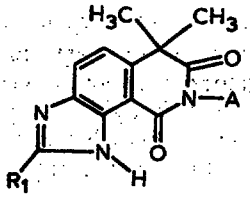
SPECIFICATION

IMIDAZO-ISOQUINOLINE-DIONES

This invention relates to new imidazo-isoquinoline-diones, to processes for their preparation and to pharmaceutical compositions containing them.

Thus, according to one feature of the present invention, there are provided compounds of general formula I,

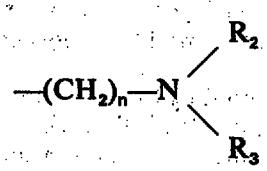


(I)

wherein

R_1 represents a C_{1-4} alkyl group (optionally substituted by a phenyl group), a cycloalkyl group containing from 3 to 6 carbon atoms or a phenyl group (optionally substituted by one or two substituents selected from halogen atoms and hydroxy, methoxy, methylmercapto, methylsulfinyl, methylsulfonyl and benzyloxy groups) and

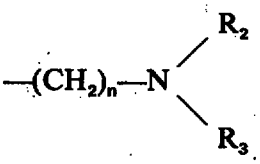
A represents a hydrogen atom or a group of formula



[in which either R_2 represents a hydrogen atom or a C_{1-4} alkyl group and R_3 represents a C_{1-4} alkyl group (optionally substituted by a dimethoxyphenyl group) or R_2 and R_3, together with the nitrogen atom to which they are attached, represent a piperidino, morpholino or 4-(C_{1-4} alkyl)-piperazino group, and n is 2 or 3]

and acid addition salts thereof.

The compounds according to the invention possess interesting pharmacological properties including an anxiolytic and especially a cardiovascular effect. The compounds according to the invention wherein A represents a hydrogen atom in particular show cardiotonic, hypotensive and platelet aggregation inhibitory effects as well as being useful intermediates in the preparation of compounds according to the invention wherein A represents a group of formula



which latter compounds in general possess antiarrhythmic activity.

It will be appreciated that, for pharmaceutical use, the salts referred to above will be physiologically compatible but other acid addition salts may find use, for example, in the preparation of compounds of general formula I and their physiologically compatible acid addition salts.

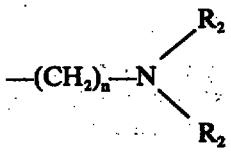
When R_1 represents a phenyl group substituted by a halogen atom, the halogen atom may, for example, be a fluorine, chlorine or bromine atom.

Thus, in the compounds according to the invention, R_1 may, by way of example only, represent a methyl, ethyl, propyl, isopropyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, benzyl, 1-phenylethyl, 1-phenylpropyl, 2-phenylethyl, 2-phenylpropyl, 3-phenylpropyl, 3-phenylprop-2-yl, phenyl, methoxyphenyl, dimethoxyphenyl, chlorophenyl, dichlorophenyl, fluorophenyl, difluorophenyl, hydroxyphenyl dihydroxyphenyl, bromophenyl, dibromophenyl, chloro-bromo-phenyl, methylmercaptophenyl, bismethylmercaptophenyl, methylsulfinylphenyl, bismethylsulfinylphenyl, methylsulfonylphenyl, bismethylsulfonylphenyl, benzyloxyphenyl, dibenzyloxyphenyl, hydroxy-methoxyphenyl, hydroxy-methylmercaptophenyl, hydroxy-methylsulfinylphenyl, hydroxy-methyl-sulfonylphenyl, hydroxy-benzyloxyphenyl, hydroxy-chlorophenyl, hydroxy-bromophenyl, methoxy-methyl-mercaptophenyl, methoxy-methylsulfinylphenyl, methoxy-methylsulfonylphenyl, methoxy-benzyloxyphenyl, methoxy-chlorophenyl, methoxy-fluorophenyl, methoxy-bromophenyl,

methylmercapto-methylsulfinylphenyl, methylmercapto-methylsulfonylphenyl, methylmercapto-benzyloxyphenyl, methylmercapto-chlorophenyl, methylmercapto-bromophenyl, methylsulfinyl-methylsulfonylphenyl, methylsulfinyl-chlorophenyl, methylsulfinyl-bromophenyl, methylsulfinyl-benzyloxyphenyl, methylsulfonyl-chlorophenyl or methylsulfonyl-bromophenyl group.

R_2 may, by way of example only, represent a hydrogen atom or a methyl, ethyl, propyl or isopropyl group and R_3 may, by way of example only, represent a methyl, ethyl, propyl, isopropyl, dimethoxybenzyl, 1-(dimethoxyphenyl)-ethyl, 2-(dimethoxyphenyl)-ethyl, 3-(dimethoxyphenyl)-propyl or 3-(dimethoxyphenyl)-prop-2-yl group or R_2 and R_3, together with the nitrogen atom to which they are attached, may, by way of example only, represent a piperidino, morpholino, N-methyl-piperazino, N-ethyl-piperazino, N-propyl-piperazino or N-isopropyl-piperazino group.

Preferred compounds according to the invention are those wherein R_1 represents a methyl, ethyl, benzyl, 1-phenylethyl, 2-phenylethyl, cyclopropyl, cyclohexyl, 4-chlorophenyl, 2-methoxy-5-methylsulfinylphenyl or 2-methoxy-5-methylsulfonylphenyl group or a phenyl group optionally substituted by one or two substituents in the 2- and/or 4-positions selected from methoxy, hydroxy, methylmercapto, methylsulfinyl, and methylsulfonyl groups and A represents a hydrogen atom or a group of formula

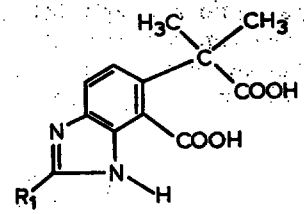


(in which either R_2 represents a hydrogen atom or a methyl, ethyl or propyl group and R_3 represents a methyl, ethyl, propyl or 2-(3,4-dimethoxyphenyl)-ethyl group or R_2 and R_3, together with the nitrogen atom to which they are attached, represent a piperidino, morpholino or N-methylpiperazino group and n is 2 or 3),

Particularly preferred compounds according to the invention are the following:
7,7-dimethyl-2-phenyl-5-(2-diethylaminoethyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione,
7,7-dimethyl-2-phenyl-5-(3-diethylaminopropyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione,
7,7-dimethyl-2-phenyl-5-(3-piperidinopropyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione,
7,7-dimethyl-2-phenyl-5-(2-dimethylaminoethyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione
and acid addition salts thereof.

The compounds of general formula I may, for example, be prepared by the following processes which processes constitute further features of the present invention:

A. Reaction of a compound of formula II,



(II)

(wherein R_1 is as hereinbefore defined) or a reactive derivative thereof with a compound of formula III,

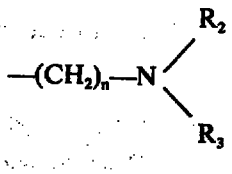
$$A—NH_2 \qquad \text{(III)}$$

(wherein A is as hereinbefore defined).

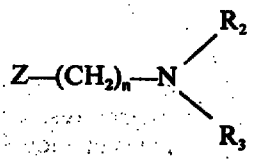
Suitable reactive derivatives of the compound of formula II which may be reacted with the compound of formula III are acid anhydride, ester, amide, imide and halide derivatives. The reaction is generally effected at temperatures of from 50 to 250°C, depending on the compound of formula II or reactive derivative thereof employed, and optionally in the presence of a solvent such as, for example, tetralin or ethylene glycol but preferably in the melt. When a compound of formula II itself is employed the reaction is preferably effected in the presence of ethylene glycol and at the boiling point of the reaction mixture.

According to a modification of the process described above, compounds of general formula I may be obtained by cyclisation of an appropriate ammonium salt or amide of the compound of formula II. Cyclisation is generally effected at elevated temperatures and optionally in the presence of a dehydrating agent such as, for example, hydrochloric acid, sulfuric acid, *p*-toluenesulfonic acid or phosphorus oxychloride.

B. For the preparation of compounds of general formula I wherein A represents a group of formula



Reaction of a compound of formula I as hereinbefore defined (wherein A represents a hydrogen atom) with a compound of formula IV,

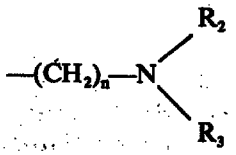


(IV)

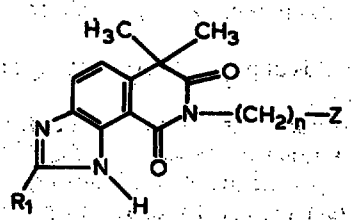
(wherein R_2, R_3 and n are as hereinbefore defined and Z represents a leaving atom or group, for example a chlorine, bromine or iodine atom or a sulfonyloxy group e.g. a *p*-toluenesulfonyloxy group).

The reaction is conveniently carried out in the presence of a solvent such as, for example, dimethylsulfoxide or dimethylformamide and of an alkali metal base e.g. sodium hydride, sodamide or potassium tert.-butoxide. The reaction may, however, be carried out in the absence of a solvent. Preferred reaction temperatures are from 0 to 200°C, most preferably 20 to 160°C.

C. For the preparation of compounds of general formula I wherein A represents a group of formula

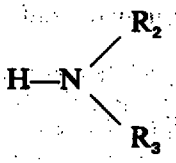


Reaction of a compound of formula V,



(V)

(wherein R_1 is as hereinbefore define and Z represents a leaving atom or group, for example a chlorine, bromine or iodine atom or a sulfonyloxy group e.g. a *p*-toluenesulfonyloxy group) with a compound of formula VI,

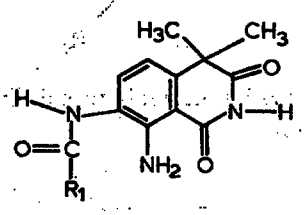


(VI)

(wherein R_2 and R_3 are as hereinbefore defined)

The reaction is conveniently effected in the presence of a solvent e.g. dioxan, dimethylsulfoxide, dimethylformamide or tetralin and optionally in the presence of a base, for example sodium carbonate, potassium carbonate or a tertiary organic base e.g. triethylamine, pyridine or collidine or of an excess of the compound of formula VI. The tertiary organic base or excess of the compound of formula VI, when used, may, if desired, serve as the solvent or the reaction may be effected in the absence of a solvent. Preferred reaction temperatures are from 50 to 200°C, most preferably the boiling point of the reaction mixture e.g. at temperatures up to 100 to 160°C.

D. For the preparation of compounds of general formula I wherein A represents a hydrogen atom:
Cyclisation of a compound of formula VII,

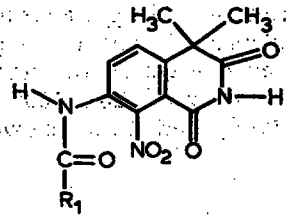


(VII)

(wherein R_1 is as hereinbefore defined) in the presence of an acidic condensation agent.

Cyclisation is preferably effected at elevated temperatures, most preferably at the boiling point of the reaction mixture. Suitable acidic condensation agents include, for example, hydrochloric acid, sulfuric acid, *p*-toluene-sulfonic acid and phosphorus oxychloride.

The compounds of general formula VII, may for example be obtained, preferably *in situ*, by reduction of a compound of formula VIII,



(VIII)

(wherein R_1 is as hereinbefore defined). Reduction may, for example, be effected by means of nascent or catalytically activated hydrogen or by means of tin-II chloride/hydrochloric acid, hydrazine/Raney nickel or iron-II sulfate and conveniently at temperatures of from 0 to 150°C, preferably 20 to 80°C. Reduction with nascent hydrogen is preferably effected with zinc/glacial acetic acid or iron/hydrochloric acid. Reduction with catalytically activated hydrogen is preferably effected with hydrogen in the presence of a catalyst such as, for example, palladium on charcoal, preferably at a hydrogen pressure of from 3 to 7 atmospheres.

E. For the preparation of compounds of general formula I wherein R_1 represents a phenyl group substituted by a methylsulfinyl group:

Oxidation of a compound of formula I as hereinbefore defined wherein R_1 represents a phenyl group substituted by a methylmercapto group whereby the desired compound of formula I is obtained.

Oxidation is preferably effected by means of about one equivalent of an oxidising agent and preferably in the presence of a solvent such as, for example, glacial acetic acid or aqueous glacial acetic acid. It is preferred to effect oxidation by means of hydrogen peroxide optionally in the presence of an alkali metal acetate e.g. sodium acetate. Preferred oxidation temperatures are from 0 to 100°C, most preferably from 10 to 50°C.

F. For the preparation of compounds of general formula I wherein R_1 represents a phenyl group substituted by a methylsulfonyl group:

Oxidation of a compound of formula I as hereinbefore defined wherein R_1 represents a phenyl group substituted by a methylmercapto or methylsulfinyl group whereby the desired compound of formula I is obtained.

When a compound of formula I wherein R_1 represents a phenyl group substituted by a methylmercapto group is to be oxidised preferably about two equivalents of an oxidising agent are used. When a compound of formula I wherein R_1 represents a phenyl group substituted by a methylsulfinyl group is to be oxidised preferably about one equivalent of an oxidising agent is used. Other preferred oxidation conditions are those described in process E above.

G. For the preparation of compounds of general formula I wherein R_1 represents a phenyl group substituted by a hydroxy group:

Debenzylation of a compound of formula I as hereinbefore defined wherein R_1 represents a phenyl group substituted by a benzyloxy group.

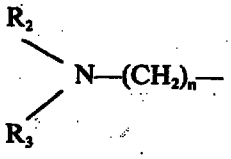
Debenzylation is preferably effected by means of catalytically activated hydrogen, e.g. with hydrogen in the presence of palladium on charcoal at a hydrogen pressure of 3 to 6 atmospheres and at a temperature of from 40 to 60°C. The debenzylation is preferably effected in the presence of methanol or ethyl acetate as solvent.

The compounds of general formula I may, if desired, be converted into their acid addition salts by reaction with an acid. Suitable acids for the preparation of physiologically compatible acid addition salts include, for example, hydrochloric, hydrobromic, sulfuric, phosphoric, lactic, citric, fumaric and maleic acids.

The compounds of general formulae II to IX used as starting materials in the processes described

above can be obtained according to known processes. For example a compound of formula II or VII may, for example, be obtained by condensation of a corresponding acylamino-amino compound. Compounds of general formula V may be obtained, for example, by reaction of a corresponding isoquinoline-dione with a corresponding halogen compound.

As mentioned above, the new compounds of general formula I and their physiologically compatible acid addition salts possess interesting pharmacological properties, including anxiolytic and particularly cardiovasculary effects. Thus, those compounds of general formula I wherein A represents a hydrogen atom as well as their physiologically compatible acid addition salts which we have tested possess particularly cardiotonic, hypotensive and platelet aggregation inhibitory effects and are thus useful in the treatment of heart insufficiency and of hypertensions. Those compounds of general formula I wherein A represents a group of formula



which we have tested exhibit in particular an antiarrhythmic effect and are thus useful in the treatment of dysrhythmia of the heart, particularly in connection with myocardiac infarction and angina pectoris. Furthermore, the compounds of formula I wherein A represents a hydrogen atom, and their acid additions alts, represent useful intermediates in the preparation of imidazo-isoquinoline-diones substituted in the 5-position by an aminoalkyl group.

For example the following compounds

A = 7,7-Dimethyl-2-(2,4-dimethoxyphenyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione hydrochloride,
B = 7,7-Dimethyl-2-(2-methoxy-4-methylsulfonyl-phenyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione,
C = 7,7-Dimethyl-2-phenylethyl-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione,
D = 7,7-Dimethyl-2-benzyl-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione,
E = 7,7-Dimethyl-2-(2-methoxyphenyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione hydrochloride,
F = 7,7-Dimethyl-2-cyclohexyl-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione,
G = 7,7-Dimethyl-2-(4-chlorophenyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione hydrochloride,
H = 7,7-Dimethyl-2-(4-methylmercaptophenyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione,
I = 7,7-Dimethyl-2-(4-methoxyphenyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione hydrochloride,
J = 7,7-Dimethyl-2-(4-hydroxyphenyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione hydrochloride,
K = 7,7-Dimethyl-2-(2-methoxy-5-methylsulfonyl-phenyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione,
L = 7,7-Dimethyl-2-(2-methoxy-5-methylsulfinyl-phenyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione hydrochloride, and
M = 7,7-Dimethyl-2-cyclopropyl-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione hydrochloride were tested with regard to their cardiotonic and blood-pressure effect and the compounds
N = 7,7-Dimethyl-2-phenyl-5-(2-diethylaminoethyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione dihydrochloride,
O = 7,7-Dimethyl-2-phenyl-5-(3-diethylaminopropyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione dihydrochloride,
P = 7,7-Dimethyl-2-phenyl-5-(3-piperidinopropyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione dihydrochloride and
Q = 7,7-Dimethyl-2-phenyl-5-(2-dimethylaminoethyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione dihydrochloride.

with regard to their anitarrhythmic effect:

1. *Cardiotonic and blood-pressure effect:*

Cats of either sex with a body weight of 2 to 4 kg were narcotized by an intraperitoneal injection of 30 mg/kg of pentobarbital-sodium. The arterial blood-pressure was determined by a Statham pressure exchanger (P23 Dc) from the *aorta abdominalis* via a PVC-catheter, which was introduced from the right *arteria femoralis*. The ventricle pressure was measured by a cathetertip manometer (type MILLAR PC-350), which was introduced in the left ventricular via the right *arteria carotis*. The indices of contractility $dp/dt_{max.}$ were obtained by a differentiating amplifier. The arterial blood-pressure and $dp/dt_{max.}$ were continuously registered by a direct-recorder. The test compounds were injected intravenously in a dose of 2 mg/kg.

The following table shows the results:

Test Substance	Influence on blood-pressure mm Hg	Increase of dp/dt %	duration min.
A	–49/–48	+ 83	> 24
B	–52/–80	+ 76	> 56
C	–40/–50	+ 87	20
D	–67/–63	+110	> 57
E	–46/–63	+ 77	12
F	–23/–40	+ 86	> 42
G	–40/–30	+ 45	9
H	–45/–45	+ 46	> 12
I	–33/–46	+ 32	> 19
J	–47/–58	+ 62	> 29
K	–70/–67	+157	>107
L	–42/–53	+ 90	> 70
M	–41/–49	+108	> 55

2. Activity on the effective refractory period of the isolated electrically stimulated left auricle of the guinea pig

Method:

Guinea pigs of either sex were killed by a blow on the neck. After opening the thorax the heart was quickly removed and transferred into Tyrode solution (37°C). The auricles were dissected and only the left auricles were used. Electrical stimulation was performed by a Grass stimulator, S4G, with square wave impulses of 1 milisec. duration and a stimulation voltage of 12 V. The auricles were suspended in Tyrode solution at 37°C containing NaCl 136.8 mVal NaCl, 2.68 mVal KCl, 0.2625mVal $MgCl_2$, 0.417 mVal NaH_2PO_4, 11.9 mVal $NaHCO_3$, 1.8 mVal $CaCl_2$, and 3 g of glucose. The solution was continuously oxygenated with O_2/CO_2 (98%/2%). The isometric contractions were measured with a force displacement transducer and recorded on a Grass polygraph (P5). The number of contractions was counted and compared with the frequency of stimulation.

The maximum stimulation frequency was measured increasing the stimulation rate every 10 seconds by 1 Hz. The maximum stimulation frequency was measured in 3 pre-tests by determining average value. During each interval of 5 minutes between measurements the stimulation rate was 0.5 Hz. After determination of the average value the test compound was added to the Tyrode solution and the stimulation rate was 0.5 Hz. During the first 5 minutes the inotropic activity of the compound was observed. Measurements were performed every 5 and 10 minutes after addition of the test compound. The average value resulting from 2 tests (5 minutes and 10 minutes – value) was taken as the maximum stimulation frequency after addition of the test compound. At first small doses were given and, after determination of the maximum stimulation frequency, the dose was increased cumulatively and the maximum stimulation frequency for that dose was measured.

Principle:

The maximum stimulation frequency is measured by increasing the stimulation rate. When the interval between two stimuli is shortened, a stimulation rate is reached at which every second stimulation falls into the refractory period of the foregoing contraction and will not be answered with a contraction. Thus the maximum stimulation frequency is a measure of the effective refractory period. Compounds which reduce the maximum stimulation frequency prolong the refractory period.

From the dose-response curves the following concentrations, which reduce the maximum stimulation frequency by 50%, wer graphically determined:

Substance	EC_{50} in µg/ml
N	1.8
O	5.0
P	6.7
Q	4.8

3. *Antiarrhythmic activity against chloroform induced ventricular fibrillation on mice:*

On placing a mouse into a chloroform-saturated atmosphere, the animal becomes anaesthetized after 40 sec., spontaneous respiration stops and, after a further 20 sec., gasping respiration is observed. When the respiration is completely suppressed, the mouse is taken out of the chloroform atmosphere, the thorax is opened and the heart is quickly dissected to allow inspection of the heart movement. For 1 minute after opening the thorax spontaneous ventricular fibrillation is obtained in nearly all the animals or can be induced by touching the heart.

Pre-treatment with antiarrhythmic compounds reduces the number of animals which show fibrillations in a dose dependent way. The dose which reduces the number of animals by 50% is calculated by means of dose-response curves and the standard error is determined (MILLER, L.C. and TAINTER, M.L., Proc. Soc. Exp. Biol. Med. *57*, 261 (1944).

The experiments were performed on male mice, body weight 20—25 g. Each dose was tested on 10 animals.

The dose was determined, at which after i.v. and p.o. administration before starting the test, the ventricular fibrillation was stopped in 50% of the animals.

Test Compound	ED_{50} mg/kg i.v.	p.o.	oral activity ED_{50} i.v. × 100/ED_{50} p.o.
N	2.4	21.2	11.1%
O	6.4	29	22.1%
P	10.5	130	8.1%
Q	6.1	23.5	26.0%

4. *Actute Toxicity:*

The acute toxicity was determined in mice after oral and intravenous administration. The dose was determined at which 50% of the animals died:

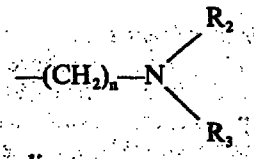
Test Compound	Toxicity
D	>300 mg/kg p.o.
F	>300 mg/kg p.o.
K	>300 mg/kg p.o.
O	LD_{50}: 92 mg/kg p.o. 61 mg/kg i.p.

According to a yet further feature of the present invention there are provided pharmaceutical 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.

For pharmaceutical administration the compounds of general formula I and their physiologically compatible acid addition salts may be incorporated into the conventional pharmaceutical preparations in either solid or liquid form, optionally in combination with other active ingredients. The compositions may, for example, be presented in a form suitable for oral, rectal or parenteral administration. Preferred forms include, for example, tablets, coated tablets, ampoules, suppositories, suspensions and solutions e.g. for injection.

The active ingredient may be incorporated in excipients customarily employed in parmaceutical compositions such as, for example, talc, gum arabic, lactose, starch, magnesium stearate, cocoa butter, aqueous or non-aqueous vehicles, fatty substances of animal or vegetable origin, paraffin derivatives, glycols, various wetting, dispersing or emulsifying agents and/or preservatives.

Advantageously the compositions may be formulated as dosage units, each unit being adapted to supply a fixed dose of active ingredient. Suitable dosage units for adults wherein the active ingredient comprises a compound according to the invention wherein A represents a hydrogen atom contain from 50 to 300 mg of active ingredient. Suitable dosage units for adults wherein the active ingredient comprises a compound according to the invention wherein A represents a group of formula



contain from 20 to 50 mg of active ingredient.

The following non-limiting examples serve to illustrate the present invention.

EXAMPLE 1

7,7-Dimethyl-2-phenyl-5H7H-imidazo[4,5-h]isoquinoline-4,5-dione hydrochloride

a) 4,4-Dimethyl-7-acetamino-8-nitro-2H,4H-isoquinoline-1,3-dione

220 g of 4,4-dimethyl-7-acetamino-2H,4H-isoquinoline-1,3-dione were added whilst stirring in portions to 800 ml of fuming nitric acid at –20°C. The mixture obtained was stirred for one hour at this temperature and then poured onto ice. The precipitate thus formed was filtered off with suction, washed neutral with water, dried in air and boiled with isopropanol. After cooling, the crystals obtained were filtered with suction and washed with ether. Yield: 222 g (85% of theory); M.p. 249°C (decomp.).

b) 4,4-Dimethyl-7-benzoylamino-8-nitro-2H,4H-isoquinoline-1,3-dione

43,8 g 4,4-dimethyl-7-acetamino-8-nitro-2H,4H-isoquinoline-1,3-dione were mixed with 200 g of xylene and 104 g of benzoyl chloride. The mixture obtained was refluxed for 10 hours whilst stirring and then, after cooling, was filtered with suction. The residue was washed with toluene and petroleum ether. Yield: 36 g (68% of theory); M.p. above 270°C.

c) 7,7-Dimethyl-2-phenyl-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione hydrochloride

17.6 g of 4,4-dimethyl-7-benzoylamino-8-nitro-2H,4H-isoquinoline-1,3-dione were hydrogenated in 1200 ml of methanol in the presence of 1.5 g of 10% Pd/C at 50°C and a hydrogen pressure of 5 atm. over 8 hours. The solution obtained of 4,4-dimethyl-7-benzoylamino-8-amino-2H,4H-isoquinoline-1,3-dione was mixed with 300 ml of saturated methanolic hydrochloric acid and refluxed for 3 hours. The catalyst was then filtered off with suction and the filtrate was evaporated to 100 ml then mixed with 100 ml of ether. The product thus precipitated was filtered off with suction and washed with ether.
Yield: 14.8 g (86.5% of theory); M.p. above 260°C.

EXAMPLE 2

7,7-Dimethyl-2-(2,4-dimethoxyphenyl)-5H,7H-imidazo[4,5-h]-isoquinoline-4,6-dione hydrochloride

a) 4,4-Dimethyl-7-(2,4-dimethoxybenzoylamino)-8-nitro-2H,4H-isoquinoline-1,3-dione

2.7 g of 4,4-dimethyl-7-amino-8-nitro-2H,4H-isoquinoline-1,3-dione were mixed with 50 ml of chloroform and 2.5 ml of triethylamine. Subsequently 2.2 g of 2,4-dimethoxybenzoyl chloride were added thereto and the resultant mixture was refluxed for 2 hours. After cooling, the mixture was evaporated and the precipitate thus obtained was filtered off with suction and digested with water whilst heating.
Yield: 3.2 g (71.1% of theory); M.p. above 250°C.

b) 7,7-Dimethyl-2-(2,4-dimethoxyphenyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione hydrochloride

Prepared analogously to Example 1c from 3.1 g of 4,4-dimethyl-7-(2,4-dimethoxybenzoylamino)-8-nitro-2H,4H-isoquinoline-1,3-dione.
Yield: 2.1 g (74.7% of theory); M.p. 248—249°C.

EXAMPLE 3

7,7-Dimethyl-2-(2-methoxy-4-methylmercapto-phenyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione hydrochloride

a) 4,4-Dimethyl-7-(2-methoxy-4-methylmercapto-benzoylamino)-8-nitro-2H,4H-isoquinoline-1,3-dione

Prepared analogously to Example 2a from 5 g of 4,4-dimethyl-7-amino-8-nitro-2H,4H-isoquinoline-1,3-dione and 2-methoxy-4-methylmercapto-benzoyl chloride.

Yield: 7.1 g (82.6% of theory); M.p. above 270°C.

b) 7,7-Dimethyl-2-(2-methoxy-4-methylmercapto-phenyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione hydrochloride

Prepared analogously to Example 1c from 7.1 g of 4,4-dimethyl-7-(2-methoxy-4-methylmercapto-benzoylamino)-8-nitro-2H,4H-isoquinoline-1,3-dione. For purification, the obtained hydrochloride was converted into the free base, the base was chromatographed on a silica gel column (eluant: chloroform/acetone 19:1) and then the hydrochloride was precipitated from acetone by addition of ethereal hydrochloric acid.
Yield: 5.6 g (80% of theory); M.p. above 250°C.

EXAMPLE 4

7,7-Dimethyl-2-(2-methoxy-4-methylsulfinyl-phenyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione

5.1 g of 7,7-dimethyl-2-(2-methoxy-4-methylmercapto-phenyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione were reacted, in 100 ml of 70% acetic acid, with 1.7 g of 30% hydrogen peroxide and the mixture obtained was left for 50 hours at room temperature (the first 3 hours with stirring). After 18 and again after 26 hours 1.3 g of 30% hydrogen peroxide were added thereto. The resultant mixture was diluted with water and ammonia was added thereto until the mixture was alkaline. The precipitate thus formed was filtered off with suction and the filtrate was extracted twice with chloroform. The chloroform phases were evaporated and the evaporation residue was combined with the precipitate. The product thus obtained was purified on a silica gel column (eluant: chloroform/acetone 19:1).
Yield: 3.5 g (66% of theory); M.p. over 260°C.

EXAMPLE 5

7,7-Dimethyl-2-(2-methoxy-4-methylsulfonyl-phenyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione

2.3 g of 7,7-dimethyl-2-(2-methoxy-4-methylmercapto-phenyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione were heated up to 40°C in 70 ml of 70% acetic acid and over 10 hours 10 ml of 30% hydrogen peroxide were added thereto. After standing overnight the resultant mixture was diluted with water and ammonia was added thereto until the mixture obtained was alkaline. The mixture was then saturated with sodium chloride and extracted several times with chloroform. The chloroform phases were evaporated and the residue was purified on a silica gel column (eluant: chloroform/acetone 19:1).
Yield: 0.7 g (28% of theory); M.p. over 250°C.

EXAMPLE 6

2,7,7-Trimethyl-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione hydrochloride

Prepared analogously to Example 1c from 16 g of 4,4-dimethyl-7-acetamino-8-nitro-2H,4H-isoquinoline-1,3-dione.
Yield: 14.3 g (93% of theory); M.p. over 260°C.

EXAMPLE 7

2-Ethyl-7,7-dimethyl-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione hydrochloride

a) 4,4-Dimethyl-7-propionylamino-8-nitro-2H,4H-isoquinoline-1,3-dione

29.1 g of 4,4-dimethyl-7-acetamino-8-nitro-2H,4H-isoquinoline-1,3-dione were refluxed for 4 hours with 50 ml of propionic acid anhydride. The mixture obtained was poured into ice-water and neutralized with sodium bicarbonate. The precipitate obtained was purified on a silica gel column (eluant: chloroform/acetone 19:1).
Yield: 21.8 g (71.5% of theory); M.p. 238—239°C.

b) 2-Ethyl-7,7-dimethyl-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione hydrochloride

Prepared analogously to Example 1c from 6.1 g of 4,4-dimethyl-7-propionylamino-8-nitro-2H,4H-isoquinoline-1,3-dione.
Yield: 4.9 g (83.5% of theory); M.p. 206—207°C.

EXAMPLE 8

7,7-Dimethyl-2-(4-methylmercaptophenyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione

a) 4,4-Dimethyl-7-(4-methylmercaptobenzoylamino)-8-nitro-2H,4H-isoquinoline-1,3-dione

Prepared analogously to Example 1b from 14.6 g of 4,4-dimethyl-7-acetamino-8-nitro-2H,4H-isoquinoline-1,3-dione and 17 g of 4-methylmercaptobenzoyl chloride (reaction time: 23 hours).
Yield: 17 g (85.1% of theory); M.p. over 265°C.

b) 7,7-Dimethyl-2-(4-methylmercaptophenyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione

17 g of 4,4-dimethyl-7-(4-methylmercaptobenzoylamino)-8-nitro-2H,4H-isoquinoline-1,3-dione were reduced analogously to Example 1c. After filtering off the catalyst the mixture obtained was evaporated to dryness. The hydrochloride residue was converted with methanolic ammonia into the free base and then purified on a silica gel column (eluant: chloroform/acetone 19:1).
Yield: 5.8 g (39% of theory); M.p. 251—253°C.

EXAMPLE 9.

7,7-Dimethyl-2-(4-methoxyphenyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione hydrochloride

Prepared analogously to Example 1c from 80.5 g of 4,4-dimethyl-7-(4-methoxybenzoylamino)-8-nitro-2H,4H-isoquinoline-1,3-dione with hydrogen chloride gas being introduced whilst refluxing.
Yield: 73.3 g (93.6% of theory); M.p. 282°C.

EXAMPLE 10

7,7-Dimethyl-2-(4-hydroxyphenyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione

a) 7,7-Dimethyl-2-(4-benzyloxyphenyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione hydrochloride

1.5 g of Raney nickel were added in portions over 1 hour to a suspension of 8.3 g of 4,4-dimethyl-7-(4-benzyloxybenzoyl-amino)-8-nitro-2H,4H-isoquinoline-1,3-dione in a solution of 3 ml of hydrazine hydrate in 100 ml of ethanol whilst stirring at room temperature. After another hour 100 ml of methanolic hydrochloric acid were added thereto and the resultant mixture was slowly heated up to boiling. After 2 hours the mixture was filtered and the residue was extracted several times with boiling ethylene glycol monomethyl ether. The ethylene glycol monomethyl ether phases were combined with the methanolic filtrate and evaporated to 100 ml *in vacuo*. The product thus precipitated was filtered off with suction and recrystallized from water/ethanol.
Yield: 4 g (44.7% of theory); M.p. 244—246°C.

b) 7,7-Dimethyl-2-(4-hydroxyphenyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione

A mixture of 2.3 of 7,7-dimethyl-2-(4-benzyloxyphenyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione, 200 ml of methanol and 0.5 g of 10% palladium-charcoal was hydrogenated at 50°C at a hydrogen pressure of 5 atm. for 4 hours. The catalyst was then filtered off and the filtrate was evaporated to 50 ml. The crystals thus precipitated were filtered off with suction.
Yield: 1.5 g (77.8% of theory); M.p. over 250°C.

EXAMPLE 11

7,7-Dimethyl-2-(2-methoxy-5-methylsulfonyl-phenyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione

a) 4,4-Dimethyl-7-(2-methoxy-5-methylmercapto-benzoylamino)-8-nitro-2H,4H-isoquinoline-1,3-dione

Prepared analogously to Example 1b (reaction time: 18 hours, the product was purified by boiling out with n-propanol) from 29.1 g of 4,4-dimethyl-7-acetamino-8-nitro-2H,4H-isoquinoline-1,3-dione and 30 g of 2-methoxy-5-methylmercapto-benozyl chloride.
Yield: 26.6 g (61.9% of theory); M.p. over 255°C.

b) 7,7-Dimethyl-2-(2-methoxy-5-methylmercapto-phenyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione hydrochloride

Prepared analogously to Example 1c from 25.7 g of 4,4-dimethyl-7-(2-methoxy-5-methylmercapto-benzoyl-amino-8-nitro-2H,4H-isoquinoline-1,3-dione.
Yield: 16.2 g (64.6% of theory); M.p. sintering at 210°C.

c) 7,7-Dimethyl-2-(2-methoxy-5-methylsulfonyl-phenyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione

8.4 g of 7,7-dimethyl-2-(2-methoxy-5-methylmercapto-phenyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione, 200 ml of glacial acetic acid, 50 ml of water, 2 g of sodium acetate and 10 ml of 30% hydrogen peroxide were heated together up to 50°C whilst stirring for 10 days, whereby, at 2 days intervals another 5 ml of 30% hydrogen peroxide were added. The resultant mixture was poured on ice and neutralized with potassium carbonate. The precipitate thus formed was filtered off with suction and recrystallized from ethylene glycol monomethyl ether.
Yield: 2.7 g (32.6% of theory); M.p. over 255°C.

EXAMPLE 12

7,7-Dimethyl-2-(4-chlorophenyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione hydrochloride

Prepared analogously to Example 1c from 38.8 g of 4,4-dimethyl-7-(4-chlorobenzoylamino)-8-nitro-2H,4H-isoquinoline-1,3-dione.
Yield: 22.5 g (59.8% of theory); M.p. over 250°C (from n-propanol).

EXAMPLE 13

7,7-Dimethyl-2-benzyl-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione

Prepared analogously to Example 1c from 29 g of 4,4-dimethyl-7-phenyl-acetylamino-8-nitro-2H,4H-isoquinoline-1,3-dione. The base was liberated from the hydrochloride by addition of ammonia, purified on a silica gel column and recrystallized from isopropanol.
Yield: 10 g (39.7% of theory); M.p. 224—225°C.

EXAMPLE 14

7,7-Dimethyl-2-phenylethyl-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione

Prepared analogously to Example 13 from 29.1 g of 4,4-dimethyl-7-(3-phenylpropionylamino)-8-nitro-2H,4H-isoquinoline-1,3-dione.

Yield: 6.3 g (18.3% of theory); M.p. 243°C.

EXAMPLE 15

7,7-Dimethyl-2-(2-methoxyphenyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione hydrochloride

Prepared analogously to Example 1c from 37.3 g of 4,4-dimethyl-7-(2-methoxybenzoylamino)-8-nitro-2H,4H-isoquinoline-1,3-dione.

Yield: 12.2 g (33.8% of theory); M.p. over 250°C (from methanol).

EXAMPLE 16

7,7-Dimethyl-2-cyclohexyl-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione

Prepared analogously to Example 1c from 9.5 g of 4,4-dimethyl-7-(cyclohexyl-carbonylamino)-8-nitro-2H,4H-isoquinoline-1,3-dione. The hydrochloride was converted into the free base with ammonia and recrystallized from methanol.

Yield: 6.5 g (79.3% of theory); M.p. 284°C (decomp.).

EXAMPLE 17

7,7-Dimethyl-2-benzyl-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione

9 g of 2-benzyl-4-carboxy-5-(2-carboxyprop-2-yl)-benzimidazole were dissolved in 80 ml of concentrated ammonia. The solution obtained was evaporated to dryness and the residue was heated up to 180°C for one hour. The product thus formed was recrystallized from isopropanol.

Yield: 4.75 g (56% of theory); M.p. 224—225°C.

EXAMPLE 18

7,7-Dimethyl-2-cyclopropyl-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione hydrochloride

a) 4,4-Dimethyl-7-(cyclopropyl-carbonylamino)-8-nitro-2H,4H-isoquinoline-1,3-dione

Prepared analogously to Example 1b from 5.8 g of 4,4-dimethyl-7-acetamino-8-nitro-2H,4H-isoquinoline-1,3-dione and 6.3 g of cyclopropane-carboxylic acid chloride (heating time: 30 hours).

Yield: 6 g (94% of theory);

(crude product, which was used in the next stage without further purification).

b) 7,7-Dimethyl-2-cyclopropyl-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione hydrochloride

Prepared analogously to Example 1c from 6 g of 4,4-dimethyl-7-(cyclopropyl-carbonylamino)-8-nitro-2H,4H-isoquinoline-1,3-dione.

Yield: 4.8 g (83% of theory); M.p. sintering at 208°C, decomp. at 240°C.

EXAMPLE 19

7,7-Dimethyl-2-(2-methoxy-5-methylsulfinyl-phenyl)-5H-7H-imidazo[4,5-h]isoquinoline-4,6-dione

3.0 g of 7,7-dimethyl-2-(2-methoxy-5-methylmercapto-phenyl)-5H,7H-imidazo[4,5-H]isoquinoline-4,6-dione were dissolved in 60 ml of glacial acetic acid and then slowly 0.88 ml of 30% hydrogen peroxide were added dropwise thereto at room temperature. After stirring for 30 minutes, the solution obtained was neutralized with saturated potassium carbonate solution, diluted with water and extracted with chloroform. The crude product obtained after evaporation of the chloroform was purified on a silica gel column (eluant: chloroform with increasing portions of acetone).

Yield: 2.2 g (74% of theory); M.p. sintering at 250°C.

EXAMPLE 20

2,7,7-Trimethyl-5-(3-diethylaminopropyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione dihydrochloride

50 ml of dimethylsulfoxide were added to 4.2 g of 2,7,7-trimethyl-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione. The solution obtained was mixed in portions with 2.6 g of a 55% suspension of sodium hydride in oil and stirred at room temperature for 2 hours. 4.8 g of 3-diethylaminopropyl bromide hydrobromide were added to the resultant mixture and stirring was continued for one hour at room temperature and for 4 hours at 80°C. After cooling the mixture obtained was diluted with water and extracted with chloroform. The chloroform phases were washed with water and evaporated. The residue was purified on a silica gel column (eluant: chloroform/acetone with ethereal hydrochloric acid.

Yield: 1.9 g (29.5% of theory); M.p. over 250°C.

EXAMPLE 21

2,7,7-Trimethyl-5-(2-diethylaminoethyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione dihydrochloride

100 ml of dimethylformamide were added to 4.2 g of 2,7,7-trimethyl-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione and the solution obtained was mixed with 3.4 g of diethylaminoethyl chloride hydrochloride and 4.1 g of potassium carbonate. The resultant mixture was refluxed for 8 hours and

then the solvent was distilled off *in vacuo*. The residue was mixed with water and the mixture obtained was extracted with chloroform. The chloroform phase was evaporated and the residue was purified on a silica gel column (eluant: chloroform/acetone 19:1). The dihydrochloride was precipitated from acetone/methanol with ethereal hydrochloric acid and recrystallized from acetone/methanol.
Yield: 1.2 (19.3% of theory); M.p. over 250°C.

EXAMPLE 22

7,7-Dimethyl-2-phenyl-5-(3-diethylaminopropyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione dihydrochloride

4.9 g of 2-phenyl-4-carboxy-5-(2-carboxyprop-2-yl)-benzimidazole were heated up to 180°C for 1 hour with 2.6 g of 3-(diethylamino)-propylamine and 20 ml of ethylene glycol. After cooling the mixture obtained was diluted with water and extracted twice with chloroform. The chloroform phases were evaporated and the residue was purified on a silica gel column (eluant: chloroform/acetone 19:1). The dihydrochloride was precipitated from acetone with ethereal hydrochloric acid.
Yield: 5.6 g (76% of theory); M.p. 205—208°C.

EXAMPLE 23

7,7-Dimethyl-2-phenyl-5-(3-diethylaminopropyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione dihydrochloride

2.6 g of a 55% suspension of sodium hydride in oil were added in portions to a solution of 5.1 g of 7,7-dimethyl-2-phenyl-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione hydrochloride in 50 ml of dimethylsulfoxide. After stirring at room temperature for one hour, 4.8 g of 3-diethylaminopropyl bromide hydrobromide were added thereto and the resultant mixture was heated up to 50°C for 3 hours. The mixture was then mixed with water and extracted several times with chloroform. The chloroform phases were evaporated and the residue was purified on a silica gel column. The dihydrochloride was precipitated from acetone with ethereal hydrochloric acid and recrystallized from methanol-acetone.
Yield: 3.7 g (50.5% of theory); M.p. 207—209°C.

EXAMPLE 24

7,7-Dimethyl-2-phenyl-5-(2-diethylaminoethyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione dihydrochloride

Prepared analogously to Example 23 from 5.1 g of 7,7-dimethyl-2-phenyl-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione hydrochloride and 3.4 g of 2-diethylaminoethyl chloride hydrochloride.
Yield: 3.8 g (53.1% of theory); M.p. over 250°C.

EXAMPLE 25

7,7-Dimethyl-2-benzyl-5-(2-morpholinoethyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione dihydrochloride

Prepared analogously to Example 23 from 1.6 g of 7,7-dimethyl-2-benzyl-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione and 1.2 g of 2-morpholinoethyl chloride hydrochloride.
Yield: 0.5 g (19.7% of theory); M.p. 243—246°C.

EXAMPLE 26

7,7-Dimethyl-2-phenethyl-5-[2-(2-(3,4-dimethoxyphenyl)-ethylamino)-ethyl]-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione dihydrochloride

a) 7,7-Dimethyl-2-phenethyl-5-(2-chloroethyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione

Prepared analogously to Example 23 at room temperature from 4.3 g of 7,7-dimethyl-2-phenethyl-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione and 2.2 g of 2-bromo-1-chloroethane. The viscous oily crude product was used in the next stage without further purification.
Yield: 5.3 g (100% of theory).

b) 7,7-Dimethyl-2-phenethyl-5-[2-(2-(3,4-dimethoxyphenyl)-ethylamino)-ethyl]-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione dihydrochloride

2.8 g of 7,7-dimethyl-2-phenethyl-5-(2-chloroethyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione were heated up to 150°C for 40 minutes with 5 ml of 2-(3,4-dimethoxyphenyl)ethylamine. After cooling, the mixture obtained was dissolved in ether and the solution obtained was extracted several times with water weakly acidified with acetic acid. The organic phase was evaporated and the residue was dissolved in acetone. The dihydrochloride was precipitated with ethereal hydrochloric acid.
Yield: 0.8 g (18.4% of theory); M.p. 207—210°C (decomp.).

EXAMPLE 27

7,7-Dimethyl-2-phenyl-5-(3-piperidinopropyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione dihydrochloride

Prepared analogously to Example 23 from 3.4 g of 7,7-dimethyl-2-phenyl-5H,7H-imidazo[4,5-

h]isoquinoline-4,6-dione hydrochloride and 3.4 g of 3-piperidinopropyl chloride.
Yield: 3.2 g (63.6% of theory); M.p. 234—238°C, (sintering at 227°C).

EXAMPLE 28

7,7-Dimethyl-2-(2-methoxyphenyl)-5-[3-(2-(3,4-dimethoxyphenyl)-ethylamino)-propyl]-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione dihydrochloride

a) 7,7-Dimethyl-2-(2-methoxyphenyl)-5-(3-chloroprop-1-yl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione

Prepared analogously to Example 23 from 3.7 g of 7,7-dimethyl-2-(2-methoxyphenyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione hydrochloride and 1.9 g of 1-bromo-3-chloropropane. The product, precipitated by addition of water to the reaction mixture, was dissolved in methylene chloride and the resultant solution was dried and evaporated. The residue was recrystallized from isopropanol.
Yield: 3.5 g (85% of theory); M.p. 154—156°C.

b) 7,7-Dimethyl-2-(2-methoxyphenyl)-5-[3-(2-(3,4-dimethoxyphenyl)-ethylamino)-propyl]-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione dihydrochloride

3.4 g of 7,7-dimethyl-2-(2-methoxyphenyl)-5-(3-chloroprop-1-yl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione were heated up to 140°C for 30 minutes with 4.2 g of 2-(3,4-dimethoxyphenyl)-ethylamine. The resultant mixture was separated by column chromatography (silica gel, eluant: chloroform/acetone 19:1). The product obtained was dissolved in acetone. The dihydrochloride was precipitated with ethereal hydrochloric acid and recrystallized from isopropanol.
Yield: 3.7 g (71.7% of theory); M.p. 192—194°C (decomp.).

EXAMPLE 29

7,7-Dimethyl-2-cyclohexyl-5-(3-di-n-propylaminopropyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione dihydrochloride

a) 7,7-Dimethyl-2-cyclohexyl-5-(3-chloropropyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione

Prepared analogously to Example 26a from 3.1 g of 7,7-dimethyl-2-cyclohexyl-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione and 1.9 g of 1-bromo-3-chloro-propane. The crude product was further processed without additional purification.

b) 7,7-Dimethyl-2-cyclohexyl-5-(3-di-n-propylaminopropyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione dihydrochloride

The crude product obtained in Example 29a was refluxed with 15 ml of di-n-propylamine for 5 hours. Excess amine was then distilled off *in vacuo* and the residue was mixed with water. The mixture obtained was extracted with methylene chloride. The organic phases were evaporated and the residue was purified on a silica gel column (eluant: chloroform/acetone 19:1). The dihydrochloride was precipitated from acetone with ethereal hydrochloric acid (very slow crystallisation), filtered off with suction and washed with acetone/ether.
Yield: 1.1 g (21% of theory, calculated on 7,7-dimethyl-2-cyclohexyl-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione); M.p. 156—158°C.

EXAMPLE 30

7,7-Dimethyl-2-benzyl-5-(3-diethylaminopropyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione dihydrochloride

Prepared analogously to Example 23 from 3.2 g of 7,7-dimethyl-2-benzyl-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione and 3.4 g of diethylaminopropyl bromide hydrobromide.
Yield: 1.3 g (25.8% of theory); M.p. 150—153°C, (sintering at 130°C) (from acetone).

EXAMPLE 31

7,7-Dimethyl-2-(4-chlorophenyl)-5-[2-[N-methyl-N-[2-(3,4-dimethoxyphenyl)-ethyl]-aminoethyl-5H,7H-imidazo[4,5-h]-4,6-dione dihydrochloride

a) 7,7-Dimethyl-2-(4-chlorophenyl)-5-(2-chloroethyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione

Prepared analogously to Example 23 from 7.5 g of 7,7-dimethyl-2-(4-chlorophenyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione and 6.9 g of 1-bromo-2-chloroethane.
Yield: 4.2 g (50.7% of theory); M.p. 176—177°C.

b) 7,7-Dimethyl-2-(4-chlorophenyl)-5-[2-[N-methyl-N-[2-(3,4-dimethoxyphenyl)-ethyl]-amino}-ethyl]-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione dihydrochloride

1.5 g of 7,7-dimethyl-2-(4-chlorophenyl)-5-(2-chloroethyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione and 1.7 g of N-methyl-N-[2-(3,4-dimethoxyphenyl)-ethyl]-amine were heated up to 150°C for 3 hours. After cooling the resultant mixture was dissolved in chloroform and the solution obtained was washed with water. The chloroform phase was evaporated and the residue was chromatographed on a silica gel column (eluant: chloroform/acetone 19:1). The dihydrochloride was precipitated from acetone by addition of ethereal hydrochloric acid and recrystallized from methylene chloride/acetone.
Yield: 0.8 g (35% of theory); M.p. 230—231°C (decomp.).

EXAMPLE 32

7,7-Dimethyl-2-(4-chlorophenyl)-5-(3-diethylaminopropyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione dihydrochloride

Prepared analogously to Example 23 from 3.5 g of 7,7-dimethyl-2-(4-chlorophenyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione and 3.1 g of 3-diethylaminopropyl bromide hydrobromide.
Yield: 1.5 g (28.5% of theory); M.p. 206—208°C.

EXAMPLE 33

7,7-Dimethyl-2-(4-chlorophenyl)-5-[2-(4-methylpiperazin-1-yl)-ethyl]-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione trihydrochloride

2.1 g of 7,7-dimethyl-2-(4-chlorophenyl)-5-(2-chloroethyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione and 10 ml of N-methylpiperazine were heated up to 130°C for 2 hours. After distilling off the excess N-methylpiperazine *in vacuo*, the residue obtained was purified on a silica gel column (eluant: chloroform/acetone 19:1). The trihydrochloride was precipitated from acetone by addition of ethereal hydrochloric acid and recystallized from ethanol.
Yield: 1 g (34.7% of theory); M.p. 263—266°C (decomp.).

EXAMPLE 34

7,7-Dimethyl-2-(2-methoxy-4-methylmercapto-phenyl)-5-(2-diethylaminoethyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione dihydrochloride

Prepared analogously to Example 23 from 2.9 g of 7,7-dimethyl-2-(2-methoxy-4-methylmercapto-phenyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione hydrochloride and 2 g of 2-diethylamino-ethyl bromide hydrobromide.
Yield: 1.3 g (33.5% of theory); M.p. 235—238°C.

EXAMPLE 35

7,7-Dimethyl-2-(4-methoxyphenyl)-5-[2-(2-(3,4-dimethoxyphenyl)-ethylamino)-ethyl]-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione dihydrochloride

Prepared analogously to Example 26b from 1g of 7,7-dimethyl-2-(4-methoxyphenyl)-5-(2-chloro-ethyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione and 3 g of 2-(3,4-dimethoxyphenyl)-ethylamine.
Yield: 0.3 g (19.5% of theory); M.p. 210—212°C (from isopropanol).

EXAMPLE 36

7,7-Dimethyl-2-phenethyl-5-(2-methylaminoethyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione dihydrochloride

3.0 g of 2-phenylethyl-4-carboxy-5-(2-carboxyprop-2-yl)-benzimidazole, 2 ml of methylamino-ethylamine and 15 ml of ethylene glycol were heated up together to 180°C for 2 hours. After distilling off the ethylene glycol *in vacuo*, the mixture obtained was dissolved in chloroform. The resultant solution was washed with a sodium chloride solution. After distilling off the chloroform, the residue obtained was dissolved in acetone and the dihydrochloride was precipitated by addition of methanolic hydrochloric acid.
Yield: 3.2 g (81.2% of theory); M.p. 181—184°C.

EXAMPLE 37

7,7-Dimethyl-2-(4-methoxyphenyl)-5-(2-methylaminoethyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione dihydrochloride

Prepared analogously to Example 36 from 3 g of 2-(4-methoxyphenyl)-4-carboxy-5-(2-carboxy-prop-2-yl)-benzimidazole and 2 ml of methylamino-ethylamine. Before precipitating the dihydrochloride, the base was chromatographed on a silica gel column (eluant: chloroform/acetone 19:1).
Yield: 1.1 g (23.6% of theory); M.p. over 260°C.

EXAMPLE 38

7,7-Dimethyl-2-phenyl-5-[3-(4-methylpiperazin-1-yl)-propyl]-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione trihydrochloride

Prepared analogously to Example 36 from 1.6 g of 2-phenyl-4-carboxy-5-(2-carboxyprop-2-yl)-benzimidazole and 0.94 g of 3-(4-methylpiperazin-1-yl)-propylamine.
Yield: 2.5 g (90% of theory); M.p. 235°C (decomp.).

EXAMPLE 39

7,7-Dimethyl-2-phenyl-5-(2-dimethylaminoethyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione dihydrochloride

Prepared analogously to Example 36 from 1.6 g of 2-phenyl-4-carboxy-5-(2-carboxyprop-2-yl)-benzimidazole and 0.53 g of 2-dimethylamino-ethylamine.
Yield: 1.5 g (66.8% of theory); M.p. 234—237°C.

EXAMPLE 40

7,7-Dimethyl-2-phenyl-5-(2-morpholinoethyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione dihydrochloride

Prepared analogously to Example 36 from 1.6 g of 2-phenyl-4-carboxy-5-(2-carboxyprop-2-yl)-benzimidazole and 0.78 g of 2-morpholino-ethylamine.
Yield: 2 g (81.4% of theory); M.p. 261—263°C.

EXAMPLE 41

7,7-Dimethyl-2-phenyl-5-(3-dimethylaminopropyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione dihydrochloride

Prepared analogously to Example 23 from 3.4 g of 7,7-dimethyl-2-phenyl-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione hydrochloride and 1.7 g of 3-dimethylamino-propyl chloride hydrochloride (temperature 50—60°C, reaction time: 18 hours).
Yield: 1.5 g (32.4% of theory); M.p. 234—235°C.

EXAMPLE 42

7,7-Dimethyl-2-cyclopropyl-5-(3-diethylaminopropyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione

Prepared analogously to Example 23 from 2.45 g of 7,7-dimethyl-2-cyclopropyl-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione hydrochloride and 2.3 g of 3-diethylamino-propyl bromide hydrobromide. The crude product was purified by chromatography on a silica gel column (eluant: chloroform with increasing parts of acetone).
Yield: 1.3 g (36% of theory); M.p. 185—187°C (decomp.).

EXAMPLE 43

2,7,7-Trimethyl-5-[3-(2-(3,4-dimethoxyphenyl)-ethylamino)-propyl]-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione difumarate

Prepared analogously to Example 22, but without a solvent, from 3.4 g of 2-methyl-4-carboxy-5-(2-carboxyprop-2-yl)-benzimidazole and 3.4 g of 3-[2-(3,4-dimethoxyphenyl)-ethylamino]-propylamine. The difumarate was precipitated from acetone.
Yield: 5.5 g (61% of theory); M.p. 134—135°C (decomp.).

EXAMPLE 44

7,7-Dimethyl-2-phenyl-5-(3-diethylaminopropyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione dihydrochloride

A mixture of 1.06 g of 5,7,7-trimethyl-2-phenyl-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione and 3 ml of 3-diethylaminopropylamine was heated up to 170°C for 30 hours. After distilling off the excess amine *in vacuo*, the residue obtained was mixed with water and further processed analogously to Example 22.
Yield: 0.29 g (20% of theory); M.p. 205—208°C.

EXAMPLE 45

7,7-Dimethyl-2-phenyl-5-(3-ethylaminopropyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione dihydrochloride

Prepared analogously to Example 22, but without a solvent and at 130°C, from 3.2 g of 2-phenyl-4-carboxy-5-(2-carboxyprop-2-yl)-benzimidazole and 3 ml of 3-ethylaminopropylamine. The dihydrochloride was precipitated from acetone with methanolic hydrochloride acid.
Yield: 3.6 g (77.7% of theory), M.p. 226—230°C.

EXAMPLE A

Tablets containing 50 mg of 7,7-dimethyl-2-phenyl-5-(3-diethylaminopropyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione dihydrochloride

Composition:

1 tablet contains:

Active ingredient	50.0 mg
Lactose	100.0 mg
Polyvinyl pyrrolidone (e.g. Kollidon 25)	5.0 mg
Carboxymethylcellulose	19.0 mg
Magnesium stearate	1.0 mg
	175.0 mg

Moist screening: 1.5 mm

Drying: in a circulation air drier at 50°C

Dry screening: 1.0 mm

The auxiliary products were added to the granulate and the mixture obtained was pressed into tablets.

Weight of tablet: 175.0 mg

Punch: 8 mm Ø

EXAMPLE B

Coated tablets containing 25 mg of 7,7-dimethyl-2-phenyl-5-(3-diethylaminopropyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione dihydrochloride

1 coated tablet contains:

Active ingredient	25.0 mg
Corn starch, dried	45.0 mg
Soluble starch	2.0 mg
Carboxymethylcellulose	7.0 mg
Magnesium stearate	1.0 mg
	80.0 mg

The active ingredient and starch were homogeneously moistened with an aqueous solution of the soluble starch.

Moist screening: 1.0 mm

Dry screening: 1.0 mm

Drying: in a circulation air drier at 50°C

The granulate and the remaining auxiliary products were mixed and pressed into coated tablet cores.

Weight of core: 80 mg

Punch: 6 mm

Radius of curvature: 5 mm

The finished cores were covered with a coating in a conventional manner.

Weight of coated tablet: 120 mg

EXAMPLE C

Suppositories containing 50 mg of 7,7-dimethyl-2-phenyl-5-(3-diethylaminopropyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione dihydrochloride

1 suppository contains:

Active ingredient	50.0 mg
Suppository mass (e.g. Witepsol H 19 and Witepsol H 45)	1,650.0 mg
	1,700.0 mg

Witepsol is a Registered Trade Mark.

Method of preparation

The suppository mass was melted. At 38°C the pulverized active ingredient was homogeneously dispersed in the melt. The suppository mass was cooled to 35°C and poured into pre-cooled moulds.

Weight of suppository: 1.7 g

EXAMPLE D

Ampoules containing 50 mg of 7,7-dimethyl-2-phenyl-5-(3-diethylaminopropyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione dihydrochloride

1 ampoule contains:

Active ingredient	50.0 mg
Sorbitol	250.0 mg
Distilled water ad	5.0 ml

Method of preparation

The active ingredient and sorbitol were dissolved in distilled water and the mixture obtained was made up to the given volume and filtered sterile.

Filling: into 5 ml ampoules

Sterilization: 20 minutes at 120°C

EXAMPLE E

Drop solution containing 5 mg/ml of 7,7-dimethyl-2-phenyl-5-(3-diethylaminopropyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione dihydrochloride

Active ingredient	5.0 g
methyl *p*-hydroxybenzoate	0.035 g
propyl *p*-hydroxybenzoate	0.015 g
aniseed oil	0.05 g
menthol	0.06 g
saccharin sodium	1.0 g
glycerine	10.0 g
ethanol	40.0 g
distilled water ad	100.0 ml

Method of preparation:

The methyl and propyl *p*-hydroxybenzoates were dissolved in the ethanol and the aniseed oil and menthol were added thereto. Subsequently, the active ingredient, glycerine and saccharin sodium were dissolved in water and the solution obtained was added to the solution obtained above. The combined solutions were filtered sterile.

EXAMPLE F

Tablets containing 100 mg of 7,7-dimethyl-2-(2-methoxy-5-methylsulfonyl-phenyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione

Composition:

1 tablet contains:

Active ingredient	100.0 mg
Lactose	50.0 mg
Polyvinyl pyrrolidone (i.e. Kollidon 25)	5.0 mg
Carboxymethylcellulose	19.0 mg
Magnesium stearate	1.0 mg
	175.0 mg

Moist screening: 1.5 mm

Drying: in a circulation air drier at 50°C

Dry screening 1 mm

The granulate and the remaining auxiliary products were mixed and the mixture obtained was pressed into tablets.

Weight of tablets: 175 mg

Punch 8 mm Ø

EXAMPLE G

Coated tablets containing 50 mg of 7,7-dimethyl-2-(2-methoxy-5-methylsulfonyl-phenyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,5-dione

1 coated tablet contains:

Active ingredient	50.0 mg
Corn starch, dried	20.0 mg
Soluble starch	2.0 mg
Carboxymethylcellulose	7.0 mg
Magnesium stearate	1.0 mg
	80.0 mg

The active ingredient and starch was moistened homogeneously with an aqueous solution of soluble starch.

Moist screening: 1.0 mm

Dry screening: 1.0 mm

Drying: in a circulation air drier at 50°C

The granulate and the auxiliary products were mixed and the mixture obtained was pressed into coated cores.

Weight of core: 80 mg

Punch: 6 mm

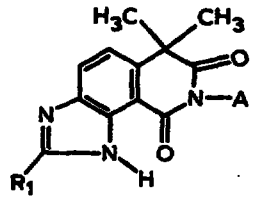
Radius of curvature: 5 mm

The finished cores were covered with a coating in a conventional manner.

Weight of coated tablet: 120 mg.

CLAIMS

1. Compounds of general formula I,

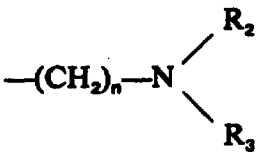


(I)

wherein

R_1 represents a C_{1-4} alkyl group (optionally substituted by a phenyl group), a cycloalkyl group containing from 3 to 6 carbon atoms or a phenyl group (optionally substituted by one or two substituents selected from halogen atoms and hydroxy, methoxy, methylmercapto, methylsulfinyl, methylsulfonyl and benzyloxy groups) and

A represents a hydrogen atom or a group of formula

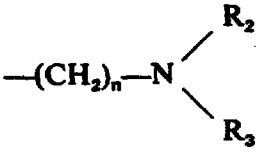


[in which either R_2 represents a hydrogen atom or a C_{1-4} alkyl group and R_3 represents a C_{1-4} alkyl group (optionally substituted by a dimethoxyphenyl group) or R_2 and R_3, together with the nitrogen atom to which they are attached, represent a piperidino, morpholino or 4-(C_{1-4} alkyl)-piperazino group, and n is 2 or 3]

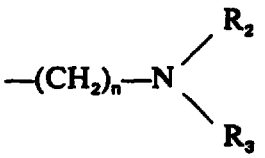
and acid addition salts thereof.

2. Compounds as claimed in claim 1 wherein A represents a hydrogen atom.

3. Compounds as claimed in claim 1 wherein A represents a group of formula



4. Compounds as claimed in claim 1 wherein R_1 represents a methyl, ethyl, benzyl, 1-phenylethyl, 2-phenylethyl, cyclopropyl, cyclohexyl, 4-chlorophenyl, 2-methoxy-5-methylsulfinyl-phenyl or 2-methoxy-5-methylsulfonyl-phenyl group or a phenyl group substituted by one or two substituents in the 2- and/or 4- positions selected from methoxy, hydroxy, methylmercapto, methylsulfinyl and methylsulfonyl groups; and A represents a hydrogen atom or a group of formula



Drying: in a circulation air drier at 50°C

The granulate and the auxiliary products were mixed and the mixture obtained was pressed into coated cores.

Weight of core: 80 mg

Punch: 6 mm

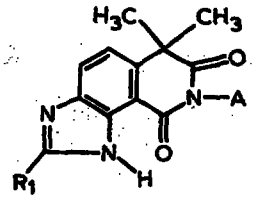
Radius of curvature: 5 mm

The finished cores were covered with a coating in a conventional manner.

Weight of coated tablet: 120 mg.

CLAIMS

1. Compounds of general formula I,

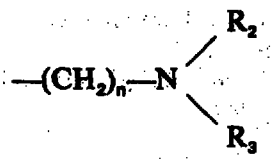


(I)

wherein

R_1 represents a C_{1-4} alkyl group (optionally substituted by a phenyl group), a cycloalkyl group containing from 3 to 6 carbon atoms or a phenyl group (optionally substituted by one or two substituents selected from halogen atoms and hydroxy, methoxy, methylmercapto, methylsulfinyl, methylsulfonyl and benzyloxy groups) and

A represents a hydrogen atom or a group of formula

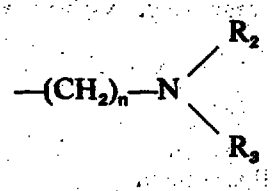


[in which either R_2 represents a hydrogen atom or a C_{1-4} alkyl group and R_3 represents a C_{1-4} alkyl group (optionally substituted by a dimethoxyphenyl group) or R_2 and R_3, together with the nitrogen atom to which they are attached, represent a piperidino, morpholino or 4-(C_{1-4} alkyl)-piperazino group, and n is 2 or 3]

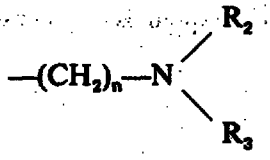
and acid addition salts thereof.

2. Compounds as claimed in claim 1 wherein A represents a hydrogen atom.

3. Compounds as claimed in claim 1 wherein A represents a group of formula



4. Compounds as claimed in claim 1 wherein R_1 represents a methyl, ethyl, benzyl, 1-phenylethyl, 2-phenylethyl, cyclopropyl, cyclohexyl, 4-chlorophenyl, 2-methoxy-5-methylsulfinyl-phenyl or 2-methoxy-5-methylsulfonyl-phenyl group or a phenyl group substituted by one or two substituents in the 2- and/or 4- positions selected from methoxy, hydroxy, methylmercapto, methylsulfinyl and methylsulfonyl groups; and A represents a hydrogen atom or a group of formula



(in which either R_2 represents a hydrogen atom or a methyl, ethyl or propyl group, and R_3 represents a methyl, ethyl, propyl or 2-(3,4-dimethoxyphenyl)-ethyl group or R_2 and R_3, together with the nitrogen atom to which they are attached represent a piperidino, morpholino or N-methylpiperazino group, and n is 2 or 3).

5. 7,7-Dimethyl-2-phenyl-5-(2-diethylaminoethyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione and acid addition salts thereof.

6. 7,7-Dimethyl-2-phenyl-5-(3-diethylaminopropyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione and acid addition salts thereof.

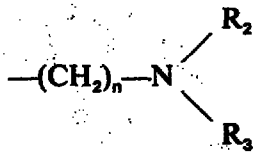
7. 7,7-Dimethyl-2-phenyl-5-(3-piperidinopropyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione and acid addition salts thereof.

8. 7,7-Dimethyl-2-phenyl-5-(2-dimethylaminoethyl)-5H,7H-imidazo[4,5-h]isoquinoline-4,6-dione and acid addition salts thereof.

9. Physiologically compatible acid addition salts of compounds of general formula I as defined in claim 1.

10. Compounds of general formula I as defined in claim 1 wherein A represents a hydrogen atom and physiologically compatible acid addition salts thereof.

11. Compounds of general formula I as defined in claim 1 wherein A represents a group of formula



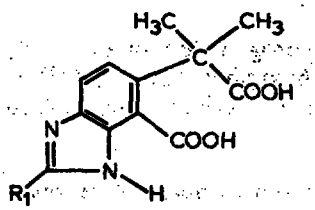
and R_1 represents a C_{1-4} alkyl group (optionally substituted by a phenyl group), a cycloalkyl group containing from 3 to 6 carbon atoms or a phenyl group (optionally substituted by one or two substituents selected from halogen atoms, methoxy groups and methylmercapto groups) and physiologically compatible acid addition salts thereof.

12. Compounds as claimed in claim 1, other than those claimed in any of claims 5 to 8, as herein specifically disclosed in any of Examples 1 to 45.

13. Compounds as claimed in claim 10 as herein specifically disclosed in any of Examples 1 to 17.

14. Compounds as claimed in claim 11, other than those claimed in any of claims 5 to 8, as herein specifically disclosed in any of Examples 20 to 41.

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



(II)

(wherein R_1 is as defined in claim 1) or a reactive derivative thereof with a compound of formula III,

$$A—NH_2 \qquad \text{(III)}$$

(wherein A is as defined in claim 1).

16. A process as claimed in claim 15 wherein an acid anhydride, ester, amide, imide or halide derivative of the compound of formula II is reacted with the compound of formula III.

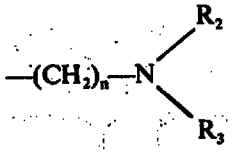
17. A process as claimed in claim 15 or claim 16 wherein the reaction is effected at temperatures of from 50 to 250°C.

18. A modification of a process as claimed in claim 15 wherein an ammonium salt or amide of the compound of formula II is cyclised.

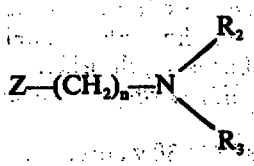
19. A process as claimed in claim 18 wherein cyclisation is effected at elevated temperatures.

20. A process as claimed in claim 18 or claim 19 wherein the cyclisation is effected in the presence of a dehydrating agent.

21. A process for the preparation of compounds of general formula I as defined in claim 1 wherein A represents a group of formula



which comprises reacting a compound of formula I as defined in claim 1 (wherein A represents a hydrogen atom) with a compound of formula IV,



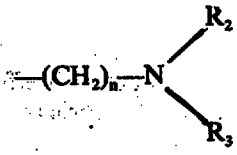
(IV)

(wherein R_2, R_3 and n are as defined in claim 1 and Z represents a leaving atom or group).

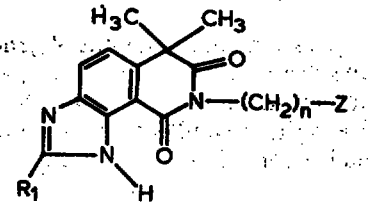
22. A process as claimed in claim 21 wherein, in the compound of formula IV, Z represents a chlorine, bromine or iodine atom or a sulfonyloxy group.

23. A process as claimed in claim 21 or claim 22 wherein the reaction is effected in the presence of an alkali metal base.

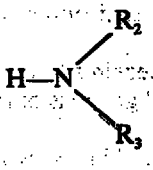
24. A process for the preparation of compounds of general formula I as defined in claim 1 wherein A represents a group of formula



which comprises reacting a compound of formula V,



(wherein R_1 is as defined in claim 1 and Z represents a leaving atom or group) with a compound of formula VI,



(VI)

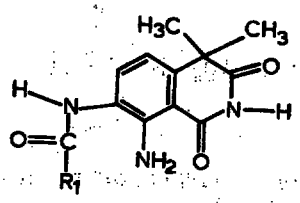
(wherein R_2 and R_3 are as defined in claim 1).

25. A process as claimed in claim 24 wherein, in the compound of formula V, Z represents a chlorine, bromine or iodine atom or a sulfonyloxy group.

26. A process as claimed in claim 24 or claim 25 wherein the reaction is effected in the presence of a base.

27. A process as claimed in any of claims 24 to 26 wherein the reaction is effected at temperatures of from 50 to 200°C.

28. A process for the preparation of compounds of general formula I as defined in claim 1 wherein A represents a hydrogen atom which comprises cyclising a compound of formula VII,



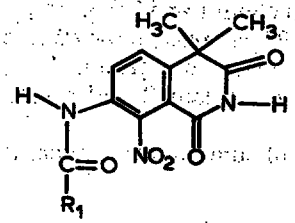
(VII)

(wherein R_1 is as defined in claim 1) in the presence of an acidic condensation agent.

29. A process as claimed in claim 28 wherein the acidic condensation agent is hydrochloric acid, sulfuric acid, *p*-toluenesulfonic acid or phosphorus oxychloride.

30. A process as claimed in claim 28 or claim 29 wherein the cyclisation is effected at elevated temperatures.

31. A process as claimed in any of claims 28 to 30 wherein the compound of formula VII is obtained by reduction of a compound of formula VIII,



(VIII)

(wherein R_1 is as defined in claim 1).

32. A process as claimed in claim 31 wherein reduction is effected by means of nascent or catalytically activated hydrogen, tin-II chloride/hydrochloric acid, hydrazine/Raney nickel or ion-II sulfate.

33. A process as claimed in claim 31 or claim 32 wherein the reduction is effected at temperatures of from 20 to 80°C.

34. A process as claimed in any of claims 31 to 33 wherein the compound of formula VII is formed *in situ*.

35. A process for the preparation of compounds of general formula I as defined in claim 1 wherein R_1 represents a phenyl group substituted by a methylsulfinyl group which comprises oxidising a compound of formula I as defined in claim 1 wherein R_1 represents a phenyl group substituted by a methylmercapto group whereby the desired compound of formula I is obtained.

36. A process as claimed in claim 35 wherein oxidation is effected by means of about one equivalent of an oxidising agent.

37. A process for the preparation of compounds of general formula I as defined in claim 1 wherein R_1 represents a phenyl group substituted by a methylsulfonyl group which comprises oxidising a compound of formula I as defined in claim 1 wherein R_1 represents a phenyl group substituted by a methylmercapto or methylsulfinyl group whereby the desired compound of formula I is obtained.

38. A process as claimed in claim 37 wherein a compound of formula I wherein R_1 represents a phenyl group substituted by a methylmercapto group is oxidised by means of about two equivalents of an oxidising agent.

39. A process as claimed in claim 37 wherein a compound of formula I wherein R_1 represents a phenyl group substituted by a methylsulfinyl group is oxidised by means of about one equivalent of an oxidising agent.

40. A process as claimed in any of claims 35 to 39 wherein oxidation is effected by means of hydrogen peroxide.

41. A process as claimed in claim 40 wherein the oxidation is effected in the presence of an alkali metal acetate.

42. A process for the preparation of compounds of general formula I as defined in claim 1 wherein R_1 represents a phenyl group substituted by a hydroxy group which comprises debenzylating a compound of formula I as defined in claim 1 wherein R_1 represents a phenyl group substituted by a benzyloxy group.

43. A process as claimed in claim 42 wherein debenzylation is effected by means of catalytically activated hydrogen.

44. A process for the preparation of acid addition salts of compounds of general formula I as defined in claim 1 which comprises reacting a compound of formula I as defined in claim 1 with an acid.

45. A process as claimed in claim 44 wherein the acid is hydrochloric, hydrobromic, sulfuric, phosphoric, lactic, citric, fumaric or maleic acid.

46. A process as claimed in any of claims 15—17, 21—27, 44 and 45 for the preparation of compounds as claimed in claim 11.

47. A process as claimed in any of claims 18—20 and 28—45 for [redacted] claimed in claim 10.

48. A process for the preparation of compounds as claimed in claim 1 substantially as herein described.

49. A process for the preparation of compounds as claimed in claim 1 substantially as herein described in any of Examples 1 to 45.

50. A process for the preparation of compounds as claimed in claim 10 substantially as herein described in any of Examples 1 to 17.

51. A process for the preparation of compounds as claimed in claim 11 substantially as herein described in any of Examples 20 to 41.

52. Compounds as claimed in claim 1 whenever prepared by a process as claimed in any of claims 15 to 45, 48 and 49.

53. Compounds as claimed in claim 10 whenever prepared by a process as claimed in claim 47 or claim 50.

54. Compounds as claimed in claim 11 whenever prepared by a process as claimed in claim 46 or claim 51.

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

56. Compositions as claimed in claim 55 in a form suitable for oral, rectal or parenteral administration.

57. Compositions as claimed in claim 55 or claim 56 in the form of tablets, coated tablets, ampoules, suppositories, suspensions and solutions.

58. Compositions as claimed in any of claims 55 to 57 wherein the active ingredient comprises a compound of formula I as defined in claim 2 or a physiologically compatible acid addition salt thereof.

59. Compositions as claimed in claim 58 in the form of dosage units.

60. Compositions as claimed in claim 59 wherein each dosage unit contains from 50 to 300 mg of active ingredient.

61. Compositions as claimed in any of claims 55 to 57 wherein the active ingredient comprises a compound of formula I as defined in claim 3 or a physiologically compatible acid addition salt thereof.

62. Compositions as claimed in claim 61 in the form of dosage units.

63. Compositions as claimed in claim 62 wherein each dosage unit contains from 20 to 50 mg of active ingredient.

64. Compositions as claimed in any of claims 61 to 63 wherein the active ingredient comprises a compound as claimed in any of claims 5 to 8.

65. Compositions as claimed in claim 61 wherein the active ingredient comprises a compound as claimed in claim 11.

66. Pharmaceutical compositions as claimed in claim 55 substantially as herein described.

67. Pharmaceutical compositions substantially as herein described in any of Examples A to E.

68. Pharmaceutical compositions substantially as herein described in Example F or Example G.

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