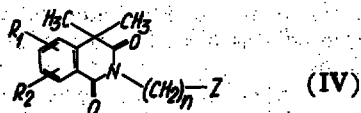
(IIIb)



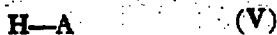
* C L M S *

(wherein R_1 , R_2 , R_3 and n are as defined in claim 6) or with an acid addition salt thereof.

12. A process for the preparation of compounds of general formula I as defined in claim 1 which comprises reacting a compound of formula



(wherein R_1 , R_2 and n are as defined in claim 1 and Z represents a group exchangeable with the group A as defined in claim 1) with a compound of formula



(wherein A is as defined in claim 1).

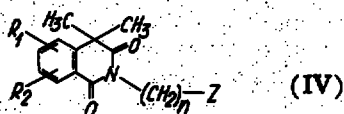
13. A process as claimed in claim 12 wherein the group Z in the compound of formula IV represents a chlorine, bromine or iodine atom or an alkylsulfonyloxy or arylsulfonyloxy group.

14. A process as claimed in claim 12 or claim 13 wherein the reaction is effected in the presence of a solvent.

15. A process as claimed in any of claims 12 to 14 wherein the reaction is effected at temperatures from -50 to $250^\circ C$.

16. A process as claimed in any of claims 12 to 15 wherein the reaction is effected in the presence of an acid binding agent.

17. A process for the preparation of compounds of general formula I as defined in claim 5 which comprises reacting a compound of formula

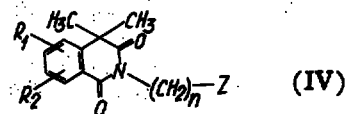


(wherein R_1 , R_2 and n are as defined in claim 5 and Z represents a group exchangeable with the group A as defined in claim 5) with a compound of formula

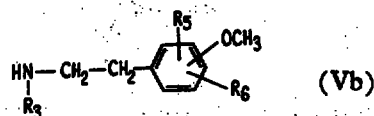


(wherein R_3 and R_4 are as defined in claim 5).

18. A process for the preparation of compounds of general formula I as defined in claim 6 which comprises reacting a compound of formula

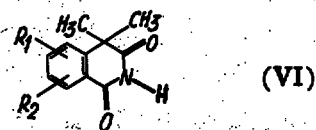


(wherein R_1 , R_2 and n are as defined in claim 6 and Z represents a group exchangeable with the group A as defined in claim 6) with a compound of formula



(wherein R_1 , R_2 and R_6 are as defined in claim 6).

19. A process for the preparation of compounds of general formula I as defined in claim 1 which comprises reacting a compound of formula



(wherein R_1 and R_2 are as defined in claim 1) or a metal salt thereof with a compound of formula



(wherein A and n are as defined in claim 1 and Z represents a group exchangeable with the group A as defined in claim 1).

20. A process as claimed in claim 19 wherein an alkali metal salt of a compound of formula VI is reacted with a compound of formula VII.

21. A process as claimed in claim 19 or claim 20 wherein Z in the compound of formula VII represents a chlorine, bromine or iodine atom or an alkylsulfonyloxy or arylsulfonyloxy group.

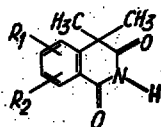
22. A process as claimed in any of claims 19 to 21 wherein the reaction is effected in the presence of an acid binding agent.

23. A process as claimed in any of claims 19 to 22 wherein the reaction is effected in the presence of a solvent.

24. A process as claimed in claim 23 wherein the reaction is effected at temperatures from $0^\circ C$ up to the boiling temperature of the solvent used.

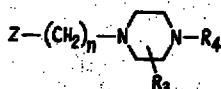
25. A process for the preparation of compounds of general formula I as defined in claim 5 which comprises reacting a compound of formula





(VI)

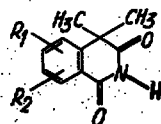
(wherein R_1 and R_2 are as defined in claim 5) or a metal salt thereof with a compound of formula



(VIIa)

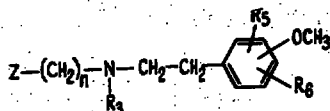
(wherein R_3 , R_4 and n are as defined in claim 5 and Z represents a group exchangeable with the group A as defined in claim 5).

26. A process for the preparation of compounds of general formula I as defined in claim 6 which comprises reacting a compound of formula



(VI)

(wherein R_1 and R_2 are as defined in claim 6) or a metal salt thereof with a compound of formula



(VIIb)

(wherein R_5 , R_6 and n are as defined in claim 6 and Z represents a group exchangeable with the group A as defined in claim 6).

27. A process for the preparation of acid addition salts of compounds of general formula I as defined in claim 1 which comprises converting a compound of formula I as defined in claim 1 into an acid addition salt thereof.

28. A process for the preparation of compounds of general formula I as defined in claim 1 and acid addition salts thereof substantially as herein described.

29. A process for the preparation of compounds of general formula I as defined in claim 5 and acid addition salts thereof substantially as herein described.

30. A process for the preparation of compounds of general formula I as defined in claim 6 and acid addition salts thereof substantially as herein described.

31. A process for the preparation of compounds of general formula I as defined in claim 1 and acid addition salts thereof substantially as herein described in Examples 1 to 39.

32. A process for the preparation of compounds of general formula I as defined in claim 5 and acid addition salts thereof substantially as herein described in Examples 1 to 26.

33. A process for the preparation of compounds of general formula I as defined in claim 6 and acid addition salts thereof substantially as herein described in Examples 27 to 39.

34. Compounds of general formula I as defined in claim 1 and acid addition salts thereof whenever prepared by a process as claimed in any of claims 7 to 33.

35. Compounds of general formula I as defined in claim 5 and acid addition salts thereof whenever prepared by a process as claimed in any of claims 10, 17, 25, 29 and 32.

36. Compounds of general formula I as defined in claim 6 and acid addition salts thereof whenever prepared by a process as claimed in any of claims 11, 18, 26, 30 and 33.

37. Pharmaceutical compositions comprising as active ingredient at least one compound of formula I as defined in claim 1 or physiologically compatible acid addition salt thereof in association with a pharmaceutical carrier or excipient.

38. Compositions as claimed in claim 37 in a form suitable for oral, rectal or parenteral administration.

39. Compositions as claimed in claim 38 in the form of tablets, coated tablets, suspensions, solutions, powders, suppositories and ampoules.

40. Compositions as claimed in claim 38 or claim 39 in the form of dosage units.

41. Compositions as claimed in claim 40 wherein each dosage unit contains from 20 to 300 mg of active ingredient.

42. Compositions as claimed in claim 40 wherein each dosage unit contains from 25 to 200 mg of active ingredient.

43. Compositions as claimed in any of claims 37 to 42 which additionally contain a further active ingredient.

44. Compositions as claimed in claim 37 wherein the compound of formula I is as defined in claim 5.

45. Compositions as claimed in claim 37 wherein the compound of formula I is as defined in claim 6.

46. Pharmaceutical compositions according to claim 37 substantially as herein described.

47. Pharmaceutical compositions according to claim 37 substantially as herein described in Examples 40 to 44.

48. Pharmaceutical compositions according to claim 44 substantially as herein described in Examples 41 to 44.

49. Pharmaceutical compositions according to claim 45 substantially as herein described in Example 40.



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