

COMPOUNDS FOR INHIBITION OF GASTRIC ACID SECRETION

TECHNICAL FIELD

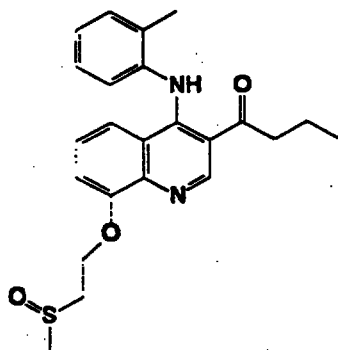
5 The present invention relates to certain salts a quinoline compound, which inhibit exogenously or endogenously stimulated gastric acid secretion and thus can be used in the prevention and treatment of gastrointestinal inflammatory diseases. In further aspects, the invention relates to salts of the invention for use in therapy; to pharmaceutical compositions
10 containing at least one salt of the invention, as active ingredient; and to the use of the salts in the manufacture of medicaments for the medical use indicated above.

15 BACKGROUND ART

Substituted quinoline derivatives that inhibit gastric acid secretion are known in the art, for example from EP-A1-259,174 and EP-A1-330,485. See also Pope, A.J. & Parsons, M.E. (1993) Trends in Pharmacological Sciences
20 14, 323-325. Salts of 4-amino-3-acyl quinoline derivatives are known from WO 92/12969.

The compound 3-butyryl-4-(2-methylphenylamino)-8-(2-methylsulfinylethoxy)quinoline is described in WO 94/29274 (publication
25 date 22 December 1994).

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DISCLOSURE OF THE INVENTION

The salts according to the invention are intended to improve the dissolution in water of the compound 3-butyryl-4-(2-methylphenylamino)-
5 8-(2-methylsulfinylethoxy)quinoline and thus improve the bioavailability *in vivo* of the said compound.

Consequently, the invention provides the compound 3-butyryl-4-(2-methylphenylamino)-8-(2-methylsulfinylethoxy)quinoline in the form of a
10 hydrochloride salt, a methanesulfonic salt or a tartaric salt.

Included in the invention are racemates as well as optical isomers of the salts according to the invention. Consequently, another aspect of the invention is the (+)-form as well as the (—)-form of the compound 3-
15 butyryl-4-(2-methylphenylamino)-8-(2-methylsulfinylethoxy)quinoline in the form of a hydrochloride salt, a methanesulfonic salt or a tartaric salt.

The salts according to the invention can be prepared by known methods, such as those disclosed in Swedish Patent Application SE 9302005-5,
20 corresponding to the published International Application WO 94/29274.

The salts according to the invention are effective as inhibitors of gastric acid secretion, and exert this effect by inhibiting the gastrointestinal H^+, K^+ -ATPase. In a more general sense, the salts of the invention may be
25 used for prevention and treatment of gastrointestinal inflammatory diseases, and gastric acid-related diseases in mammals including man, such as gastritis, gastric ulcer, duodenal ulcer, reflux esophagitis and Zollinger-Ellison syndrome.

30 Furthermore, the salts may be used for treatment of other gastrointestinal disorders where gastric antisecretory effect is desirable, e.g. in patients with gastrinomas, and in patients with acute upper gastrointestinal bleeding. They may also be used in patients in intensive care situations,

and pre-and postoperatively to prevent acid aspiration and stress ulceration.

5 A further aspect of the invention is consequently a salt according to the invention for use in therapy, or more specifically for use in inhibition of gastric acid secretion and/or for treatment of gastrointestinal inflammatory diseases.

10 Yet a further aspect of the invention is a pharmaceutical formulation comprising a salt according to the invention as active ingredient. For clinical use, the salts according to the invention can be formulated into pharmaceutical formulations for oral, rectal, parenteral or other mode of administration, as disclosed in e.g. WO 94/29274.

15 The salts according to the invention can also be used in formulations together with other active ingredients, e.g. for the treatment or prophylaxis of conditions involving infection by *Helicobacter pylori* of human gastric mucosa. Such other active ingredients may be antimicrobial agents, especially:

- 20
- β -lactam antibiotics such as amoxicillin, ampicillin, cephalothin, cefaclor or cefixime;
 - macrolides such as erythromycin, or clarithromycin;
 - tetracyclines such as tetracycline or doxycycline;
 - aminoglycosides such as gentamycin, kanamycin or amikacin;

25

 - quinolones such as norfloxacin, ciprofloxacin or enoxacin;
 - others such as metronidazole, nitrofurantoin or chloramphenicol; or
 - preparations containing bismuth salts such as bismuth subcitrate, bismuth subsalicylate, bismuth subcarbonate, bismuth subnitrate or bismuth subgallate.

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Included in the invention is therefore also the use of a salt according to the invention for the manufacture of a medicament for (i) the inhibition of gastric acid secretion, (ii) the treatment of gastrointestinal inflammatory

diseases, or (iii) the treatment or prophylaxis of conditions involving infection by *Helicobacter pylori* of human gastric mucosa. In case (iii), the said salt is adapted to be administered in combination with at least one antimicrobial agent.

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Included in the invention is also a method for (i) inhibiting gastric acid secretion, (ii) the treatment of gastrointestinal inflammatory diseases, or (iii) the treatment or prophylaxis of conditions involving infection by *Helicobacter pylori* of human gastric mucosa, which comprises administering to a mammal, including humans, in need of such inhibition an effective amount of a salt according to the invention. In case (iii), the salt is administered in combination with at least one antimicrobial agent.

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Yet a further aspect of the invention is a pharmaceutical formulation for use in (i) the inhibition of gastric acid secretion, (ii) the treatment of gastrointestinal inflammatory diseases, or (iii) the treatment or prophylaxis of conditions involving infection by *Helicobacter pylori* of human gastric mucosa, wherein the active ingredient is a salt according to the invention. In case (iii), the salt is in combination with at least one antimicrobial agent.

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EXAMPLES

Example 1

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Preparation of 3-butyryl-4-(2-methylphenylamino)-8-(2-methylsulfinylethoxy)quinoline

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3-Butyryl-4-(2-methylphenylamino)-8-(2-methylthioethoxy)quinoline (0.15 g, 0.38 mmol) was dissolved in methylene chloride (3 ml) and cooled to -20°C. A solution of 71% m-CPBA (0.089 g, 0.36 mmol) in 1 ml of methylene chloride was added dropwise. The temperature was allowed to rise to room temperature whereafter the solution was stirred for 15 min at room temperature. The reaction mixture was washed with a saturated

sodium bicarbonate solution. The organic layer was dried over sodium sulfate and evaporated. Chromatography with methylene chloride:methanol 10:1 as the eluent gave 0.064 g (41%) of the desired product.

5

(¹H-NMR, 300 MHz, CDCl₃) 1.04 (t,3H), 1.82 (m,2H), 2.34 (s,3H), 2.80 (s,3H), 3.08 (t,2H), 3.21 (m,1H), 3.44 (m,1H), 4.62 (m,2H), 6.89 (d,1H), 6.94-7.16 (m,5H), 7.28 (d,1H), 9.20 (s,1H), 11.82 (s,1H).

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Example 2

Resolution of 3-butyryl-4-(2-methylphenylamino)-8-(2-methylsulfinylethoxy)quinoline

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A mixture of 3-butyryl-4-(2-methylphenylamino)-8-(2-methylsulfinylethoxy)quinoline (9.3 g, 0.023 mmol) and D-(–)-tartaric acid (3.45 g, 0.023 mmol) in methanol (180 ml) was heated to reflux. The solution was allowed to cool to room temperature and stirred for 60 h. The precipitate was filtered off and washed with a total amount of 20 ml methanol giving 6.1 g of the tartaric salt (the filtrate was used in Example 3). Recrystallization from methanol was repeated 3 times yielding 3.05 g, 1.30 g and finally 1.05 g of the tartaric salt of Example 3. The salt was neutralized with a saturated sodium bicarbonate in methylene chloride and water. The organic layer was dried over sodium sulfate and the solvent was evaporated. Trituration with isopropyl ether gave 0.7 g of the pure (+)-enantiomer.

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*Example 3**Resolution of 3-butyryl-4-(2-methylphenylamino)-8-(2-methylsulfinylethoxy)quinoline*

- 5 The filtrate from the first crystallization in Example 2 was evaporated. The salt was neutralized with a saturated sodium bicarbonate solution in methylene chloride and water. The organic layer was dried over sodium sulfate and the solvent was evaporated. The solid residue (4.6 g, 0.011 mole) and L-(+)-tartaric acid (1.68 g, 0.011 mole) were dissolved in warm
- 10 methanol (110 ml). The solution was allowed to cool to room temperature and stirred for 72 h. The precipitate was filtered off and washed with a total amount of 11 ml methanol giving 1.5 g of the tartaric salt. Recrystallization from methanol gave 1.05 g of the tartaric salt of Example 57. The salt was neutralized with a saturated sodium bicarbonate solution
- 15 in methylene chloride and water. The organic layer was dried over sodium sulfate and the solvent was evaporated. Trituration with isopropyl ether gave 0.7 g of the pure (–)-enantiomer.

- The enantiomers were separated on a 250 X 4.6 mm i.d. Chiralpak AD
- 20 column (Daciel, Japan) using the following parameters:
n-hexane: 2-propanol: acetonitrile: diethyl amine (82: 18: 2: 0.1);
temperature: +35°C; flow rate: 0.8 ml/min.
Retention times: Example 2: 14.5 min, Example 3: 18.4 min.

- 25 Example 2: (¹H-NMR, 300 MHz, DMSO-d₆) 0.95 (t, 3H), 1.55-1.8 (m, 2H), 2.3 (s, 3H), 2.75 (s, 3H), 3.05-3.25 (m, 3H), 3.33-3.5 (m, 1H), 4.3 (s, 2H), 4.45-4.65 (m, 2H) 6.85 (d, 1H), 7.05-7.25 (m, 4H), 7.3 (d, 1H), 7.35 (d, 1H), 9.15 (s, 1H)
- 30 Example 3: (¹H-NMR, 400 MHz, DMSO-d₆) 0.95 (t, 3H), 1.5-1.7 (m, 2H), 2.3 (s, 3H), 2.75 (s, 3H), 3.05-3.2 (m, 3H), 3.35-3.5 (m, 1H), 4.3 (s, 2H), 4.45-4.6 (m, 2H) 6.85 (d, 1H), 7.05-7.2 (m, 4H), 7.25 (dd, 1H), 7.35 (d, 1H), 9.15 (s, 1H)

Example 4

Preparation of the hydrochloride salt of 3-butyryl-4-(2-methylphenylamino)-8-(2-methylsulfinylethoxy)quinoline

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3-Butyryl-4-(2-methylphenylamino)-8-(2-methylsulfinylethoxy) quinoline (10.2 g, 24.8 mmol) was dissolved in methylene chloride (80 ml). A solution of hydrogen chloride in isopropanol was added until a pH value below 3 was obtained. The solvent was evaporated and the residue treated with ethyl acetate (100 ml). The product was filtrated and washed with ethyl acetate. Yield 9.6 g (86%).

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(¹H-NMR, 300 MHz, CDCl₃) 1.03 (t, 3H), 1.80 (m, 2H), 2.25 (s, 3H), 2.87 (s, 3H), 3.12-3.25 (m, 3H), 4.08 (m, 1H), 4.68 (m, 2H), 6.90-7.39 (m, 7H), 9.34 (s, 1H), 13.35 (s, 1H).

Example 5

Preparation of the methanesulfonic acid salt of 3-butyryl-4-(2-methylphenylamino)-8-(2-methylsulfinylethoxy)quinoline

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Methanesulfonic acid (0.145 g, 1.51 mmol) was added to 3-butyryl-4-(2-methylphenylamino)-8-(2-methylsulfinylethoxy)quinoline (0.62 g, 1.51 mmol) in ethanol (10 ml). The solvent was evaporated. Trituration with ethyl acetate gave 0.4 g (52 %) of the desired product.

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(¹H-NMR, 300 MHz, CDCl₃) 1.05 (t, 3H), 1.75 (m, 2H), 2.25 (s, 3H), 2.75 (s, 3H), 2.90 (s, 3H), 3.10-3.20 (m, 3H) 3.85 (m, 1H), 4.70 (m, 2H), 6.95 (d, 1H), 7.10-7.45 (m, 6H), 9.90 (s, 1H), 13.35 (s, 1H)

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BIOLOGICAL TESTS

In vitro experiments

- 5 Inhibiting effect on acid secretion *in vitro* in isolated rabbit gastric glands was measured as described by Berglindh et al. (1976) Acta Physiol. Scand. 97, 401-414.

Bioavailability

- 10 Bioavailability was assessed by calculating the quotient between the area under blood/plasma concentration (AUC) curve following (i) intraduodenal (i.d.) or oral (p.o.) administration and (ii) intravenous (i.v.) administration from the rat or the dog, respectively.

Potency for inhibition of acid secretion

- 15 The potency for inhibition of acid secretion is measured in the rat or dog intravenously, intraduodenally or orally.

Inhibiting effect on acid secretion in female rats

- 20 Female rats of the Sprague-Dawley strain were used. They were equipped with cannulated fistulae in the stomach (lumen) and the upper part of the duodenum, for collection of gastric secretions and administration of test substances, respectively. A recovery period of 14 days after surgery was allowed before testing commenced.
- 25 Before secretory tests, the animals were deprived of food but not water for 20 h. The stomach was repeatedly washed through the gastric cannula with tap water (37°C), and 6 ml of Ringer-Glucose given subcutaneously. Acid secretion was stimulated with infusion during 3 h (1.2 ml/h, subcutaneously) of pentagastrin and carbachol (20 and 110 nmol/kg h, respectively), during which time gastric secretions were collected in 30-min
- 30 fractions. Test substances or vehicles were given intravenously or intraduodenally at 60 min after starting the stimulation, in a volume of 1.0 ml/kg. Gastric juice samples were titrated to pH 7.0 with NaOH, 0.1 M,

and acid output calculated as the product of titrant volume and concentration.

Further calculations were based on group mean responses from 4-5 rats.

- 5 The acid output during the periods after administration of test substances or vehicle were expressed as fractional responses, setting the acid output in the 30-min period preceding administration to 1.0. Percentage inhibition was calculated from the fractional responses elicited by test compound and vehicle. ED₅₀ values were obtained from graphical interpolation on log
- 10 dose-response curves, or estimated from single-dose experiments assuming a similar slope for all dose-response curves. After i.d. administration of 6 µmol/kg, the compound according to Example 4 gave an inhibition of 85% of the acid secretion.

15 *Bioavailability in rat*

- Adult rats of the Sprague-Dawley strain were used. One to three days prior to the experiments all rats were prepared by cannulation of the left carotid artery under anaesthesia. The rats used for intravenous experiments were also cannulated in the jugular vein (Popovic (1960) J. Appl. Physiol.
- 20 15, 727-728). The cannulas were exteriorized at the nape of the neck.

Blood samples (0.1 - 0.4 g) were drawn repeatedly from the carotid artery at intervals up to 5.5 hours after given dose. The samples were frozen until analysis of the test compound.

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- The area under the blood concentration vs. time curve, AUC, was determined by the log/linear trapezoidal rule and extrapolated to infinity by dividing the last determined blood concentration by the elimination rate constant in the terminal phase. The systemic bioavailability (F%) following
- 30 intraduodenal or oral administration was calculated as
- $$F(\%) = (\text{AUC (p.o. or i.d.)} / \text{AUC (i.v.)}) \times 100.$$

Inhibition of gastric acid secretion and bioavailability in the conscious dog.

Labrador retriever or Harrier dogs of either sex were used. They were equipped with a duodenal fistula for the administration of test compounds or vehicle and a cannulated gastric fistula or a Heidenhaim-pouch for the collection of gastric secretion.

Before secretory tests the animals were fasted for about 18 h but water was freely allowed. Gastric acid secretion was stimulated for up to 6.5 h infusion of histamine dihydrochloride (12 ml/h) at a dose producing about 80% of the individual maximal secretory response, and gastric juice collected in consecutive 30-min fractions. Test substance or vehicle was given orally, i.d. or i.v., 1 or 1.5 h after starting the histamine infusion, in a volume of 0.5 ml/kg body weight. In the case of oral administration, it should be pointed out that the test compound is administered to the acid secreting main stomach of the Heidenham-pouch dog.

The acidity of the gastric juice samples were determined by titration to pH 7.0, and the acid output calculated. The acid output in the collection periods after administration of test substance or vehicle were expressed as fractional responses, setting the acid output in the fraction preceding administration to 1.0. Percentage inhibition was calculated from fractional responses elicited by test compound and vehicle. ED₅₀-values were obtained by graphical interpolation on log dose-response curves, or estimated under the assumption of the same slope of the dose-response curve for all test compounds. All results are based on acid output during the period from 1.5 to 2 hours after dosing.

Blood samples for the analysis of test compound concentration in plasma were taken at intervals up to 4 h after dosing. Plasma was separated and frozen within 30 min after collection and later analyzed. The systemic bioavailability (F%) after oral or i.d. administration was calculated as described above in the rat model.

THIS SHEET HAS BEEN
REPLACED

CLAIMS

1. The compound 3-butyryl-4-(2-methylphenylamino)-8-(2-methylsulfinylethoxy)quinoline in the form of a hydrochloride salt, a methanesulfonic salt or a tartaric salt.
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2. The compound according to claim 1 in the form of a hydrochloride salt.
3. The compound according to claim 1 in the form of a methanesulfonic salt.
10
4. The compound according to claim 1 in the form of a tartaric salt.
5. The compound (+)-3-butyryl-4-(2-methylphenylamino)-8-(2-methylsulfinylethoxy)quinoline in the form of a hydrochloride salt, a methanesulfonic salt or a tartaric salt.
15
6. The compound (-)-3-butyryl-4-(2-methylphenylamino)-8-(2-methylsulfinylethoxy)quinoline in the form of a hydrochloride salt, a methanesulfonic salt or a tartaric salt.
20
7. A salt as claimed in any one of claims 1-6 for use in therapy.
8. A salt as claimed in any one of claims 1-6 for use in inhibition of gastric acid secretion and/or for treatment of gastrointestinal inflammatory diseases.
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9. A pharmaceutical formulation comprising a salt as claimed in any one of claims 1-6 as active ingredient.
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10. Use of a salt as claimed in any one of claims 1-6 for the manufacture of a medicament for the inhibition of gastric acid secretion.

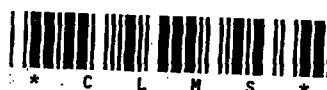


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11. Use of a salt as claimed in any one of claims 1-6 for the manufacture of a medicament for the treatment of gastrointestinal inflammatory diseases.
12. Use of a salt as claimed in any one of claims 1-6 for the manufacture of a medicament for the treatment or prophylaxis of conditions involving infection by *Helicobacter pylori* of human gastric mucosa, wherein the said salt is adapted to be administered in combination with at least one antimicrobial agent.
13. A method for inhibiting gastric acid secretion which comprises administering to a mammal, including humans, in need of such inhibition an effective amount of a salt as claimed in any one of claims 1-6.
14. A method for the treatment of gastrointestinal inflammatory diseases which comprises administering to a mammal, including humans, in need of such treatment an effective amount of a salt as claimed in any one of claims 1-6.
15. A method for the treatment or prophylaxis of conditions involving infection by *Helicobacter pylori* of human gastric mucosa, which comprises administering to a mammal, including humans, in need of such treatment an effective amount of a salt as claimed in any one of claims 1-6, wherein the said salt is administered in combination with at least one antimicrobial agent.
16. A pharmaceutical formulation for use in the inhibition of gastric acid secretion wherein the active ingredient is a salt according to any one of claims 1-6.
17. A pharmaceutical formulation for use in the treatment of gastrointestinal inflammatory diseases wherein the active ingredient is a salt according to any one of claims 1-6.

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* C L H S *

18. A pharmaceutical formulation for use in the treatment or prophylaxis of conditions involving infection by *Helicobacter pylori* of human gastric mucosa, wherein the active ingredient is a salt according to any one of claims 1-6 in combination with at least one antimicrobial agent.

