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54 Virsraksts: **Terapeitiski aktīvs benzimidazols un tā iegūšanas paņēmiens**

57 Kopsavilkums: Piedāvāts 5-hlor-2-[(3,4-dimetoksi-2-piridinil)metil]sulfinil-1H-benzimidazols un tā farmaceutiski saderīgi sāļi, kā arī starpprodukts, ārstēšanas līdzekļi, kas satur piedāvāto savienojumu kā aktīvo vielu.

Izgudrojuma nosaukums: "Terapeitiski aktīvs benzimidazols un panēmiens tā iegūšanai"

Patentformulas punkti

1. 5-Hlor-2-(((3,4-dimetoksi-2-piridinil)metil)sulfinil)-1H-benzimidazols (savienojums I), tā farmaceutiski piememamās sāļis un tā optiskie izomēri.
2. Savienojums pēc punkta 1, iegūts nātrijs sāls veidā.
3. Savienojums pēc punkta 1, iegūts magnijs sāls veidā.
4. Ārstniecības līdzeklis, kas satur savienojumu pēc punkta 1 kā aktīvo vielu.
5. Savienojums pēc punkta 1, kas paredzēts pielietošanai ārstniecībā.
6. Savienojums pēc punkta 1, kas paredzēts kunga skābes izdalīšanās nomāšanai zidītājos, ieskaitot oīlvēku.

7. Savienojums pēc punkta 1, kas paredzēts kuņģa un zarnu trakta iekaisuma procesu ārstēšanai zīdītājos, ieskaitot oīlvēku.
8. Savienojuma pēc punkta 1, pielietojums tādu ārstniecības līdzekļu ražošanā, kas paredzēti kuņģa skābes izdalīšanās nomākšanai zīdītājos, ieskaitot oīlvēku.
9. Savienojuma pēc punkta 1, pielietojums tādu ārstniecības līdzekļu ražošanā, kas paredzēti kuņģa un zarnu trakta iekaisuma procesu ārstēšanai zīdītājos, ieskaitot oīlvēku.
10. Patēmis savienojuma pēc punkta 1 iegūšanai, kas atšķiras ar to, ka 5-hlor-2-[(3,4-dimetoksi-2-pīridinil)-metil]tio)-1H-benzimidazolu oksidē par savienojumu pēc punkta 1 un, ja vajadzīgs, pārvērē to salī vai optiski tīrā izomērā.
11. 5-Hlor-2-[(3,4-dimetoksi-2-pīridinil)metil]tio)-1H-benzimidazols.

Therapeutically active substituted benzimidazole and
process for its preparation

DESCRIPTION

5

Field of the invention

The object of the present invention is to provide a novel
compound, and therapeutically acceptable salts thereof,
10 which inhibit exogenously or endogenously stimulated
gastric acid secretion and thus can be used in the
prevention and treatment of peptic ulcer.

The present invention also relates to the use of the
15 compound of the invention, especially therapeutically
acceptable salts thereof, for inhibiting gastric acid
secretion in mammals including man. In a more general
sense, the compound of the invention may be used for
prevention and treatment of gastrointestinal inflammatory
20 diseases, and gastric acid-related diseases in mammals
including man, such as gastritis, gastric ulcer, duodenal
ulcer, reflux esophagitis, and Zollinger-Ellison
syndrome. Furthermore, the compound may be used for
treatment of other gastrointestinal disorders where
25 gastric antisecretory effect is desirable e.g. in patients
with gastrinomas, and in patients with acute upper
gastrointestinal bleeding. It may also be used in patients
in intensive care situations, and pre- and postoperatively
to prevent acid aspiration and stress ulceration. The
30 compound of the invention may also be used for treatment
or prophylaxis of inflammatory conditions in mammals,
including man, especially those involving lysozymal
enzymes. Conditions that may be specifically mentioned
are rheumatoid arthritis and gout. The compound may also
35 be useful in the treatment of diseases related to bone
metabolism disorders as well as the treatment of glaucoma.

The invention also relates to pharmaceutical compositions containing the compound of the invention, or a therapeutically acceptable salt thereof, as active ingredient. In a further aspect, the invention relates to
5 processes for preparation of such new compound, to a novel intermediate in the preparation of the compound and to the use of the active compound for the preparation of pharmaceutical compositions for the medical use indicated above.

10

It is a specific primary object of the invention to provide a compound with a high level of bioavailability. The compound of the invention will also exhibit high stability properties at neutral pH and a high potency in
15 regard to inhibition of gastric acid secretion. Bioavailability is defined as the fraction, or percent, of the administered dose of compound that is absorbed unchanged into the systemic blood. Potency is in this application defined as the ED₅₀ value.

20

Prior art and background of the invention

Benzimidazole derivatives intended for inhibiting gastric acid secretion are disclosed in numerous patent documents.
25 Among these can be mentioned GB 1 500 043, GB 1 525 958, US 4 182 766, US 4 255 431, US 4 599 347, US 4 555 518, US 4 727 150, US 4 628 098, EP 208 452 and Derwent abstract 87-294449/42. Benzimidazole derivatives proposed for use in the treatment or prevention of special
30 gastrointestinal inflammatory diseases are disclosed in US 4 539 465.

The invention

35 Compounds described in the prior art, as described above, are effective acid secretion inhibitors, and are thus

useful as antiulcer compounds. In order to further enhance the usefulness of this type of drugs, a higher bioavailability has been desired, but still the compounds should have a high potency in inhibiting gastric acid secretion and also a high chemical stability at neutral pH.

It has been recognized that 2-[(2-pyridinylmethyl)-sulfinyl]-1H-benzimidazoles tested show a great variability in bioavailability as well as in potency and stability, and it is difficult to identify compounds possessing all the three advantageous properties. There is no guidance in the prior art on how to obtain compounds with this combination of properties.

It has been found that the compound of the invention shows exceedingly high bioavailability, and still the compound is very effective as inhibitor of gastric acid secretion and exhibits a high chemical stability in solution at a neutral pH. Thus the compound of the invention can be used in the indications given above in mammals including man.

The compound of the invention is 5-chloro-2-[[3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (compound I) and physiologically acceptable salts thereof.

The compound of the invention has an asymmetric centre in the sulfur atom, i.e. exists as two optical isomers (enantiomers). Both the pure enantiomers, racemic mixtures (50% of each enantiomer) and unequal mixtures of the two are within the scope of the present invention. Also one synthetic intermediate compound and process for the preparation are within the scope.

Preparation

The compound of the invention, may be prepared according to the following method:

5

Oxidizing 5-chloro-2-[[[3,4-dimethoxy-2-pyridinyl) methyl]thio-1H-benzimidazole (compound II) to give the compound of the invention. This oxidation may be carried out by using an oxidizing agent such as nitric acid, 10 hydrogen peroxide, (optionally in the presence of vanadium compounds), peracids, peresters, ozone, dinitrogen tetroxide, iodosobenzene, N-halosuccinimide, 1-chlorobenzotriazole, t-butylhypochlorite, diazabicyclo-[2,2,2]-octane bromine complex, sodium metaperiodate, 15 selenium dioxide, manganese dioxide, chromic acid, ceric ammonium nitrate, bromine, chlorine, and sulfuric chloride. The oxidation usually takes place in a solvent, such as halogenated hydrocarbons, alcohols, ethers, ketones.

20

The oxidation may also be carried out enzymatically by using an oxidizing enzyme or microbially by using a suitable microorganism.

25 Depending on the process conditions and the starting materials, the compound of the invention is obtained either in neutral or salt form. Both the neutral compound and the salts of this are included within the scope of the invention. Thus, basic, neutral or mixed salts may be 30 obtained as well as hemi, mono, sesqui or polyhydrates.

Alkaline salts of the compound of the invention are exemplified by its salts with Li^+ , Na^+ , K^+ , Mg^{2+} , Ca^{2+} , and $\text{N}^+(\text{R})_4$, where R is (1-4 C)alkyl. Particularly 35 preferred are the Na^+ , Ca^{2+} and Mg^{2+} salts. Especially preferred are the Na^+ and Mg^{2+} salts. Such salts may be

prepared by reacting the compound with a base capable of releasing the desired cation.

5 Examples of bases capable of releasing such cations, and examples of reaction conditions are given below.

a) Salts wherein the cation is Li^+ , Na^+ or K^+ are prepared by treating the compound of the invention with LiOH , NaOH or KOH in an aqueous or nonaqueous medium or with LiOR ,
10 LiNH_2 , LiNR_2 , NaOR , NaNH_2 , NaNR_2 , KOR , KNH_2 or KNR_2 , wherein R is an alkyl group containing 1-4 carbon atoms, in a nonaqueous medium.

b) Salts wherein the cation is Mg^{2+} or Ca^{2+} , are prepared
15 by treating the compound of the invention with Mg(OR)_2 , Ca(OR)_2 or CaH_2 , wherein R is an alkyl group containing 1-4 carbon atoms, in a nonaqueous solvent such as an alcohol (only for the alcoholates), e.g. ROH , or in an ether such as tetrahydrofuran.

20

Racemates obtained can be separated into the pure enantiomers. This may be done according to known methods, e.g. from racemic diastereomeric salts by means of chromatography or fractional crystallization.

25

The starting materials described in the intermediate examples may be obtained according to processes known per se.

30 For clinical use the compound of the invention is formulated into pharmaceutical formulations for oral, rectal, parenteral or other modes of administration. The pharmaceutical formulation contains the compound of the invention normally in combination with a pharmaceutically
35 acceptable carrier. The carrier may be in the form of a solid, semi-solid or liquid diluent, or a capsule. These

pharmaceutical preparations are a further object of the invention. Usually the amount of active compound is between 0.1-95% by weight of the preparation, between 0.2-20% by weight in preparations for parenteral use and
5 between 1-50% by weight in preparations for oral administration.

In the preparation of pharmaceutical formulations containing the compound of the present invention in the
10 form of dosage units for oral administration the compound selected may be mixed with a solid, powdered carrier, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives, gelatin, or another suitable carrier, stabilizing substances such as alkaline
15 compounds e.g. carbonates, hydroxides and oxides of sodium, potassium, calcium, magnesium and the like as well as with lubricating agents such as magnesium stearate, calcium stearate, sodium stearyl fumarate and polyethylenglycol waxes. The mixture is then processed
20 into granules or pressed into tablets. Granules and tablets may be coated with an enteric coating which protects the active compound from acid catalyzed degradation as long as the dosage form remains in the stomach. The enteric coating is chosen among
25 pharmaceutically acceptable enteric-coating materials e.g. beeswax, shellac or anionic film-forming polymers such as cellulose acetate phthalate, hydroxypropyl-methylcellulose phthalate, partly methyl esterified methacrylic acid polymers and the like, if preferred in combination with a
30 suitable plasticizer. To the coating various dyes may be added in order to distinguish among tablets or granules with different active compounds or with different amounts of the active compound present.

35 Soft gelatine capsules may be prepared with capsules containing a mixture of the active compound of the

invention, vegetable oil, fat, or other suitable vehicle for soft gelatine capsules. Soft gelatine capsules may also be enteric-coated as described above. Hard gelatine capsules may contain granules or enteric-coated granules of the active compound. Hard gelatine capsules may also contain the active compound in combination with a solid powdered carrier such as lactose, saccharose, sorbitol, mannitol, potato starch, amylopectin, cellulose derivatives or gelatine. The hard gelatine capsules may be enteric-coated as described above.

Dosage units for rectal administration may be prepared in the form of suppositories which contain the active substance mixed with a neutral fat base, or they may be prepared in the form of a gelatine rectal capsule which contains the active substance in a mixture with a vegetable oil, paraffin oil or other suitable vehicle for gelatine rectal capsules, or they may be prepared in the form of a ready-made micro enema, or they may be prepared in the form of a dry micro enema formulation to be reconstituted in a suitable solvent just prior to administration.

Liquid preparation for oral administration may be prepared in the form of syrups or suspensions, e.g. solutions or suspensions containing from 0.2% to 20% by weight of the active ingredient and the remainder consisting of sugar or sugar alcohols and a mixture of ethanol, water, glycerol, propylene glycol and/or polyethylene glycol. If desired, such liquid preparations may contain colouring agents, flavouring agents, saccharine and carboxymethyl cellulose or other thickening agents. Liquid preparations for oral administration may also be prepared in the form of a dry powder to be reconstituted with a suitable solvent prior to use.

Solutions for parenteral administration may be prepared as a solution of the compound of the invention in a pharmaceutically acceptable solvent, preferably in a concentration from 0.1% to 10% by weight. These solutions
5 may also contain stabilizing agents and/or buffering agents and may be manufactured in different unit dose ampoules or vials. Solutions for parenteral administration may also be prepared as a dry preparation to be reconstituted with a suitable solvent
10 extemporaneously before use.

The typical daily dose of the active substance will depend on various factors such as for example the individual requirement of each patient, the route of
15 administration and the disease. In general, oral and parenteral dosages will be in the range of 5 to 500 mg per day of active substance.

The invention is illustrated by the following examples.
20

Example 1

Preparation of 5-chloro-2-[[[(3,4-dimethoxy-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole
25

5-chloro-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]thio]-1H-benzimidazole (645 mg, 0.0019 mol) was dissolved in 25 ml CH_2Cl_2 and mixed with NaHCO_3 (323 mg, 0.0038 mol) dissolved in 10 ml H_2O . The stirred mixture was cooled to
30 0°C and treated with MCPBA (84%, 389 mg, 0.0019 mol) dissolved in 6 ml CH_2Cl_2 . After reacting for 10 min the layers were separated and the aqueous layer extracted with 5 ml CH_2Cl_2 . The organic layers were combined and extracted with 20 ml water containing NaOH (154 mg, 0.0038
35 mol). The latter aqueous layer was collected (residual

CH₂Cl₂ distilled off on the rotavapor) and treated with two portions of HCOOCH₃ (2 x 118 μl, 0.0038 mol).

5 The solid thus formed was collected, washed with a small volume of ice cold water leaving 253 mg (38%) pure product as a white powder. The mother liquor was quickly extracted with 20 + 10 ml CH₂Cl₂. The organic layers were combined, dried over MgSO₄, and evaporated leaving a foam which upon treatment with CH₃CN spontaneously
10 crystallized. The solid was collected, washed with a small volume of ice cold CH₃CN affording additional 225 mg (34%) pure title compound. NMR data is given below.

Example 2

15

Preparation of 5-chloro-2-[[[(3,4-dimethoxy-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole, sodium salt

20 5-chloro-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (4.1 g; 11.65 mmol) dissolved in dichloromethane (100 ml) and sodium hydroxide (0.46 g; 11.5 mmol) dissolved in water (100 ml) were transferred to a separatory funnel. The mixture was shaken to equilibrium whereupon the solvent phases were separated. The water
25 solution was washed with dichloromethane (2 x 25 ml) and then freeze dried. The residue was recrystallized from ethyl acetate/diethyl ether.

30 Yield: 3.7 g (86 %) of the title compound. NMR data is given below.

Table 1

Ex.	Solvent	NMR data δ ppm
5	1 CDCl ₃ (500 MHz)	3.84(s, 3H), 3.88(s, 3H), 4.70(d, 1H), 4.84(d, 1H), 6.80(d, 1H), 7.26(dd, 1H), 7.55(d, 1H), 7.58(d, 1H), 8.16(d, 1H),
10	2 D ₂ O δ (D ₂ O, 4.82) (300 MHz)	3.69(s, 3H), 3.91(s, 3H), 4.64(d, 1H), 4.80(d, 1H), 7.04(d, 1H), 7.20(m, 1H), 7.60(d, 1H), 7.67(d, 1H), 8.11(d, 1H)

Preparation of synthetic intermediates15 Example I 1. Preparation of 3,4-dimethoxy-
2-chloromethylpyridine.

3,4-Dimethoxy-2-hydroxymethylpyridine (0.34 g, 0.002 mol) was dissolved in CH₂Cl₂ (8 ml). SOCl₂ (0.27 g, 0.00227 mol) in CH₂Cl₂ (2 ml) was added under stirring at room temperature. After 10 min the mixture was neutralized with NaHCO₃ (5 ml). The phases were separated, the CH₂Cl₂ phase was washed with NaCl-solution, dried over Na₂SO₄ and evaporated giving the desired product (0.61 g, 88%).

25

Example I 230 Preparation of 5-chloro-2-[[(3,4-dimethoxy-2-pyridinyl)-
methyl]thio]-1H-benzimidazole

2-chloromethyl-3,4-dimethoxypyridine hydrochloride (896 mg, 0.004 mol) was dissolved in 25 ml MeOH and treated with NaOH (390 mg, 0.008 mol) dissolved in 1.5 ml H₂O. 5-chloro-2-mercapto-1H-benzimidazole (812 mg, 0.0044 mol) was added and the resulting mixture allowed to react for

2h at room temperature. The solvent was evaporated and the residue partitioned between 50 ml 2.5 % NaOH and 75 ml CH₂Cl₂. The aqueous layer was separated and extracted twice with 25 ml CH₂Cl₂. The organic layers were combined, washed with 25 ml H₂O, dried over MgSO₄, and the solvent was evaporated.

The crude product was triturated with approximately 5 ml of EtOAc saturated with NH₃. The solid was collected and the mother liquor reprocessed furnishing 650 mg (48%) of the title compound as an off white powder.

Identifying data for the starting compound according to the example are given in Table 2.

Table 2

Ex.	Solvent	NMR data δ ppm (500 MHz)
I-2	CD ₂ Cl ₂	3.96(s, 3H), 3.99(s, 3H), 4.46(s, 2H), 6.96(d, 1H), 7.18(dd, 1H), 7.48(d, 1H), 7.56(d, 1H), 8.31(d, 1H).

The best mode of carrying out the invention known at present is to use the sodium salt of the compound of the formula I, thus the compound described in Example 2.

Pharmaceutical preparations containing the compound of the invention as active ingredient are illustrated in the following formulations.

Syrup

A syrup containing 1% (weight per volume) of active substance was prepared from the following ingredients:

	Compound according to Example 1	1.0 g
	Sugar, powder	30.0 g
	Saccharine	0.6 g
	Glycerol	5.0 g
5	Flavouring agent	0.05 g
	Ethanol 96%	5.0 g
	Distilled water q.s. to a final volume of	100 ml

Sugar and saccharine were dissolved in 60 g of warm water.
 10 After cooling the active compound was added to the sugar solution and glycerol and a solution of flavouring agents dissolved in ethanol were added. The mixture was diluted with water to a final volume of 100 ml.

15 Enteric-coated tablets

An enteric coated tablet containing 50 mg of active compound was prepared from the following ingredients:

20	I	Compound according to Example 1 as Mg salt	500 g
		Lactose	700 g
		Methyl cellulose	6 g
		Polyvinylpyrrolidone cross-linked	50 g
25		Magnesium stearate	15 g
		Sodium carbonate	6 g
		Distilled water	q.s.
	II	Cellulose acetate phthalate	200 g
30		Cetyl alcohol	15 g
		Isopropanol	2000 g
		Methylene chloride	2000 g

35 I Compound according to example 1, powder, was mixed with lactose and granulated with a water solution of methyl cellulose and sodium carbonate. The wet mass was

forced through a sieve and the granulate dried in an oven. After drying the granulate was mixed with polyvinylpyrrolidone and magnesium stearate. The dry mixture was pressed into tablet cores (10 000 tablets),
 5 each tablet containing 50 mg of active substance, in a tableting machine using 7 mm diameter punches.

II A solution of cellulose acetate phthalate and cetyl alcohol in isopropanol/methylene chloride was sprayed onto
 10 the tablets I in an Accela Cota[®], Manesty coating equipment. A final tablet weight of 110 mg was obtained.

Solution for intravenous administration

15 A parenteral formulation for intravenous use, containing 4 mg of active compound per ml, was prepared from the following ingredients:

20	Compound according to Example 2	4 g
	Sterile water to a final volume of	1000 ml

The active compound was dissolved in water to a final volume of 1000 ml. The solution was filtered through a
 25 0.22 μm filter and immediately dispensed into 10 ml sterile ampoules. The ampoules were sealed.

Capsules

30 Capsules containing 30 mg of active compound were prepared from the following ingredients:

	Compound according to Example 1	300 g
	Lactose	700 g
35	Microcrystalline cellulose	40 g
	Hydroxypropyl cellulose low-substituted	62 g

Disodium hydrogen phosphate	2 g
Purified water	q.s.

The active compound was mixed with the dry ingredients
 5 and granulated with a solution of disodium hydrogen
 phosphate. The wet mass was forced through an extruder and
 spheronized and dried in a fluidized bed dryer.

500 g of the pellets above were first coated with a
 10 solution of hydroxypropyl methylcellulose, 30 g, in water,
 750 g, using a fluidized bed coater. After drying, the
 pellets were coated with a second coating as given below:

Coating solution:

15	Hydroxypropyl methylcellulose phthalate	70 g
	Cetyl alcohol	4 g
	Acetone	200 g
	Ethanol	600 g

20

The final coated pellets were filled into capsules.

Suppositories

25 Suppositories were prepared from the following ingredients
 using a welding procedure. Each suppository contained 40
 mg of active compound.

	Compound according to Example 1	4 g
30	Witepsol H-15	180 g

The active compound was homogenously mixed with Witepsol
 H-15 at a temperature of 41°C. The molten mass was volume
 filled into pre-fabricated suppository packages to a net
 35 weight of 1.84 g. After cooling the packages were heat

sealed. Each suppository contained 40 mg of active compound.

5 Biological Effects

Bioavailability

Choice of Species for Testing.

10 The results from tests on two different animal species, rat and dog, vary in regard to measured level of bioavailability for the same compound. We believe that the rat is the more relevant species for bioavailability testing. This is based on our belief that liver
15 metabolism has the most predominant impact upon bioavailability, and that the liver metabolic pattern in man for this type of compounds is quite similar to that of the male rat (more so than of the female rat and the dog). Moreover, test results of bioavailability in the male rat
20 will tend to give a broader "spread" compared with the test results in the dog, and thus the male rat model will give more clear differences in bioavailability between different compounds. Stated in another way, the bioavailability as tested in the male rat can be expected
25 to give a better estimate of the relative differences in man between different test compounds compared with the test results obtained when using the same compounds in the dog.

30 Assessment of Bioavailability.

Bioavailability is assessed by calculating the quotient between the area under plasma concentration (AUC) curve following intraduodenal (id) administration and
35 intravenous (iv) administration from the rat or the dog. Low, therapeutically relevant doses, were used. This

method is scientifically recognized as valid for assessing bioavailability (see for instance: M. Rowland and T.N. Tozer, Clinical Pharmacokinetics, 2nd ed., Lea & Febiger, London 1989, p 42). The data from both the rat and the dog
5 are provided in Table 3.

Rough Screening Model.

Since the bioavailability model described above is time
10 and labour intensive, and requires a large number of plasma analyses, also a rough screening model, based on relative potencies to inhibit acid secretion, has been used (see for instance: A. Goth, Medical Pharmacology, 7th
ed., C.V. Mosby Company, Saint Louis 1974, p 19). Thus,
15 the ratio (called "Bioavailability" in Table 3) between the ED₅₀ at intravenous administration and the ED₅₀ at intraduodenal administration was calculated. Also these data are provided in Table 3.

20 Potency

The potency for inhibition of acid secretion has been measured in the male rat and the dog, both intravenously and intraduodenally. When it comes to relevance of the
25 animal test data for potency of a given compound in man for the present type of compounds, it is believed that potency in man will correspond to a level somewhere between what is measured in the male rat and what is measured in the dog. Potency data from the two animal
30 species are given in Table 3.

Biological Tests

Inhibition of Gastric Acid Secretion in the Conscious Male
35 Rat.

Male 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 fourteen days recovery period after surgery was allowed before testing commenced.

Before secretory tests, the animals were deprived of food but not water for 20 h. The stomach was repeatedly washed through the gastric cannula, and 6 ml of Ringer-Glucose given s.c. Acid secretion was stimulated with a infusion during 3.5 h (1.2 ml/h, s.c.) of pentagastrin and carbachol (20 and 110 nmol/kg h, respectively), during which time gastric secretions were collected in 30-min fractions. Test substances or vehicle were given iv or id at 90 min after starting the stimulation, in a volume of 1 ml/kg. Gastric juice samples were titrated to pH 7.0 with NaOH, 0.1 mol/L, and acid output calculated as the product of titrant volume and concentration. Further calculations were based on group mean responses from 4-5 rats. 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 dose-response curves, or estimated from single-dose experiments assuming a similar slope for all dose-response curves. An estimation of the bioavailability was obtained by calculating the ratio ED₅₀iv/ED₅₀id. The results reported are based on gastric acid secretion during the second hour after drug/vehicle administration.

Bioavailability in the Male Rat.

Male adult rats of the Sprague-Dawley strain were used. One day, prior to the experiments, all rats were prepared
 5 by cannulation of the left carotid artery under anaesthesia. The rats used for the intravenous experiments, were also cannulated in the jugular vein. (Ref. V Popovic and P Popovic, J Appl Physiol 1960;15,727-728). The rats used for the intraduodenal experiments,
 10 were also cannulated in the upper part of the duodenum. The cannulas were exteriorized at the nape of the neck. The rats were housed individually after surgery and were deprived of food, but not water, before administration of the test substances. The same dose (4 μ mol/kg) were given
 15 iv and id as a bolus for about one minute (2 ml/kg).

Blood samples (0.1-0.4 g) were drawn repeatedly from the carotid artery at intervals up to 4 hours after given dose. The samples were frozen as soon as possible until
 20 analysis of the test compound.

The area under the blood concentration vs time curve, AUC, was determined by the linear trapezoidal rule and extrapolated to infinity by dividing the last determined
 25 blood concentration by the elimination rate constant in the terminal phase. The systemic bioavailability (F%) following intraduodenal administration was calculated as

$$30 \quad F(\%) = \frac{AUC_{id}}{AUC_{iv}} \times 100$$

Inhibition of Gastric Acid Secretion and Bioavailability in the Conscious Dog.

35

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 ventricular fistula for the collection of gastric secretions.

5

Before secretory tests the animals were fasted for about 18 h but water was freely allowed. Gastric acid secretion was stimulated by a 4 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 id or iv 1 h after starting the histamine infusion, in a volume of 0.5 ml/kg body weight. 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 from single-dose experiments under the assumption of the same slope of the dose-response curve for all test compounds. All results reported are based on acid output 2 h after dosing.

Blood samples for the analysis of test compound concentration in plasma were taken at intervals up to 3 h after dosing. Plasma was separated and frozen within 30 min after collection. AUC (area under the plasma concentration - time curve), extrapolated to infinite time, was calculated by the linear trapezoidal rule. The systemic bioavailability (F%) after id administration was calculated as $100 \times (\text{AUC}_{\text{id}}/\text{AUC}_{\text{iv}})$.

Chemical Stability

The chemical stability of various compounds of the invention has been followed kinetically at low concentration at 37°C in aqueous buffer solution at different pH values. The results in Table 3 show the half life ($t_{1/2}$) at pH 7, that is the time period after which half the amount of the original compound remains unchanged.

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Results of biological and stability tests

Table 3 gives a summary of the test data available for the compound of the invention and a structurally closely related compound generically disclosed in the prior art, called Ref. in Table 3, namely 5-fluoro-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole within the scope of EP 208 452. As can be seen from Table 3 the compound according to the invention has a high bioavailability ($F = 97\%$ in the rat), high potency ($ED_{50}^{iv} = 1.3 \mu\text{mol/kg}$, $ED_{50}^{id} = 2.6 \mu\text{mol/kg}$ in the rat) and high chemical stability ($t_{1/2} = 30 \text{ h}$). The bioavailability of the compound of the invention has a much higher value (97% vs 47%) compared to that of the Ref. compound, although the Ref. compound has higher potency and stability. ($ED_{50}^{iv} = 0.85 \mu\text{mol/kg}$, $ED_{50}^{id} = 1.75 \mu\text{mol/kg}$ and $t_{1/2} = 58 \text{ h}$ for the Ref compound).

Table 3, Biological Test Data and Stability Data

Test compound Example no.	Inhibition of acid secretion		Dog ED ₅₀ ($\mu\text{mol/kg}$)	Rat, ED ₅₀ ($\mu\text{mol/kg}$)	Route of adm.	"Bioavailability" measured by the Rough Screening Model Rat ED ₅₀ iv/ED ₅₀ id(%)	Bioavailability measured by the AUL-method F%		Chemical Stability at pH 7 half-life (t 1/2) h
	iv	id					Dog	Rat	
1	1.75 ²⁾	1.2				50	n.t.	97	30
Ref.	n.t.	1.1 ¹⁾		0.85		49	n.t.	47	58

n.t. = not tested

1) Dog 1 1.0 $\mu\text{mol/kg}$ gave no effect
 Dog 2 2.0 $\mu\text{mol/kg}$ gave 70 % inhibition
 ED₅₀ value was estimated from one dog.

2) Only one dog

Claims:

1. 5-Chloro-2-[[[3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (compound I)
5 and physiologically acceptable salts thereof, as well as its optical enantiomers
2. A compound according to claim 1 in the form of its sodium salt.
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3. A compound according to claim 1 in the form of its magnesium salt.
4. A pharmaceutical composition containing as active
15 ingredient a compound according to claim 1.
5. A compound as defined in claim 1 for use in therapy.
6. A compound as defined in claim 1 for use in inhibiting
20 gastric acid secretion in mammals including man.
7. A compound as defined in claims 1 for use in the treatment of gastrointestinal inflammatory diseases in mammals including man.
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8. Use of a compound according to claim 1 in the manufacture of a medicament for inhibiting gastric acid secretion in mammals including man.
- 30 9. Use of a compound according to claim 1 in the manufacture of a medicament for the treatment of gastrointestinal inflammatory diseases in mammals including man.
- 35 10. A process for the preparation of a compound according to claim 1, by oxidizing 5-chloro-2-[[[3,4-dimethoxy-2-

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pyridinyl)methyl]thio]-1H-benzimidazole to the compound according to claim 1 and, if desired, convert it to a salt or into a pure optical isomer.

- 5 11. 5-Chloro-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]thio-1H-benzimidazole.