

RANITIDINE DERIVATIVES

This invention relates to salts of a furan derivative having action on histamine receptors, to a process for the preparation thereof, to pharmaceutical compositions containing them and to their use in therapeutics. More particularly the invention is concerned with salts of ranitidine formed with bismuth complexes of carboxylic acids.

Ranitidine is the approved name for N-[2-[[[5-[(dimethylamino)-methyl]-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine which, together with its physiologically acceptable salts, is described and claimed in British Patent Specification No. 1565966. Reference is made in British Patent Specification No. 1565966 to physiologically acceptable salts formed with inorganic and organic acids. Such salts include hydrochlorides, hydrobromides and sulphates, and salts formed with aliphatic mono- and di-carboxylic acids such as acetates, maleates and fumarates.

Ranitidine is a potent histamine H_2 -antagonist which, in the form of its hydrochloride salt, is widely used in the treatment of conditions where there is an advantage in lowering gastric acidity. Such conditions include duodenal and gastric ulceration, reflux oesophagitis and Zollinger-Ellison syndrome. Ranitidine may also be used prophylactically in surgical procedures, and in the treatment of allergic and inflammatory conditions where histamine is a known mediator.

Bismuth salts and preparations, such as bismuth citrate, bismuth and ammonium citrate, sodium bismuthyl tartrate, acid bismuth sodium tartrate, acid solution of bismuth, concentrated solution of bismuth, and solution of bismuth and ammonium citrate, which are described in for example the British Pharmaceutical Codex (1949), have long been used as antacids in the treatment of hyperacidity and dyspepsia. In addition, before the advent of histamine H_2 -antagonists, by which they have now essentially been superseded, such bismuth preparations were also used in the treatment of gastrointestinal ulcers.

In recent years evidence has emerged that Campylobacter pylori is associated with histological gastritis, non-ulcer dyspepsia and

hypochlorhydria, and may be involved in the pathogenesis of gastric and duodenal ulcer disease.

Campylobacter pylori is susceptible to bismuth compounds such as bismuth subcitrate (in the form of, for example, tripotassium dicitrate bismuthate) and bismuth subsalicylate.

A number of the bismuth compounds referred to above are acidic complexes formed between bismuth and a carboxylic acid such as citric or tartaric acid or salts thereof with ammonia or an alkali metal. It has now been found that the basic H₂-receptor antagonist ranitidine will form salts with such complexes, and the resulting products possess a useful and advantageous profile of activity.

The present invention thus provides novel salts formed between ranitidine and a complex of bismuth with a carboxylic acid, and solvates of such salts. Suitable carboxylic acids are those which are capable of forming a complex with bismuth, and which complexes are, in turn, capable of forming a salt with ranitidine.

Carboxylic acids which are capable of forming complexes with bismuth to give bismuth-carboxylic acid complexes for use according to the invention may be, for example, carboxylic acids which contain at least three functional groups in addition to the carboxyl group which is available for salt formation with ranitidine. Of the three or more remaining functional groups, three, which may be for example carboxyl and/or hydroxy groups, shall be capable of complexing with trivalent bismuth, to give a trivalent bismuth complex.

In instances where the carboxylic acid can exhibit optical and/or geometric isomerism, the invention is intended to include all optical isomers including racemates, and/or geometric isomers. Solvates, including hydrates, are also included within the scope of the invention.

Examples of suitable carboxylic acids which are capable of forming complexes with bismuth for use according to the invention are citric, tartaric and ethylenediaminetetraacetic acid. Further examples of suitable carboxylic acids are propylcitric and agaricic acids.

Tartaric acid and, more especially, citric acid are preferred. Agaricic acid represents a further preferred acid for use according to the invention.

Particular salts according to the invention are

- N-[2-[[[5-[(dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine 2-hydroxy-1,2,3-propanetricarboxylate bismuth (3+) complex, also known as ranitidine bismuth citrate;
- 5 N-[2-[[[5-[(dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine [(R-R*R*)]-2,3-dihydroxybutanedioate bismuth (3+) complex, also known as ranitidine bismuth tartrate;
- N-[2-[[[5-[(dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine 2-hydroxy-1,2,3-nonadecane
- 10 tricarboxylate bismuth (3+) complex, also known as ranitidine bismuth agaricicate; and
- N-[2-[[[5-[(dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine N,N'-ethanediylbis[N-(carboxymethyl)-glycine]bismuth (3+) complex, also known as ranitidine bismuth-EDTA.

15 Preferred salts according to the invention are

- N-[2-[[[5-[(dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine 2-hydroxy-1,2,3-propanetricarboxylate bismuth (3+) complex; and
- 20 N-[2-[[[5-[(dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine [(R-R*R*)]-2,3-dihydroxybutanedioate bismuth (3+) complex.

Another preferred salt according to the invention is

N-[2-[[[5-[(dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine 2-hydroxy-1,2,3-nonadecane

25 tricarboxylate bismuth (3+) complex.

Ranitidine bismuth citrate represents a particularly preferred compound of the invention.

The salts according to the invention possess a particularly advantageous combination of properties for the treatment of

30 gastrointestinal disorders, especially peptic ulcer disease and other gastroduodenal conditions, for example gastritis and non-ulcer dyspepsia.

Salts according to the invention thus possess the H₂-antagonist antisecretory properties associated with ranitidine together with

35 antibacterial activity against Campylobacter pylori. In addition, salts of the invention possess cytoprotective properties. They also display activity against the human gastric pepsins, with preferential

inhibition of pepsin 1, a pepsin isozyme associated with peptic ulcer.

The antisecretory activity of compounds of compounds according to the invention has been demonstrated in vivo against histamine-induced gastric acid secretion in the Heidenhain pouch dog. The antibacterial activity of the salts against Campylobacter pylori and their ability to inhibit human pepsins have been demonstrated in vitro. In addition, antibacterial activity against campylobacter like organisms has been demonstrated in vivo in ferrets. Cytoprotective activity has been demonstrated in vivo by the ability of the salts to inhibit ethanol-induced gastric lesions in rats.

A further feature of the salts according to the invention is that they are water soluble and give stable aqueous solutions. Under normal circumstances many bismuth salts and complexes, including those formed with carboxylic acids of the type used in forming salts of the invention, are insoluble. Bismuth citrate, for example, has a solubility (under neutral aqueous conditions, of only 0.2% on a weight to volume (w/v) basis, whereas ranitidine bismuth citrate is soluble in water to the extent of more than 50% w/v.

Thus the observed properties of salts according to the invention, such as ranitidine bismuth citrate, serve to emphasise the fact that they are distinct chemical entities which can be clearly distinguished from simple mixtures (e.g. admixtures of equimolar proportions) of ranitidine and a complex formed between bismuth and a carboxylic acid.

Salts according to the invention may also be distinguished from simple mixtures of ranitidine and a complex formed between bismuth and a carboxylic acid on the basis of infra-red spectroscopy. Thus there are major spectral changes in going from a simple mixture of ranitidine and a bismuth-carboxylic acid complex to a salt according to the invention. The infra-red spectrum of a simple physical mixture of ranitidine and bismuth citrate, for example, has major peaks at $\nu_{\max}$ 1131, 988 and 603cm^{-1} which are absent in the infra-red spectrum of ranitidine bismuth citrate.

Salts according to the invention may be prepared by reacting ranitidine with an appropriate bismuth - carboxylic acid complex (e.g. bismuth citrate or bismuth ammonium citrate), in a suitable solvent such as water, and separating the salt thus formed from the solution.

According to a further aspect the invention provides a salt formed between ranitidine and a complex of bismuth with a carboxylic acid, including solvates of such salts, said salt being prepared by reacting ranitidine with a bismuth carboxylic acid complex.

5 According to one particular further aspect, the invention provides ranitidine bismuth citrate, including solvates thereof when prepared by reacting ranitidine with a complex of bismuth with citric acid.

The reaction between ranitidine and an appropriate bismuth-carboxylic acid complex to give a salt according to the invention is preferably carried out at elevated temperature for example 10 at a temperature within the range of 40 to 100°C. Once the reaction is complete (when for example the mixture has reached neutrality as judged by pH and/or dissolution is complete), the suspension or solution is cooled and filtered, and the required ranitidine salt may be obtained 15 from the filtrate, by evaporation followed by extraction and trituration of the resulting residue using for example an alcohol e.g. methanol or ethanol, a ketone e.g. acetone or an ether e.g. diethyl ether. Alternatively, the reaction mixture may be evaporated directly, followed by extraction and trituration of the resulting residue. 20 Further alternative procedures for isolating the desired salt include spray drying of the filtrate, or addition of the filtrate (optionally after dilution with e.g. water) to a suitable anti-solvent (e.g. an alcohol such as ethanol) at an elevated temperature (e.g. the reflux temperature of the anti-solvent) which results in precipitation of the 25 product.

The intermediate bismuth - carboxylic acid complexes may in general be prepared by the procedures described in the British Pharmaceutical Codex (1949). Thus, for example, a suspension of a suitable bismuth salt (e.g. bismuth oxynitrate) and an appropriate 30 carboxylic acid (e.g. citric or tartaric acid) in a solvent such as water may be heated at for example 90 to 100°C, the reaction being judged as complete when for example one drop of the mixture yields a clear solution when added to weak aqueous ammonia. The suspension is then optionally diluted with water, and the desired bismuth-carboxylic 35 acid complex may be recovered by filtration. Bismuth ammonium citrate

may for example be prepared, in situ if desired, by treating bismuth citrate with an appropriate amount of aqueous ammonia.

The salts according to the invention may be formulated for administration in any convenient way and the invention includes within its scope pharmaceutical compositions containing a salt according to the invention adapted for use in human or veterinary medicine. Such compositions, which are primarily intended for oral administration, may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers or excipients. Tablets represent a preferred type of composition.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets (including chewable or suckable tablets) or capsules. Such compositions may be prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sulphate). Tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

A proposed dose of the salts of the invention for internal administration to man is 100mg to 1g, preferably 100 to 800mg, more particularly 150 to 600 mg, of the active ingredient per unit dose. The unit dose may be administered, for example, one to four times

daily, preferably once or twice. The exact dose will depend on the nature and severity of the condition being treated, and it will also be appreciated that it may be necessary to make routine variations to the dosage depending on the age and weight of the patient.

5 The invention is illustrated by the following Examples in which temperatures are in °C. Thin layer chromatography (t.l.c.) was carried out on silica, eluting with dichloromethane:ethanol:0.88 ammonia, 70:8:1 (System A) or ethyl acetate:isopropanol:0.88 ammonia:water, 25:15:4:2 (System B), and using u.v., iodoplatinate and potassium permanganate for detection, unless indicated otherwise.

Preparation 1

2-Hydroxy-1,2,3-propanetricarboxylic acid, bismuth (3⁺) complex (1:1) ("Bismuth citrate")

15 A mixture of bismuth oxynitrate (22.96g) and citric acid (33.60g) in water (80ml) was heated on a steam bath with frequent stirring for 30min, by which time one drop of the suspension added to weak aqueous ammonia gave a clear solution. The mixture was diluted with water, filtered, and the residue washed well with water until free of nitrate
20 and excess citric acid. The residue was dried under vacuum to give the title compound (32.18g).

Analysis Found: C, 18.08; H, 1.34; O, 28.80; Bi, 52.
C₆H₅BiO₇ · 0.11H₂O requires C, 18.01; H, 1.32; O, 28.44; Bi, 52.2%.
Water assay indicated 0.49% H₂O ≡ 0.11 mol.

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Preparation 2

[R-(R*R*)]-2,3-Dihydroxybutanedioic acid, bismuth (3⁺) complex (2:1) ("Bismuth tartrate")

A mixture of (+)-tartaric acid (27g) and bismuth oxynitrate (8.61g) in water (50ml) was heated at 90-100° with occasional stirring for
30 30min, by which time a small portion of the product dissolved completely in weak aqueous ammonia. The mixture was cooled to room temperature then filtered and the filtrate washed well with water until free from water soluble materials. The residue was dried at 70-80° in vacuo to give the title compound (14.78g).

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Analysis Found: C, 18.44; H, 1.81; O, 39.04; Bi, 40.
 $C_8H_9Bi \cdot 0.12 \cdot 0.43 H_2O$ requires C, 18.70; H, 1.93; O, 38.70; Bi, 40.7%.
Water assay indicated 1.54% $H_2O \equiv 0.43 \text{ mol}$.

Preparation 3

- 5 2-Hydroxy-1,2,3-nonadecanetricarboxylic acid, bismuth (3+) complex
(1:1) ("Bismuth agaricicate")

A mixture of (-)-2-hydroxy-1,2,3-nonadecanetricarboxylic acid (agaricic acid, 9.15g) and bismuth oxynitrate (5.74g) in water (50ml) was heated at 90-95° for 4h. The acidic mixture was filtered and the residue
10 washed well with water until the filtrates were neutral. The residue was washed well with hot methanol (3x50ml) then dried to give the title compound (12.286g).

Analysis Found: C, 43.52; H, 6.34; O, 18.49;
Bi, 31.

- 15 $C_{22}H_{37}BiO_7 \cdot 0.1 C_{22}H_{40}O_7 \cdot 0.11 H_2O$ requires C, 43.63; H, 6.24; O, 18.76%;
Bi, 31.4%.

Water assay indicated 0.31% $H_2O \equiv 0.11 \text{ mol}$.

Preparation 4

- 20 N,N'-1,2-Ethanedylbis[N-(carboxymethyl)glycine]bismuth (3+) complex
(1:1) ("Bismuth-EDTA").

A mixture of bismuth oxynitrate (20.09g) and N,N'-1,2-ethanedylbis[N-(carboxymethyl)glycine] (EDTA; 17.57g) in water (100ml) was heated at 90-95° for 2h. The hot suspension was filtered and the residue re-heated at 90-95° with water (4x70ml) until almost all the
25 solid had dissolved. On each extraction, the suspension was filtered and the strongly acidic filtrates evaporated in vacuo to approximately 70ml. The mixture from the extractions was cooled to 18° and the precipitated solid filtered off and washed free of nitric acid with cold water, then ethanol and ether, and dried to give the title
30 compound (18.52g)

Analysis Found: C, 23.27; H, 2.49; N, 5.41; O, 26.43; Bi, 41.
 $C_{19}H_{13}BiN_2O_8 \cdot 0.5 H_2O$ requires C, 23.68; H, 2.78; N, 5.52; O, 26.81; Bi, 41.2%
Water assay indicated 1.819% $H_2O \equiv 0.5 \text{ mol}$.

Example 1

N-[2-[[[5-[(Dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine 2-hydroxy-1,2,3-propanetricarboxylate bismuth (3+) complex (1:1:1) ("Ranitidine bismuth citrate")

- 5 A mixture of bismuth citrate (2.08g) and N-[2-[[[5-[(dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine (ranitidine; 1.57g) in water (15ml) was heated at 90-95° until the suspension became neutral to pH paper (ca 15min). The mixture was cooled to room temperature and unreacted bismuth citrate (0.657g) was
10 filtered off. The filtrate was evaporated to dryness in vacuo to give a hard gum. Methanol (50ml) was added to the gum, and the mixture evaporated to give a residue which was heated with methanol (70ml) and cooled. The cloudy supernatant liquid was decanted off and the residue triturated to a powder with methanol (50ml) and the suspension
15 filtered. The residue was washed with methanol and dried to give the title compound (1.98g). T.l.c. (System A) Rf 0.35 (ranitidine) and Rf zero (bismuth citrate).

Analysis Found: C,30.67; H,3.97; N,7.10; O,23.60; S,3.97;
Bi,29.

- 20 $C_{19}H_{27}BiN_4O_{10}S$, 0.1 $C_6H_5BiO_7$, 0.16 C_2H_5OH , 0.48 H_2O requires
C,31.14; H,3.86; N,7.29; O,23.65; S,4.17;
Bi,29.9%.

Water assay indicated 1.06% $H_2O \equiv 0.48$ mol.

N.m.r. indicated 0.16 mol ethanol.

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Example 2

N-[2-[[[5-[(Dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine 2-hydroxy-1,2,3-propanetricarboxylate bismuth (3+) complex (1:1:1) ("Ranitidine bismuth citrate")

- To a mixture of bismuth citrate (3.98g.) with water (15ml) was added
30 sufficient aqueous 0.88 ammonia to dissolve the solid. The solution was filtered through Hyflo^(RTM) and the combined filtrate and washings evaporated in vacuo. The solution was re-evaporated with water until the supernatant vapour above the residue was no longer basic to pH 1-14 paper (water 5x70ml). To a solution of the residue in water (30ml) was added ranitidine (3.14g) and the solution which formed was evaporated

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to dryness in vacuo. The water soluble residue was re-evaporated with water until no more basic vapour was detectable (16x80ml). The residue was dried by rotary evaporation under vacuum at 80-90° and the powdery residue removed with the aid of ether. The residue was ground to a fine powder which was suspended in ether and filtered. The resulting product was dried to give the title compound (6.814g). T.l.c.

(System A) Rf 0.3 (ranitidine) and Rf zero (bismuth citrate).

N.m.r. δ (DMSO-d₆) 2.57 (2H,d, 1/2 AB of CH₂CO), 2.8-2.9 (m, CH₃NH, CH₂CH₂S and 1/2 AB of CH₂CO), 2.87 (s, (CH₃)₂N⁺), 3.47 (2H,t, CH₂CH₂NH), 3.86 (2H,s,CH₂S), 4.35 (2H,s,CH₂N⁺), 6.10 and 6.67 (2H, d + d, furan =CH's). (RTM)

I.r. $\nu_{\max}$ (Nujol) 3454 (-OH), 3267 and 3200 (-NH-), and 1620, 1570 and 1260 (-NHC(=CHNO₂)NH- + -CO₂-)cm⁻¹.

Analysis Found: C,31.54; H,4.04; N,8.02; O,23.31; S,4.32; Bi,28.

C₁₃H₂₂N₄O₃S.C₆H₅BiO₇.0.34H₂O requires

C,31.75; H,3.88; N,7.80; O,23.02; S,4.46%; Bi,29.1%.

Water assay indicated 0.85% H₂O $\equiv$ 0.34mol.

Example 3

N-[2-[[[5-[(Dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine 2-hydroxy-1,2,3-propanetricarboxylate bismuth (3+) complex (1:1:1) ("Ranitidine bismuth citrate")

A mixture of ranitidine (44.0g) and bismuth citrate (40.0g) in water (70ml) was heated at 90-95° for 30 minutes. The cloudy solution was filtered, diluted with water (20ml) then added over 23 minutes with stirring to industrial methylated spirit (IMS; 2.4 litres), heated under reflux. The resulting suspension was heated for 15 minutes then cooled to ambient temperature. The title compound (63.0g) was collected by filtration, washed with IMS (2 x 200ml) and dried in vacuo at 40°. T.l.c.(System B) Rf 0.49 (ranitidine) and Rf zero (bismuth citrate), detection : u.v., iodine.

Example 4

N-[2-[[[5-[(Dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine 2-hydroxy-1,2,3-propanetricarboxylate bismuth (3⁺) complex (1:1:1) ("Ranitidine bismuth citrate")

- 5 Ranitidine (44.0g) was added to a suspension of bismuth citrate (55.7g) in 1.0 molar aqueous ammonia (56ml) and water (92ml). The suspension was heated at 90° for 5 minutes then the resulting cloudy solution was filtered and diluted with water (10ml). The title compound (10.3g) was isolated by spray drying the resulting solution
10 (40ml of a total volume of 195ml). T.l.c. (System B) Rf 0.49 (ranitidine) and Rf zero (bismuth citrate), detection : u.v., iodine.

Example 5

- N-[2-[[[5-[(Dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine [(R-(R*R*))]-2,3-dihydroxybutanedioate bismuth (3⁺) complex (1:1:1) ("Ranitidine bismuth tartrate")

- Ranitidine (5.02g) was added to a slurry of bismuth tartrate (2.02g) in water (10ml) and the mixture warmed gently with stirring until solution was effected. The solution was filtered through Hyflo and
20 the combined filtrate and washings evaporated in vacuo to give a thick gum which became a frothy solid on further evaporation. This was re-evaporated with methanol (3x50ml) and the gummy residue extracted with hot methanol (50mlx3). The semi-solid residue was triturated with methanol (20ml) until a cream coloured fine suspension was formed
25 which was filtered. The residue was reduced to a fine suspension by trituration of the residue with methanol (20ml) then filtered and the residue washed with methanol then ether and dried to give the title compound (1.853g). T.l.c. (System A) Rf 0.35 (ranitidine) and Rf zero (bismuth tartrate).

- I.r. $\nu_{\max}$ (KBr) 3600-2000 (complex series of bands, -NH- + -OH),
30 1750-1500 (series of bands, -NHC(=CHNO₂)NH- + -CO₂⁻ + -CO₂H), and 1233 (-NHC(=CHNO₂)NH-)cm⁻¹.

Analysis Found: C, 28.03; H, 3.59; N, 6.84; O, 24.85; S, 3.87.

C₁₃H₂₂N₄O₃S.C₄H₃O₆Bi.0.33 C₈H₉BiO₁₂.0.15 CH₃OH requires

C, 28.22; H, 3.42; N, 6.65; O, 24.90; S, 3.81%.

N.m.r. indicated 0.15mol methanol.

Example 6

N-[2-[[[5-[(Dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine 2-hydroxy-1,2,3-nonadecane tricarboxylate bismuth (3⁺) complex (1:1:1) ("Ranitidine bismuth agaricicate")

A mixture of bismuth agaricicate (containing agaricic acid, 0.1mol and water, 0.1mol) (4.26g) and ranitidine (3.77g) in water (10ml) was heated at 90-95° for 4h. The solution was diluted with water (15ml) and the heating continued for 1h. The opalescent liquid was filtered through Hyflo whilst hot and the filtrate evaporated to dryness with the aid of ethanol. The gummy residue was re-evaporated with ethanol (3x30ml) to give a gum. This was dissolved in ethanol (50ml) and the solution filtered through Hyflo. The combined filtrate and washings were evaporated in vacuo to give a gum. This was mixed with hot acetone (70ml) and, after heating the mixture for 10min, the supernatant liquid was decanted off. This procedure was repeated and the semi-solid residue triturated with acetone (50ml) to give a fine suspension. This was filtered off and the residue washed well with acetone and dried to give the title compound (4.69g) as a buff coloured solid.

Analysis Found: C,45.37; H,6.50; N,5.36; O,17.43; S,3.01

$C_{35}H_{59}N_4O_{10}S_{Bi} \cdot 0.05C_{22}H_{40}O_7 \cdot 0.5H_2O$ requires

C,44.85; H,6.46; N,5.80; O,17.96; S,3.32%

Water assay indicated 1.04% H₂O $\equiv$ 0.5 mol.

T.l.c. (System A) Rf 0.35 (ranitidine) and Rf zero (bismuth agaricicate/agaricic acid). T.l.c. (Chloroform:methanol:acetic acid: water, 15:5:1:1) Rf 0.3 (ranitidine), detection: u.v, iodoplatinate, potassium permanganate and bromocresol green stain and Rf 0.6 (agaricic acid), detection: bromocresol green stain.

Example 7

N-[2-[[[5-[(Dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine N,N'-ethanedylbis[N-(carboxymethyl)-glycine]bismuth (3⁺) complex (1:1:1) ("Ranitidine bismuth-EDTA")

To a mixture of bismuth-EDTA (2.99g) and ranitidine (2.2g) was added water (15ml) and the mixture warmed to effect complete solution. A small amount of precipitate which formed was filtered off through

- Hyflo. The solution was evaporated to dryness in vacuo and the residue re-evaporated with methanol (2x15ml). The residue was dissolved in warm methanol (20ml) and the solution filtered through Hyflo. The filtrate was evaporated to dryness to give a semi solid which was dissolved in methanol (10ml). Cooling caused precipitation of an oil and after standing for 60h, a white solid formed. This was filtered off and the residue washed with methanol. The solid was re-suspended in ethanol and filtered and the residue washed with methanol. The solid was re-suspended in ethanol and filtered and the residue washed with ethanol then ether and dried to give the title compound (3.786g). T.l.c. (System A) Rf 0.35 (ranitidine) and Rf zero (Bismuth-EDTA). Analysis Found: C,33.57; H,4.45; N,10.09; S,3.70; Bi,24. $C_{13}H_{22}N_4O_3S \cdot C_{10}H_{13}BiN_2O_8 \cdot H_2O$ requires C,33.26; H,4.49; N,10.12; S,3.86; Bi,25.2%.
- 15 Water assay indicated 2.24% $H_2O \equiv 1.0$ mole.

The following Examples A to D illustrate pharmaceutical compositions according to the invention in which the active ingredient is in particular ranitidine bismuth citrate. Other compounds according to the invention may be formulated in a similar manner.

Example A Tablets

Tablets may be prepared by the normal methods such as direct compression or wet granulation.

The tablets may be film coated with suitable film forming materials, such as hydroxypropyl methylcellulose, using standard techniques.

(i) Direct Compression

	<u>mg/tablet</u>
Active ingredient	380mg
Lactose	145mg
Microcrystalline Cellulose	140mg
Cross-linked Polyvinylpyrrolidone	28mg
Magnesium Stearate	7mg
Compression weight	700mg

The active ingredient, microcrystalline cellulose, lactose and cross-linked polyvinylpyrrolidone are sieved through a 500µm sieve and blended in a suitable mixer. The magnesium stearate is sieved through a 250µm sieve and blended with the active blend. The blend is compressed into tablets using suitable punches.

(ii) Wet Granulation

		<u>mg/tablet</u>
10	Active ingredient	380mg
	Lactose	215mg
	Pregelatinised Starch	70mg
	Cross-linked Polyvinylpyrrolidone	28mg
	Magnesium Stearate	7mg
15	Compression weight	700mg

The active ingredient, lactose and pregelatinised starch are blended together and granulated with water. The wet mass is dried and milled. The magnesium stearate and cross-linked polyvinylpyrrolidone are screened through a 250µm sieve and blended with the granule. The resultant blend is compressed using suitable tablet punches.

Example B Suckable/Chewable Tablets

		<u>mg/tablet</u>
25	(i) Active ingredient	380mg
	Polyvinylpyrrolidone	28mg
	Sweetener/Flavour	qs
	Magnesium Stearate	7mg
30	Mannitol	700mg
	to	700mg
	Compression weight	700mg

The active ingredient, sweetener/flavour and mannitol are blended together and granulated with a solution of polyvinylpyrrolidone. The wet mass is dried, milled and lubricated with magnesium stearate (meshed through a 250µm sieve). The resultant granule is compressed into tablets using suitable punches.

	<u>mg/tablet</u>
(ii) Active ingredient	380mg
Hydroxypropyl methylcellulose	20mg
Magnesium Stearate	7mg
Flavour	qs
Xylitol	to 700mg
Compression weight	700mg

The active ingredient, xylitol and flavour are blended together, granulated using a solution of the hydroxypropyl methylcellulose in aqueous ethanol, and dried. The granule is milled, lubricated with magnesium stearate (meshed through a 250µm sieve) and compressed into tablets using suitable punches.

Example C Capsules

	<u>mg/capsule</u>
(i) Active ingredient	380mg
Pregelatinised Starch	65mg
Magnesium Stearate	5mg
Fill weight	450mg

The active ingredient and pregelatinised starch are screened through a 500µg mesh sieve, blended together and lubricated with magnesium stearate (meshed through a 250µm sieve). The blend is filled into hard gelatin capsules of a suitable size.

		<u>mg/capsule</u>
	(ii) Active ingredient	380mg
	Lactose	75mg
	Polyvinylpyrrolidone	20mg
	Cross-linked Polyvinylpyrrolidone	20mg
5	Magnesium Stearate	5mg
	Fill weight	500mg

10 The active ingredient and lactose are blended together and wet massed with a solution of polyvinylpyrrolidone. The mass is dried and milled and blended with cross-linked polyvinylpyrrolidone and magnesium stearate (screened through a 250µm mesh). The resultant blend is filled into hard gelatin capsules of a suitable size.

15 Example D Oral Syrup

	Active ingredient	380mg
	Hydroxypropyl Methylcellulose	45mg
	Propyl Hydroxybenzoate	1.5mg
20	Butyl Hydroxybenzoate	0.75mg
	Saccharin Sodium	5mg
	Sorbitol Solution	1.0ml
	Suitable Buffers	qs
	Suitable Flavours	qs
25	Purified Water	to 10ml

30 The hydroxypropyl methylcellulose is dispersed in a portion of hot purified water together with the hydroxybenzoates and the solution is allowed to cool to room temperature. The saccharin sodium, flavours and sorbitol solution are added to the bulk solution. The active ingredient is dissolved in a portion of the remaining water and added to the bulk solution. Suitable buffers may be added to control the pH in the region of maximum stability. The solution is made up to volume, filtered and filled into suitable containers.

CLAIMS

1. A salt formed between ranitidine and a complex of bismuth with a carboxylic acid, or a solvate of such a salt.
2. A salt as claimed in claim 1, wherein the carboxylic acid contains at least three functional groups in the molecule in addition to the carboxyl group which is available for salt formation with ranitidine.
3. A salt as claimed in claim 1, wherein the carboxylic acid is citric acid, tartaric acid, ethylenediaminetetraacetic acid, propylcitric acid or agaricic acid.
4. A salt as claimed in claim 1, wherein the carboxylic acid is citric acid or tartaric acid.
5. A salt as claimed in claim 1, wherein the carboxylic acid is citric acid.
6. N-[2-[[[5-[(dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine 2-hydroxy-1,2,3-propanetricarboxylate bismuth (3^+) complex, and solvates thereof.
7. N-[2-[[[5-[(dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine [(R-R*R*)]-2,3-dihydroxybutanedioate bismuth (3^+) complex, and solvates thereof.
8. N-[2-[[[5-[(dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine 2-hydroxy-1,2,3-nonadecane tricarboxylate bismuth (3^+) complex, and solvates thereof.
9. N-[2-[[[5-[(dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine N,N'-ethanediyldis[N-(carboxymethyl)glycine]bismuth(3^+) complex, and solvates thereof.
10. A pharmaceutical composition comprising a salt as claimed in any of claims 1 to 9, together with at least



one pharmaceutically acceptable carrier or diluent.

11. A pharmaceutical composition as claimed in claim 10, in a form adapted for oral administration.

12. A pharmaceutical composition as claimed in claim 10, in the form of tablets.

13. A pharmaceutical composition as claimed in claim 11 or 12, in unit dose form containing 100 mg to 1 g of the salt per unit dose.

14. A pharmaceutical composition as claimed in claim 11 or 12, in unit dose form containing 100 to 800 mg of the salt per unit dose.

15. A pharmaceutical composition as claimed in claim 11 or 12, in unit dose form containing 150 to 600 mg of the salt per unit dose.

16. A pharmaceutical composition comprising N-[2-[[[5-[(dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine 2-hydroxy-1,2,3-propanetricarboxylate bismuth (3^+) complex, or a solvate thereof together with at least one pharmaceutically acceptable carrier or diluent.

17. A pharmaceutical composition as claimed in claim 16 in a form adapted for oral administration in the form of tablets.

18. A pharmaceutical composition as claimed in claim 17 in unit dose form containing 100 to 800 mg of the complex or a solvate thereof.

19. A salt as claimed in any of claims 1 to 9, for use as an active therapeutic agent.

20. A process for the preparation of a salt as claimed in any of claims 1 to 9, which comprises reacting ranitidine with a bismuth carboxylic acid complex in a suitable solvent and separating the salt thus formed from the solution.

21. A process for the preparation of N-[2-[[[5-[(dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine 2-hydroxy-1,2,3-



propanetricarboxylate bismuth (3^+) complex, which comprises reacting ranitidine with a complex of bismuth with citric acid in a suitable solvent and separating the salt thus formed from the solution.

22. A process as claimed in claim 20 or 21, wherein the solvent is water.

23. A process as claimed in any of claims 20 to 22, wherein the reaction is carried out at elevated temperature.

24. A process as claimed in any of claims 20 to 22, wherein the reaction is carried out at a temperature of 40 to 100°C.

25. A salt formed between ranitidine and a complex of bismuth with a carboxylic acid, or a solvate of such a salt, the said salt having been prepared by reacting ranitidine with a bismuth carboxylic acid complex.

26. Ranitidine bismuth citrate or a solvate thereof, when prepared by reacting ranitidine with a complex of bismuth with citric acid.

