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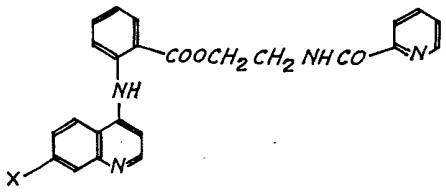
(19)

(54) 4-AMINOQUINOLINES, PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

(71) We, PIERRE FABRE S.A., a French Societe Anonyme, of 125, rue de la Faisanderie, Paris 16eme, France, 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 4-aminoquinolines, to a process for their preparation and to pharmaceutical compositions containing them.

The present invention provides compounds of the general formula



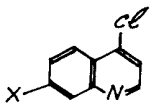
(I)

in which X is a halogen atom or a trifluoromethyl group.

Preferred compounds of the general formula I are β-nitotinamidoethyl N-(7-chloroquinolyl-4)-anthranilate and β-nicotinamidoethyl N-(7-trifluoromethylquinolyl-4)-anthranilate.

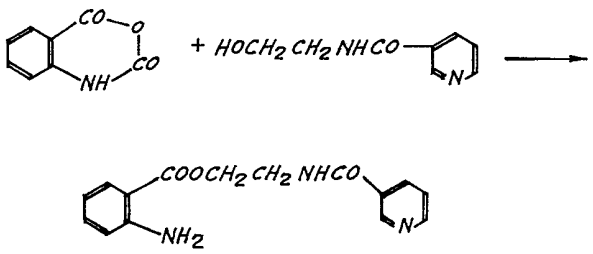
The compounds of the general formula I are bases which can be converted into acid addition salts with mineral and organic acids. Physiologically tolerable acid addition salts are preferred.

The compounds of the general formula I can be prepared in accordance with the present invention by reacting a 4-chloroquinoline of the general formula



(II)

in which X has the meaning given above, with β-nicotinamidoethyl anthranilate. The latter can be prepared by reacting isatoic anhydride with N-(β-hydroxyethyl)-nicotinamide according to the following scheme.



The compounds of the present invention exhibit good analgesic properties and possess very low ulcerogenic activity. They have low toxicity values and may therefore be used safely as drugs for the treatment of various types of pain, especially persistent pain which can be relieved only by prolonged treatment. The present invention therefore also provides pharmaceutical compositions comprising as active ingredient a compound of the general formula I or a physiologically tolerable acid addition salt thereof, in admixture or conjunction with a pharmaceutically suitable carrier.

The pharmaceutical compositions may be in a form suitable for oral, parenteral, rectal or local administration, for example in the form of compressed tablets, gelatin-coated tablets, capsules, elixirs or suppositories, and may contain other active ingredients that are therapeutically compatible. Compositions for oral administration suitably contain from 50 to 500 mg of active ingredient per unit dose for a maximum daily intake of 1800 mg of active ingredient. Compositions for rectal administration suitably contain from 100 to 800 mg of active ingredient per unit dose.

The following Examples illustrate the invention.

EXAMPLE 1.

β-nicotinamidoethyl anthranilate

Into a 10 litre vessel there are introduced 1344 g (8.3 mol) of isatoic anhydride, 5 litres of dioxan, 1328 (8 mol) of N-(β-hydroxyethyl)-nicotinamide and 48 g (1.2 mol) of sodium hydroxide. The whole is heated for 2 hours at 80°C. A large amount of CO_2 is given off. The dioxan is evaporated off *in vacuo* and the anthranilate is precipitated. 5 litres of water are added and the whole is filtered.

After drying, there is obtained a 90% yield of the title compound, which has the following characteristics:

Molecular formula: $C_{15}H_{15}N_3O_3$
Melting point: 133°C
Molecular weight: 285.3
Infra red spectrum: ν C=C (aromatic) at 1575 cm^{-1}
ν C=O (acid) at 1630 cm^{-1}
ν C=O (ester) at 1680 cm^{-1}
Thin layer chromatography:
—support: silica gel
—solvent: ethyl acetate
—development: UV and iodine
—Rf: 0.28
Solubility characteristics: insoluble in water
2.5% soluble in alcohol,
100% soluble in dimethyl acetamide.

EXAMPLE 2.

β-nicotinamidoethyl N-(7-chloroquinolyl-4)-anthanilate (F 1531)

Into a 10 litre vessel there are introduced 1072 g (3.77 mol) of β-nicotinamidoethyl anthranilate, 4.5 litres of ethanol and 800 g (3.4 mol) of 4.7-dichloroquinoline hydrochloride. The reaction mixture is stirred and heated under reflux for 6 hours. The β-nicotinamidoethyl N-(7-chloroquinolyl-4)-anthranilate hydrochloride formed is precipitated.

The mixture is filtered, the residue is dissolved in 8 litres of water and neutralised by addition of 584 g of sodium bicarbonate dissolved in 30 litres of water.

The free base obtained is filtered off and recrystallised from 12 litres of chloroform.

There is obtained an 85% yield of the title compound which has the following characteristics:

Molecular formula: $C_{24}H_{19}ClN_4O_3$
Molecular weight: 446.9
Melting point: 174°C
Elemental analysis: conforms to formula
Infra red spectrum: ν C=C (aromatic) at 1575 cm^{-1}
ν C=O (amide) at 1620 cm^{-1}
ν C=O (ester) at 1680 cm^{-1}
Thin layer chromatography:
—support: silica gel
—solvent: butanol/acetic acid/water 6/2/2
—development: UV and iodine
—Rf: 0.57
Solubility characteristics: 20% soluble in a 1N solution of hydrochloric acid.

EXAMPLE 3.

β-nicotinamidoethyl N-(7-trifluoromethylquinolyl-4)-anthranilate (F 1636)

Into a 50 litre vessel there are introduced 2.77 kg of β-nicotinamidoethyl anthranilate, 2.47 kg of 4-chloro-7-trifluoromethylquinoline and 25 litres of 1N hydrochloric acid.

The whole is heated at 80°C for a few hours, allowed to cool to ambient temperature and neutralised with a solution of bicarbonate solution.

The mixture is filtered and the residue is washed with water and recrystallised from ethanol.

There is obtained 3.78 kg (yield≃80%) of the title compound which has the following characteristics:

Molecular formula: $C_{25}H_{19}F_3N_4O_3$
Molecular weight: 480.45
Melting point: 191°C
Elemental analysis: conforms to formula
Infra red spectrum: ν C=C (aromatic) at 1575 cm^{-1}
ν C=O (amide) at 1615 cm^{-1}
ν C=O (ester) at 1665 cm^{-1}
Thin layer chromatography:
—support: silica gel
—solvent: butanol/acetic acid/water 6/2/2
—development: UV and iodine
—Rf: 0.71
Solubility characteristics: 8% soluble in dimethyl formamide.

PHARMACOLOGICAL TESTS

In the tests described below, β - nicotinamidoethyl N - (7 - chloroquinolyl - 4)-anthranilate is referred to as F 1531 and β - nicotinamidoethyl N - (7 - trifluoromethylquinolyl - 4) - anthranilate as F 1636.

(A) *Toxicology*

Toxicity tests were carried out on a common mouse weighing about 20 grams, The compounds to be tested were administered orally and intrapertoneally. The LD_{50} is calculated according to the method of MILLER and TAINTER (Proc. Soc. Exper. Biol. Med. 1944,57, 261).

Compound	Oral mg/kg	I.P. mg/kg
glafenine	1500 ± 500	≃500
F 1531	2800 ± 500	>500
F 1636	3200 ± 500	>1000

(B) *Pharmacodynamics*

(1) *Analgesic properties*

(a) According to the method of SIEGMUND *et al* (J. Pharmacol. Exptl. Therap. 1957, 119, 453), the compounds are administered orally 30 minutes before the injection of a solution of phenyl benzoquinone.

Compound	ED_{50}
aspirin	100 mg/kg
glafenine	36 mg/kg
F 1531	28 mg/kg
F 1636	15 mg/kg

(b) Electric stimulation of a rabbit's tooth, according to CHEYNOL (Therapie 1959, XIV, P. 350 to 360).

The compounds F 1531 and F 1636 displayed an action superior to that of the comparison product (glafenine); at a dose of 100 mg/kg administered orally, the maximum action is seen about 60 minutes after administration.

(2) *Ulcerogenic properties in rats*

Tests were carried out for indication of ulceration in rats subjected to strain for 7 hours.

The compounds were administered orally in amounts of 10 ml/kg to male animals weighing from 200 to 230 grams, which had been starved for 24 hours, the carrier being an aqueous 4% solution of Tween 80.

The indication of ulceration is calculated according to the criteria established by PFEIFFER *et al* (Arch. Int. Pharmacodyn. 1971, 190, 6—13).

Compound	dose	N	indication of ulceration	standard deviation
carrier	5 ml/kg	10	2.2	±0.2
F 1531	100	10	5.3	±0.65
F 1636	100	10	4.2	±0.6
glafenine	100	10	8.8	±1.10
aspirin	300	10	13.1	±1.50

(3) *Absence of central properties*

The doses of F 1531 causing a mouse to fall from a horizontal rod of scratched wood, of 4 cm diameter and rotating at 8 revolutions per minute, are identical to the lethal doses. The same applies to the doses causing the loss of the contraction reflex.

In a study of the potentialisation of narcosis in mice induced by 350 mg/kg of chloral hydrate (IP method), a dose of 100 mg/kg of F 1531, administered orally 30 minutes previously, involves neither potentialisation nor reduction of the narcosis compared with the controls treated with the carrier alone. The same results apply to F 1636.

EXAMPLE 4.

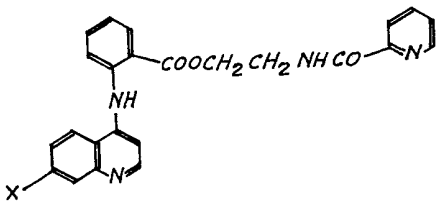
(a) *compressed tablets* F 1531 150 mg
Excipient

(b) *adult-strength suppository* F 1531 200 mg/suppository
Excipient

(c) *gelatin-coated tablets* F 1636 75 mg
Meprobamate 100 mg

WHAT WE CLAIM IS:—

1. A compound of the general formula



in which X is a halogen atom or a trifluoromethyl group.

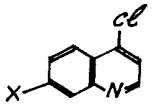
2. β-Nicotinamidoethyl N-(7-chloroquinolyl-4)-anthranilate.

3. β-Nicotinamidoethyl N-(7-trifluoromethylquinolyl-4)-anthranilate.

4. An acid addition salt of a compound according to any one of claims 1 to 3.

5. An acid addition salt according to claim 4 which is physiologically tolerable.

6. A process for the preparation of a compoud according to claim 1, which comprises reacting a 4-chloroquinoline of the general formula



in which X is a halogen atom or a trifluoromethyl group, with β-nicotinamidoethyl anthranilate.

7. A process according to claim 6 carried out substantially as described in Example 2 or Example 3 herein.

8. A pharmaceutical composition comprising as active ingredient a compound according to claim 1 or a physiologically tolerable acid addition salt thereof, in admixture or conjunction with a pharmaceutically suitable carrier.

9. A composition according to claim 8 in a form suitable for oral, parenteral, rectal or local administration.

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