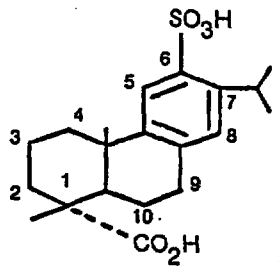
Description

This invention relates to a pharmaceutically acceptable salt of sulfodehydroabietic acid of the formula:



(I)

for use as an active therapeutic substance, e.g. for use in the therapeutic treatment and/or prophylaxis of gastro-intestinal diseases.

It is known that sulfodehydroabietic acid (I) (chemical name: 1:4a - dimethyl - 1 - carboxy - 6 - sulfo - 7 - isopropyl - 1,2,3,4,4a,9,10,10a - octahydrophenanthrene) is prepared by sulfonation of pseudopimaric acid, pyroabietic acid or dehydroabietic acid (U.S. Patent No. 2,121,032, J. Am. Chem. Soc., Vol. 60, pp. 2340—2341 (1938), ibid., Vol. 60, pp. 2631—2636 (1938) and ibid., Vol. 63, pp. 1838—1843 (1941)). It is also known that sodium and p-toluidine salts of sulfodehydroabietic acid are obtained by conventional neutralization of said abietic acid. Moreover, U.S. Patent No. 2,121,032 discloses that sulfodehydroabietic acid (I) is useful as a detergent and wetting agent. However, no pharmacological activity of a salt of sulfodehydroabietic acid has been known up to now.

We have now found that a pharmaceutically acceptable salt of sulfodehydroabietic acid (I) shows useful therapeutic effects on gastro-intestinal diseases. That is, it has a potent anti-peptic ulcer activity and is useful for the therapeutic treatment and/or prophylaxis of peptic ulcer diseases or gastritis. For example, salts of sulfodehydroabietic acid (I) show preventive effects against pepsin secretion, gastric acid secretion, pylorus-ligated ulcers, drug-induced ulcers and stress-induced ulcers. Further, salts of sulfodehydroabietic acid (I) increase mucosal resistance by enhancing gastric mucus secretion. Therefore, the compounds of the present invention can be used for the treatment and/or prophylaxis of a wide variety of gastro-intestinal diseases including gastritis and acute or chronic peptic ulcer diseases (e.g., gastric ulcer and duodenal ulcer). Moreover, the compounds of the present invention show no substantial mineralo-corticoid- or aldosterone-like effect and can be used without unfavourable side effects such as hypokalaemia. For example, when a test compound was administered orally to rats, sulfodehydroabietic acid monosodium salt at a dose of 500 or 1000 mg/kg showed no substantial change in urinary sodium-potassium ratio. Further, the toxicity of the compounds of the present invention are remarkably low. For example, the 50% lethal dose (LD_{50}) of sulfodehydroabietic acid monosodium salt estimated by oral administration thereof to rats was more than 2,000 mg/kg.

Salts of sulfodehydroabietic acid (I) which can be used for therapeutic treatment or prophylaxis of the above-mentioned gastro-intestinal diseases include the salts thereof with any pharmaceutically acceptable cation-forming substance. Examples of such salts are those of sulfodehydroabietic acid (I) with metals, metal hydroxides or amines, and the amines may be primary, secondary, tertiary or quaternary amines e.g. alkylamines, di-alkylamines, trialkylamines, alkylenediamines, cycloalkylamines, arylamines, aralkyl-amines, heterocyclic amines, α-amino acids, ω-amino acids, peptides or quaternary amines derived therefrom. In addition, these alkylamines, alkylenediamines, cycloalkylamines, aryl or aralkylamines, heterocyclic amines, amino acids and so forth may be optionally substituted with a group or groups selected from hydroxy, alkoxy, carboxy, acyl, acyloxy, aminoalkyl, alkylamino, alkyl, guanidino, carbamoyl, methylthio, mercapto, dialkylsulfonium and halogen groups; and further the amino acids or peptides may be if required, in the form of the corresponding acid amides or esters. Specific examples of the salts of sulfodehydroabietic acid with metals or metal hydroxides are the salts thereof with alkali metals e.g. sodium, lithium or potassium; alkaline earth metals e.g. magnesium, calcium or barium; or aluminium or aluminium hydroxide [the salt with aluminium hydroxide may be either the sulfodehydroabietic acid mono (aluminium monohydroxide) salt or the sulfodehydroabietic acid di(aluminium dihydroxide)salt]. Examples of the salts of sulfodehydroabietic acid with mono-, di-, or trialkylamines are the salts thereof with alkylamines, e.g. methylamine, ethylamine, propylamine or isopropylamine; dialkylamines e.g. dimethylamine, diethylamine or di-n-propylamine; trialkylamines e.g. trimethylamine or triethylamine; dialkylamino-alkylamines e.g. 2-dimethylaminoethylamine or 2-diethylamino-ethylamine; alkoxy-alkyl-amines e.g. 2-methoxyethylamine or 3 - ethoxy - n - propylamine; or hydroxyalkylamines e.g. ethanolamine, or 3 - hydroxy - n - propylamine. Examples of the salts of sulfodehydroabietic acid with the cycloalkylamines are the salts thereof with cyclopropylamine, cyclobutylamine, cyclopentylamine or cyclohexylamine. Examples of the sulfodehydroabietic acid with the aralkylamines are the salts thereof with benzylamine, phenethylamine or 4-methoxyphenethylamine. Examples of the salts of sulfodehydroabietic acid with the arylamines are the salts thereof with alkyl N - acyl - p - aminobenzoates

e.g. ethyl N - piperidinoacetyl - p - aminobenzoate, ethyl N - prolyl - p - aminobenzoate or ethyl N - pipecolyl - p - aminobenzoate. Examples of the salts of sulfodehydroabietic acid with the heterocyclic amines are the salts thereof with morpholine, piperazine, 2 - (3,4 - dihydroxyphenyl) - 8,8 - dimethyl - 5,8 - diazoniaspiro[4.5]decane, 1 - (2 - dimethyl - aminoethyl) - 4 - phenyl - 2 - pyrrolidone, homocysteine thiolactone or 1 - ethyl - 2 - aminomethyl - pyrrolidine. Moreover, representative examples of the α- or ω-amino acids which can be used to form the salts with sulfodehydroabietic acid are shown by the formulae:

(III)

or

(III)

wherein R^1 is hydrogen, amino, guanidino, carbamoyl, dimethylthionia that is $(CH_3)_2S+$ 4-imidazolyl, mercapto or methylthio, R^2 is hydroxy, alkoxy, amino, alkylamino, dialkylamino, cycloalkylamino or p-alkoxyanilino, R^3 is hydroxy or alkoxy, A is a single bond or straight or branched alkylene, and B is straight alkylene (said alkylene being optionally substituted with aryl). Examples of the α- or ω-amino acids which can be used in the present invention are lysine, ornithine, arginine, asparagine, glutamine, methionine, histidine, ethyl cysteinate, ethyl asparaginate, ethyl glutaminate, asparagine amide, glutamine amide, asparagine methylamide, glutamine methylamide, asparagine isopropylamide, glutamine isopropylamine, asparagine octylamide, glutamine octylamide, glutamine di-n-propylamide, asparagine cyclohexylamide, glutamine cyclohexylamide, asparagine p-methoxyanilide, glutamine p-methoxyanilide, S-methylmethionine (i.e., 3 - (S,S - dimethylthionia) - α - aminobutyric acid), 6-aminocaproic acid, or methyl 4 - amino - 3 - phenylbutylate. Furthermore, examples of the peptides which can be used to form the salts of the invention are dipeptides e.g. carnosine, homocarnosine (i.e., N - γ - aminobutyryl - histidine), anserin (i.e., N - β - alanyl - 1 - methyl - histidine) or balenin (i.e., N - β - alanyl - 2 - methylhistidine.

Of the above-mentioned various salts, a preferred subgenus is a salt of sulfodehydroabietic acid with an alkali metal; an alkali earth metal; aluminium; aluminium hydroxide; or an amine selected from the group consisting of alkyl(C_{1-5})amine, di - alkyl(C_{1-5})amine, tri - alkyl(C_{1-5})amine, cycloalkyl(C_{3-6})amine, di - alkyl - (C_{1-5})amino - alkyl(C_{1-5})amine, alkoxy(C_{1-5}) - alkyl(C_{1-5})amine, alkylene(C_{2-6})diamine, aralkyl - (C_{7-8})amine, alkyl(C_{1-5}) N - piperidinoacetyl - p - aminobenzoate, alkyl(C_{1-5}) N - prolyl - p - aminobenzoate, alkyl(C_{1-5}) N - pipecolyl - p - aminobenzoate, morpholine, piperazine, 2 - (3,4 - dihydroxyphenyl) - 8,8 - dimethyl - 5,8 - diazoniaspiro[4.5]decane, 1 - (2 - dimethylaminoethyl) - 4 - phenyl - 2 - pyrrolidone, homocysteine thiolactone, an α-amino acid of the formula (II) in which R^1 is amino, guanidino, carbamoyl, dimethylthionia, 4-imidazolyl, mercapto or methylthio, R^2 is hydroxy, alkoxy(C_{1-5}), amino, alkyl(C_{1-5})amino, di - alkyl - (C_{1-5})amine, cycloalkyl(C_{3-6})amino or p-alkoxy (C_{1-5})anilino and A is straight alkylene(C_{1-5}), a ω-amino acid of the formula (III) in which R^3 is hydroxy or alkoxy (C_{1-5}) and B is straight alkylene (C_{1-5}) (said alkylene being optionally substituted with phenyl); or carnosine.

Another preferred subgenus is a salt of sulfodehydroabietic acid with a metal selected from the group consisting of lithium, potassium sodium, magnesium, calcium and aluminium; aluminium hydroxide; or an amine selected from the group consisting of alkyl(C_{1-5})amine, cycloalkyl(C_{3-6})amine, di - alkyl(C_{1-5}) - amino - alkyl(C_{1-5})amine, alkoxy(C_{1-5}) - alkyl(C_{1-5})amine, alkylene(C_{2-6})diamine, morpholine, arginine, glutamine, asparagine, lysine, S-methyl-methionine or carnosine.

A further preferred subgenus is a salt of sulfodehydroabietic acid with sodium, calcium, aluminium, aluminium hydroxide, (2-dimethylaminoethyl)amine, cyclohexylamine, isopropylamine, morpholine, (2-methoxyethyl)-amine, ethylenediamine, tetramethylenediamine, hexamethylenediamine, arginine, glutamine, asparagine, lysine, S-methyl-methionine or carnosine.

Of the above-mentioned various salts, all sulfodehydroabietic acid salts except the sodium and p-toluidine salts thereof are novel compounds.

Pharmaceutically acceptable salts of sulfodehydroabietic acid (I) can be readily obtained. For example, the metal salt of sulfodehydroabietic acid (I) may be prepared by neutralizing the compound (I) with a metal hydroxide (e.g., sodium hydroxide, potassium hydroxide, lithium hydroxide, calcium hydroxide, aluminium hydroxide), a metal carbonate (e.g., sodium carbonate, potassium carbonate, lithium carbonate) or a metal bicarbonate (e.g., sodium bicarbonate, potassium bicarbonate) in a solvent. The solvent may be, for example, water, methanol, ethanol, tetrahydrofuran, dimethylsulfoxide, dimethylformamide or a mixture thereof. It is preferred to carry out the neutralization reaction at a temperature of 0 to 100°C. Further, sulfodehydroabietic acid monosodium salt can be prepared for example by treating sulfodehydroabietic acid disodium salt with an acid (e.g. hydrochloric acid). For example, sulfodehydroabietic acid disodium salt is dissolved in water, and the solution is then adjusted to a pH of 2.0

to 5.0, especially 3.7 to 3.8, with hydrochloric acid. The resultant precipitates are collected by a conventional method, for example, by filtration, whereby sulfodehydroabietic acid monosodium salt is obtained. Alternatively, sulfodehydroabietic acid monosodium salt can be prepared for example by partially neutrallizing the compound (I) with sodium hydroxide, sodium bicarbonate, sodium carbonate or sodium acetate. The partial neutralization reaction is preferably carried out by suspending sulfodehydroabietic acid in water, and then adjusting the suspension to a pH of 2.0 to 5.0, especially 3.7 to 3.8, by the addition of sodium hydroxide, sodium bicarbonate, sodium carbonate or sodium acetate. A metal salt of sulfodehydroabietic acid (I) other than the sodium salt may be prepared for example, by reacting sulfodehydroabietic acid sodium salt with a metal halide (e.g., calcium chloride, aluminium chloride), a metal sulfate (e.g., magnesium sulfate) or a metal nitrate (e.g., barium nitrate) in an aqueous solvent (e.g., water). The reaction is preferably carried out at a temperature of 0 to 100°C. Alternatively, the metal salt such as the calcium or magnesium salt may be prepared for example by reacting sulfodehydroabietic acid silver salt with a metal halide (e.g., calcium chloride, magnesium chloride) in an aqueous solvent (e.g., water). It is preferred to carry out the reaction at a temperature of 0 to 100°C.

On the other hand, the aluminium hydroxide salt of sulfodehydroabietic acid (I) may be prepared for example by reacting the compound (I) with aluminium alkoxide (e.g., aluminium methoxide, aluminium ethoxide, aluminium isopropoxide) in the presence of water in a solvent. The solvent may be, for example, methanol, ethanol, isopropanol or dimethylsulfoxide. This reaction is preferably carried out at a temperature of 0 to 60°C.

Further, the salts of sulfodehydroabietic acid (I) with the amine may also be prepared for example in the same manner as described above, i.e., by neutralizing the compound (I) with the amine in a solvent, or by reacting sulfodehydroabietic acid silver salt with a hydrohalide (e.g., hydrochloride) or quaternary salt of the amine in a solvent. The solvent for the neutralization reaction may be, for example, water, methanol, or ethanol. It is preferred to carry out the neutralization reaction at a temperature of 0 to 100°C. On the other hand, the solvent for the reaction of sulfodehydroabietic acid silver salt with the hydrohalide or quaternary salt of the amine may be water for example, and the reaction is preferably carried out at a temperature of 0 to 100°C.

The pharmaceutically acceptable salt of sulfodehydroabietic acid is preferably administered in a solid dosage form such as for example tablets, capsules, powders or granules, or in a liquid dosage form such as for example, solutions or suspensions. The salt of sulfodehydroabietic acid may be administered either orally or parenterally, while it is generally preferred to administer it through oral route. In order to prepare pharmaceutical preparations suitable for oral administration, the active ingredient is worked up with pharmaceutical adjuvants or excipients. Suitable adjuvants for the solid dosage form such as tablets or capsules are, for example, binders (e.g., acacia, gelatine, dextrin, hydroxypropyl cellulose, methyl cellulose, polyvinylpyrrolidone), diluents (e.g., lactose, sucrose, mannitol, corn starch, potato starch, calcium phosphate, calcium citrate, crystalline cellulose), lubricants (e.g., magnesium stearate, calcium stearate, stearic acid, talc, anhydrous silicic acid), disintegrants (e.g., corn starch, potato starch, carboxymethyl cellulose and its calcium salt, alginic acid), wetting agents (e.g. sodium lauryl sulfate) and so forth. On the other hand, suitable adjuvants for the liquid dosage form such as solutions or suspensions are, for example, liquid vehicles (e.g., water), suspending agents (e.g., acacia, gelatin, methyl cellulose, sodium carboxymethyl cellulose, hydroxymethyl cellulose, aluminium stearate gel), surfactants (e.g., lecithin, sorbitan mono-oleate, glycerin monostearate), non-aqueous vehicles (e.g., glycerin, propylene glycol, vegetable oil) and so forth. The liquid dosage form may further contain preservatives (e.g., methyl p-hydroxy-benzoate, propyl p-hydroxy benzoate), flavouring agents and/or colouring agents.

The therapeutic dose of the salt of sulfodehydroabietic acid (I) will of course vary with the condition of the disease of the patient to be treated and its severity. In general, however, it may be used at a dose of about 20 to about 300 mg, more especially about 40 to about 120 mg, per kilogram of body weight per day.

As mentioned above, the salt of sulfodehydroabietic acid (I) shows potent anti-ulcer activity without aldosterone-like side effects and is useful for the treatment or prophylaxis of gastro-intestinal diseases in a warm-blooded animal, including man, such as peptic ulcer diseases and gastritis. The term "peptic ulcer disease" has historically been used to describe the diseases characterised by ulceration of the upper gastro-intestinal tract and include the disease characterized by ulceration of the body of the stomach, commonly called gastric ulcers as well as the diseases characterised by ulceration of the duodenum, commonly called duodenal ulcers. Accordingly, the term "peptic ulcer disease" used throughout the specification and claims should be interpreted to include both of the above-mentioned gastric ulcers and duodenal ulcers.

The following Experiments and Examples are merely for illustrative purposes and are not to be construed as a limitation of the present invention.

Experiment 1

Preventive effect on acid and pepsin secretions

(Method)

Male SD-strain rats (6 to 7 weeks old) were starved for 48 hours, and the the pylori were ligated. Immediately after ligation, a solution or suspension of a test compound in distilled water was administered orally into the stomachs in an amount of 0.2 ml per 100 g of body weight (Dose: 100 mg/kg). Five hours

after the administration of the test compound, the rats were sacrificed and the stomachs were removed. The gastric contents were centrifuged at 2,500 rpm for 10 minutes and the gastric juice was cooled as the supernatant. The concentration of pepsin in the gastric juice was determined by Anson's method (c.f., J. Gen. Physiol., 22, pp. 77—89 (1938)) using hemoglobin as the substrate, and the preventive effect of the test compound on the pepsin secretion was estimated in terms of "decrease in pepsin concentration" according to the following formula:

$$\text{Decrease (\%) in pepsin concentration} = \left[1 - \frac{\text{Average value of pepsin concentration in gastric juice of medicated rats}}{\text{Average value of pepsin concentration in gastric juice of non-medicated rats}}\right] \times 100$$

and in terms of "the decrease in acidity of gastric juice" according to the following formula:

$$\text{Decrease (\%) in acidity of gastric juice} = \left[1 - \frac{\text{Acid concentration in gastric juice of medicated rats}}{\text{Acid concentration in gastric juice of non-medicated rats}}\right] \times 100$$

(Results)

The results are shown in the following Tables 1 & 2.

TABLE 1

Nos.	Salts of sulfodehydroabietic acid used	Decrease (%) in pepsin concentration
1.	Monosodium salt	96
2.	Disodium salt	92
3.	Calcium salt	99
4.	2/3 Aluminum salt	95
5.	2 Aluminum dihydroxide salt	69
6.	Aluminum monohydroxide salt	91
7.	2 (2-Dimethylaminoethyl)amine salt	92
8.	2 Cyclohexylamine salt	71
9.	2 Isopropylamine salt	95
10.	2 Morpholine salt	92
11.	2 (2-Methoxyethyl)amine salt	98
12.	Tetramethylenediamine salt	84
13.	Ethylenediamine salt	94
14.	Hexamethylenediamine salt	94
15.	L-Arginine salt	77
16.	L-Glutamine salt	90
17.	L-Asparagine salt	90
18.	L-Lysine salt	94
19.	Carnosine salt	72
20.	L-S-Methylmethionine salt	84

TABLE 2

Nos.	Salts of sulfodehydroabietic acid used	Decrease (%) in acidity of gastric juice
1.	Monosodium salt	43
2.	Disodium salt	54
3.	Calcium salt	30
4.	2 (2-Dimethylaminoethyl)amine salt	31
5.	2 Isopropylamine salt	40
6.	Tetramethylenediamine salt	36
7.	Hexamethylenediamine salt	32
8.	L-Glutamine salt	39
9.	L-Asparagine salt	38

Experiment 2
Effect on Shay rat ulcers
(Method)

Male SD-strain rats (6 to 7 weeks old) were starved for 48 hours and then the pylori were ligated. Immediately after ligation, a solution or suspension of a test compound in distilled water was administered orally into the stomachs in an amount of 2.0 ml per 100 g of body weight (Dose: 200 or 300 mg/kg). Seventeen hours after the administration of the test compound, the degree of ulceration in forestomach was examined according to the method of Takagi et al (Chem. Pharm. Bull., 11(10), pp. 1282—1290 (1963)) with a modified scoring system. Depending on the diameter of each lesion, the ulcers were classified into the following 4 grades.

	Ulcer score
Ulcer with diameter less than 1 mm:	1 point
Ulcer with diameter of 1—3 mm:	3 points
Ulcer with diameter of 3—5 mm:	5 points
Ulcer with diameter over 5 mm or perforation:	10 points

The ulcer index was calculated by the sum of the number of ulcers in each degree multiplied by respective ulcer score.

Further, based on the ulcer index determined above, the preventive effect of the test compound on Shay rat ulcer was calculated by the following formula:

$$\text{Preventive effect on Shay rat ulcers (\%)} = \left[1 - \frac{\text{The average value of ulcer indexes in medicated rats}}{\text{The average value of ulcer indexes in non-medicated rats}} \right] \times 100$$

(Results)

The results are shown in the following Table 3.

TABLE 3

Test compounds	Dose (mg/kg)	Preventive effect on Shay rat ulcers (%)
(The compounds of the present invention)		
Sulfodehydroabietic acid monosodium salt	200	100
Sulfodehydroabietic acid disodium salt	200	93
Sulfodehydroabietic acid calcium salt	300	100
(Positive control)		
Carbenoxolone disodium salt	300	40

Experiment 3
Effect on stress-induced ulcers
(Method)

Male ddY-strain mice (4 weeks old) weighing about 20 g were starved for about 7 hours. A solution of a test compound in distilled water was administered orally to the mice in an amount of 0.1 ml per 10 g of body weight (Dose: 100 mg/kg). Immediately after administration of the test compound, the mice were placed in a stress cage and immersed to the level of the cervix in a water bath (24±0.5°C) for 16 hours. Then, the stomach was removed and slightly inflated by injecting 1.2 ml of a 1% formalin solution to fix the inner layers of the gastric walls. The stomach was then incised along the greater curvature, and the number of ulcerations was examined.

(Results)

Sulfodehydroabietic acid disodium salt showed 22% decrease in the number of stress-induced ulcers.

Experiment 4
Effect on aspirin-induced ulcers
(Method)

Male Donryu-strain rats (8 to 9 weeks old) were starved overnight, and a solution or suspension of a test compound in distilled water was administered orally into the stomachs in an amount of one ml per 100 g of body weight. Half an hour later, a suspension of aspirin in 0.25% carboxymethyl cellulose (CMC) solution was administered orally to the rats in an amount of 0.5 ml per 100 g of body weight (Dose: 200 mg/kg). Four hours after the administration of aspirin, the rats were sacrified and the stomachs were removed and inflated by injecting 10 ml of 1% formalin solution to fix the inner layers of the gastric walls. The stomach was then incised along the greater curvature and the lengths of the lesions were measured and summated to give the ulcer index (in mm) for each animal. The preventive effect of the test compound on aspirin-induced ulcers was calculated by the following formula:

$$\text{Preventive effect on aspirin-induced ulcers (\%)} = \left[1 - \frac{\text{The average value of ulcer indexes in medicated rats}}{\text{The average value of ulcer indexes in non-medicated rats}}\right] \times 100$$

(Results)

The results are shown in the following Table 4.

TABLE 4

Test compounds	Dose (p.o.)	Preventive effect on aspirin-induced ulcers (%)
Sulfodehydroabietic acid monosodium salt	0.8 m mol./kg (400 mg/kg)	68
Sulfodehydroabietic acid carnosine salt	2 m mol./kg (1,248 mg/kg)	33
Sulfodehydroabietic acid S-methylmethionine salt	2 m mol./kg (1,086 mg/kg)	85
Sulfodehydroabietic acid disodium salt	2 m mol./kg (847 mg/kg)	82

Experiment 5

(Effect on gastric mucus secretion)

The stimulating effect of a test compound on gastric mucus secretion was examined by the method of Corne et al. (J. Physiol., *242*, pp. 116—117 (1974); J. Pharm. Pharmacol., *33*, pp. 348—352 (1981)). Male Sprague-Dawley rats (6—7 weeks old; one group: 6 rats) were fasted for 20 hours before the experiments. Water was given *ad libitum* and coprophagy was prevented by using cages with wide-mesh floors. A test compound dissolved or suspended in distilled water was administered orally to the rats at a dose of 100 mg/kg. One hour after the administration of the test compound, the stomachs were dissected, opened along the greater curvature, rinsed in ice-cold 0.25 M sucrose, and the rumen was discarded. Then, the stomachs were incubated in 10 ml of a 0.15 M sucrose-0.05 M sodium acetate solution (pH 5.8) containing alcian blue (1 mg/ml), at room temperature for 1.5 hours. Finally, the stomachs were placed in 15 ml of a 0.5 M magnesium chloride solution for 2 hours with occasional shaking and then removed, and the magnesium chloride solution was shaken briefly with 10 ml of diethyl ether. The optical density of the aqueous layer was read at 605 nm, and the degree of alcian blue binding was expressed as µg alcian blue/g of tissue. The stimulating effect of the test compound on gastric mucus secretion was estimated in terms of "the increase in alcian blue binding" which was calculated by the following formula:

$$\text{Increase (\%) in alcian blue binding} = \left[\frac{\text{µg alcian blue/g tissue in medicated rats}}{\text{µg alcian blue/g tissue in non-medicated rats}} - 1 \right] \times 100$$

(Results)

The results are shown in the following Table 5.

TABLE 5

Test compounds	Stimulating effect on gastric mucus secretion	
	Alcian blue binding (µg/g tissue)	Increase (%) in alcian blue binding
Control (water)	198.5± 6.4	—
Sulfodehydroabietic acid monosodium salt	287.3±34.2	45
Sulfodehydroabietic acid disodium salt	247.7±18.4	25
Sulfodehydroabietic acid calcium salt	284.7±14.9	44

Experiment 6
(protective effect on gastric mucous membrane)

Protective effect on a test compound on gastric mucous membrane was examined by the method of Daigo et al. (Yakugaku Zasshi, *101,* 452—457 (1981)). Male Sprague-Dawley rats (6—7 weeks old; one group: 5 rats) were fasted for 20 hours before the experiments. Water was given *ad libitum* and coprophagy was prevented by using cages with wide-mesh floors. The stomach was excised, opened along the greater curvature, rinsed in physiological saline solution, and the rumen was discarded. The stomach was incubated in 10 ml of an artificial gastric juice (100 mM HCl, 0.3% pepsin, 0.2% NaCl) containing a test compound, at 37°C for 60 minutes. After the incubation, 2 ml of 7% trichloroacetic acid were added to 0.5 ml of medium, and the mixture was centrifuged. The amount of tyrosine in the supernatant was measured by using Folin-Ciocelteu reagent (J. gen. Physiol., *16,* 59—63 (1932)), and expressed as mg tyrosine/g tissue. The protective effect of the test compound on gastric mucous membrane was estimated in terms of "the inhibition of digestion of mucous membrane" which was calculated by the following formula:

$$\text{Inhibition (\%) of digestion of mucous membrane} = \left[1 - \frac{\text{mg tyrosine/g tissue estimated by adding test compound}}{\text{mg tyrosine/g tissue estimated without adding test compound}}\right] \times 100$$

(Results)

The results are shown in the following Table 6.

TABLE 6

Test compound	Concentration in artificial gastric juice (mg/ml)	Protective effect on gastric mucous membrane: Amount of tyrosine (mg/g tissue)	Protective effect on gastric mucous membrane: Inhibition (%) of digestion of mucous membrane
Control (no addition)	—	2.42±0.15	—
Sulfodehydroabietic acid monosodium salt	1	1.61±0.13	33
	4	0.95±0.07	61
Sulfodehydroabietic acid disodium salt	1	1.64±0.12	32
	4	0.82±0.07	66
Sulfodehydroabietic acid calcium salt	1	1.72±0.08	29
	4	0.86±0.04	64

Experiment 7
Effect on urine volume and urinary electrolytes
(Method)

Male SD-strain rats (6 to 7 weeks old) were starved overnight, and a physiological saline solution (3 ml/100 g of body weight) was orally administered to the rats. One hour later, a solution or suspension of a test compound in a 0.25% CMC-physiological saline solution was administered orally to the rats in an amount of 3 ml per 100 g of body weight (Dose: 50 and 500 mg/kg). Immediately after administration of the test compound, the rats were placed into a metabolic cage (2 rats per cage) and deprived of water and food for 5 hours. The urine samples which were excreted during a 5 hour period were collected. Sodium and potassium in the urine was estimated by a flame photometer (Hitachi Model-205).

(Results)

The results are shown in the following Table 7.

TABLE 7

Test compounds	Dose (mg/kg)	Urine volume (ml)	Na/K
(The test compound of the present invention)			
Sulfodehydroabietic acid calcium salt	50	11.5	5.2
	500	11.3	6.8
Carbenoxolone disodium salt	50	9.3	3.2
Control	—	12.3	5.8

Carbenoxolone (chemical name: 3 - β - hydroxy - 11 - oxoolean - 12 - en - 30 - oic acid hydrogen succinate) disodium salt is known to protect animals from experimentally-induced gastric ulceration and, in human gastric ulcer patients, has been shown in numerous clinical trials to be an effective gastric anti-ulcer agent. However, carbenoxolone disodium salt has a side effect such as an aldostetone-like effect. As can be seen from Table 7, the compound of the present invention is quite free from such side effect.

Experiment 8
Effect on urinary electrolytes
(Method)

Male SD-strain rats (6 to 7 weeks old, one group: 5—8 rats) were starved overnight, and a physiological saline solution (3 ml/100 g of body weight was orally administered to the rats. One hour later, a solution of a test compound in a 0.25% CMC-physiological saline solution was administered orally to the rats in an amount of 3 ml per 100 g of body weight (Dose: 50, 500 or 1,000 mg/kg). Immediately after administration of the test compound, the rats were placed into a metabolic cage (one rat per cage) and deprived of water and food for 4 hours. The urine samples which were excreted during a 4 hour period were collected. Sodium and potassium in the urine was estimated by a flame photometer (Hitachi model-205).

(Results)

The results are shown in the following Table 8.

TABLE 8

Test compound	Dose mg/kg p.o.	Urine volume (ml)	Na/K ratio
Sulfodehydroabietic acid disodium salt	500	4.8±0.4	7.4±1.0
	1000	4.3±0.3	5.9±0.4
Carbenoxolone disodium salt	50	5.2±0.3	3.7±0.3*
Control	—	5.7±0.6	6.1±0.3

* =significantly different ($p<0.01$) from control

Experiment 9
Effect on urinary electrolytes
(Method)

Male SD-strain rats (6 to 7 weeks old, one group: 6 rats) were starved overnight, and a physiological saline solution (3 ml/100 g of body weight) was orally administered to the rats. One hour later, a suspension of a test compound in a physiological saline solution was administered orally to the rats in an amount of 3 ml per 100 g of body weight (Dose; 500 or 1,000 mg/kg). Immediately after administration of the test compound, the rats were placed into a metabolic cage (one rat per cage) and deprived of water and food for 4 hours. The urine samples which were excreted during a 4 hour period were collected. Sodium and potassium in the urine was estimated by a flame photometer (Hitachi Model-205).

(Results)

The results are shown in the following Table 9.

TABLE 9

Test compound	Dose mg/kg	Urine volume (ml)	Na/K ratio
Sulfodehydroabietic acid monosodium salt	500	6.2±0.5	5.6±0.5
	1000	4.7±0.4	5.9±0.2
Control (physiological saline)	—	6.5±0.3	5.8±0.6

Experiment 10

After male SD-strain rats (6—7 weeks old) were starved for 20 hours, a solution or suspension of a test compound in distilled water was administered orally to the rats in an amount of one ml per 100 g of body weight. After administration of the test compound, the rats were allowed free access to water and food. The mortality of the rats were observed for 7 days and the 50% lethal dose (LD_{50}) was calculated therefrom.

The results are shown in the following Table 10.

TABLE 10

Test compounds	LD_{50} (mg/kg)
Sulfodehydroabietic acid monosodium salt	>2000
Sulfodehydroabietic acid disodium salt	>2000
Sulfodehydroabietic acid calcium salt	>2000

Experiment 11

After male ddY-strain mice (4 weeks old) were starved for 4 hours, a suspension of a test compound in distilled water containing a small amount of Tween 80 was administered orally to the mice in an amount of 0.1 ml per 10 g of body weight. After administration of the test compound, the mice were allowed free access to water and food. The mortality of the mice was observed for 7 days and the 50% lethal dose (LD_{50}) was calculated therefrom. As a result, the LD_{50} of sulfodehydroabietic acid calcium salt was more than 2,000 mg/kg.

Example 1

10 g of sulfodehydroabietic acid hemihydrate (chemical name; 1,4a - dimethyl - 1 - carboxy - 6 - sulfo - 7 - isopropyl - 1,2,3,4,4a,9,10,10a - octahydro - phenanthrene hemihydrate) are suspended in 50 ml of water, and 2.1 g of sodium hydroxide are added thereto under stirring. The mixture is treated with activated charcoal, and then condensed to a total volume of 20 ml under reduced pressure. The condensed solution is heated to make a clear solution, and the solution is allowed to stand at room temperature. The crystalline precipitates are collected by filtration, and then dried in air. 10.4 g of sulfodehydroabietic acid disodium salt $8\frac{1}{2}$ hydrate (chemical name: 1,4a - dimethyl - 1 - carboxy - 6 - sulfo - 7 - isopropyl - 1,2,3,4,4a,9,10,10a - octahydro - phenanthrene disodium salt $8\frac{1}{2}$ hydrate) are thereby obtained.

M.p. >300°C

$[\alpha]_D^{20}$=+48.2° (C=2.5, H_2O)

IRv_{max}^{nujol} (cm^{-1}): 3483 (broad), 1540, 1461, 1377, 1192, 1158, 1097, 1067

Concomitantly, the crystalline precipitates mentioned above are dried over phosphorus pentoxide at 160°C under a pressure of 3 mm Hg for 17 hours, whereby sulfodehydroabietic acid disodium salt anhydrate is obtained.

M.p. >300°C

$[\alpha]_D^{20}$=+64.6° (C=2.5, H_2O)

IRv_{max}^{KBr} (cm^{-1}): 1556, 1485, 1395, 1185, 1098, 1059, 1046

The sulfodehydroabietic acid disodium salt $8\frac{1}{2}$ hydrate obtained above is recrystallized from an aqueous 95% methanol solution and then dried in air, whereby sulfodehydroabietic acid disodium salt 1/2 hydrate is obtained.

M.p. >300°C

$[\alpha]_D^{20}$=+58.2° (C=2.5, H_2O)

IRv_{max}^{nujol} (cm^{-1}): 3444 (broad, 1583, 1570, 1461, 1407, 1380, 1229, 1195, 1174, 1098, 1061, 1045, 1034

Example 2

5 g of sulfodehydroabietic acid disodium salt anhydrate (chemical name: 1,4a - dimethyl - 1 - carboxy - 6 - sulfo - 7 - isopropyl - 1,2,3,4,4a,9,10,10a - octahydro - phenanthrene disodium salt anhydrate) are dissolved in 50 ml of water, and the solution is adjusted to pH 3.7 with about 12 ml of 1N-hydrochloric acid.

The precipitates are collected by filtration, dried in air and then recrystallized from water. 3.87 g of sulfodehydroabietic acid monosodium salt 5 hydrate (chemical name; 1,4a - dimethyl - 1 - carboxy - 6 - sulfo - 7 - isopropyl - 1,2,3,4,4a,9,10,10a - octahydro - phenanthrene monosodium salt 5 hydrate) are thereby obtained.

M.p. >300°C

$[\alpha]_D^{20}$=+59.4° (C=0.5, H_2O)

IRv_{max}^{Nujol} (cm^{-1}): 3513—3421 (broad), 1689, 1633 1461, 1377, 1276, 1197, 1187, 1163, 1097, 1058, 1048, 1037

When the precipitates are recrystallized from ethanol instead of water, sulfodehydroabietic acid monosodium salt 6.7 hydrate containing 3/4 ethanol is obtained.

M.p. >300°C

$[\alpha]_D^{20}$=+66.2° (C=0.5, H_2O)

IRv_{max}^{Nujol} (cm^{-1}): 3418 (broad), 1712, 1461, 1385, 1247, 1211, 1190, 1166, 1137, 1100, 1034, 1008

Example 3

6.1 g of sulfodehydroabietic acid are suspended in 15 ml of water, and the suspension is adjusted to pH 3.72 by adding about 13.5 ml of an aqueous 1N sodium hydroxide solution thereto under stirring. The mixture is heated to make a clear solution, and the solution is allowed to stand at room temperature. The crystalline precipitates are collected by filtration and then dried in air. 5.5 g of sulfodehydroabietic acid monosodium salt 5 hydrate are thereby obtained.

The physico-chemical properties of the product are identical with those of the product obtained in Example 2.

Example 4

3.98 g of sulfodehydroabietic acid are suspended in 20 ml of water, and 0.5 g of sodium bicarbonate is added thereto. Then, 1.35 g of sodium chloride are added to the mixture, and the mixture is heated. Water is added to the mixture until the mixture becomes a clear solution. The solution is allowed to stand at room temperature. The crystalline precipitates are collected by filtration and then recrystallized from water. 3.5 g of sulfodehydroabietic acid monosodium salt 5 hydrate are thereby obtained.

The physico-chemical properties of the product are identical with those of the product obtained in Example 2.

Example 5

1.36 g of sulfodehydroabietic acid monohydrate are dissolved in 10 ml of ethanol, and a solution of 288 mg of lithium hydroxide monohydrate in 3 ml of water is added thereto under cooling. 100 ml of acetone are added to the mixture, and the precipitates are collected therefrom. 1.4 g of sulfodehydroabietic acid dilithium salt monohydrate are obtained.

M.p. >300°C

IRv_{max}^{nujol} (cm^{-1}): 3430, 1540, 1400, 1160

Example 6

1.36 g of sulfodehydroabietic acid monohydrate and 0.383 g of potassium hydroxide are treated in the same manner as described in Example 5, whereby 1.3 g of sulfodehydroabietic acid dipotassium salt monohydrate are obtained.

M.p. >300°C

IRv_{max}^{nujol} (cm^{-1}): 3500—3200 (broad), 1530, 1190

Example 7

To a solution of 5 g of sulfodehydroabietic acid disodium salt anhydrate in 20 ml of water is added a solution of 1.5 g of calcium chloride in 10 ml of water. The precipitated solid is filtered, washed with a small amount of water and air dried. The dried solid is immersed in 20 ml methanol and the undissolved materials are removed. The methanol solution is warmed to boiling point temperature, and 4 ml of water are added thereto. After cooling, the precipitated crystals are filtered, washed with water and air dried to give 2.5 g of sulfodehydroabietic acid calcium salt 2.5 hydrate.

M.p. >300°

$[\alpha]_D^{20}$=+54.8° (C=0.5, MeOH)

IRv_{max}^{nujol} (cm^{-1}): 3535, 3354 (br.), 1544, 1464, 1401, 1379, 1229, 1216, 1190, 1100, 1061, 1046

Example 8

5 g of sulfodehydroabietic acid are dissolved in 200 ml of water, and 1.25 g of calcium chloride 25 ml of

water are added dropwise thereto. When the clear solution is warmed to 80—85°C, crystals are precipitated slowly. After the precipitation is completed, the crystals are filtered while hot, washed with hot water and air dried to give 3.5 g of sulfodehydroabietic acid calcium salt 2.5 hydrate.

The physico-chemical properties of the product are identical with those of the product obtained in Example 7.

Example 9

5 g of sulfodehydroabietic acid disodium salt anhydrate are dissolved in 20 ml of water, and 1.56 g of magnesium sulfate in 10 ml of water are added thereto. The solvent is distilled to half of its original volume, and the precipitated solids are filtered, washed with water and air dried. The dried solids are recrystallized from water to give 3.99 g of sulfodehydroabietic acid magnesium salt 7.4 hydrate.

M.p. >300°

$[\alpha]_D^{20}$=+50.9° (C=2.5, H_2O)

IRv_{max}^{nujol} (cm^{-1}): 3413 (br.), 1678, 1517, 1461, 1390, 1169, 1097, 1056, 1045, 1034

Example 10

1.32 g of sulfodehydroabietic acid disodium salt anhydrate are dissolved in 6 ml of water, and a 50% aqueous aluminium chloride solution is added dropwise thereto until precipitation is complete. 2 ml of ethanol are added to the mixture, and the precipitates are collected, washed with water and ethanol and then dried. 1.0 g of sulfodehydroabietic acid 2/3 aluminium salt 7/3 hydrate is obtained.

M.p. >300°C

IRv_{max}^{nujol} (cm^{-1}): 3500—3100 (br.), 1600, 1440, 1200, 1150, 1030

Example 11

A solution of 1.62 g of aluminium isopropoxide in 12 ml of ethanol and 0.288 g of water are added to 10 ml of an ethanol solution containing 1.52 g of sulfodehydroabietic acid monohydrate, and the mixture is concentrated under reduced pressure to dryness. 1.71 g of sulfodehydroabietic acid di(aluminium dihydroxide) salt dihydrate are obtained as a colourless crystalline powder.

M.p. >300°C

IRv_{max}^{nujol} (cm^{-1}): 3400 (br), 1570, 1440, 1200, 1160, 1100, 1050, 1030

Example 12

1.36 g of sulfodehydroabietic acid monohydrate are dissolved in 10 ml of methanol, and 404 mg of isopropylamine are added thereto. The mixture is evaporated under reduced pressure to remove the solvent. The residue is recrystallized from methanol, whereby 1.4 g of sulfodehydroabietic acid di(isopropylamine) salt are obtained as needles.

M.p. >300°C

IRv_{max}^{nujol} (cm^{-1}): 2750—2500, 1610, 1520, 1380, 1190, 1160, 1020

Example 13

1.3 g of sulfodehydroabietic acid monohydrate and 0.2 g of cyclohexylamine are treated in the same manner as described in Example 12, whereby 0.9 g of sulfodehydroabietic acid di(cyclohexylamine) salt is obtained as needles.

M.p. >300°C (recrystallized from methanol)

IRv_{max}^{nujol} (cm^{-1}): 2800—2400, 1625, 1510, 1370, 1210, 1135, 1020

Example 14

1.3 of sulfodehydroabietic acid monohydrate and 0.36 g of 2-dimethylaminoethylamine are treated in the same manner as described in Example 12, whereby 0.8 g of sulfodehydroabietic acid di(2-dimethylaminoethylamine)salt monohydrate is obtained as needles.

M.p. 240—242°C (decomp.) (recrystallized from ethanol-tetrahydrofuran)

IRv_{max}^{nujol} (cm^{-1}): 3500—3050, 2780—2300, 1620, 1520, 1190, 1180, 1150, 1020

Example 15

1.3 g of sulfodehydroabietic acid monohydrate and 0.2 g of morpholine are treated in the same manner as described in Example 12, whereby 1.24 g of sulfodehydroabietic acid dimorpholine salt hemihydrate are obtained as needles.

M.p. 288—290°C (decomp.) (recrystallized from methanol-acetone)

IRv_{max}^{nujol} (cm^{-1}): 3600—3300, 2750—2500, 1630, 1360, 1180, 1140, 1100, 1030

Example 16

1.3 g of sulfodehydroabietic acid monohydrate and 0.353 g of piperazine are treated in the same manner as described in Example 12, whereby 0.82 g of sulfodehydroabietic acid piperazine salt hemihydrate is obtained as needles.

M.p. >300°C

IRv_{max}^{nujol} (cm^{-1}): 3450, 2750—2500, 1630, 1180, 1095, 1035

Example 17

1.3 of sulfodehydroabietic acid monohydrate and 0.616 g of 2-methoxyethylamine are treated in the same manner as described in Example 12, whereby 0.98 g of sulfodehydroabietic acid di(2-methoxyethylamine)salt is obtained as needles.

M.p. 275—277°C (recrystallized from methanol-ethyl acetate)

IRv_{max}^{nujol} (cm^{-1}): 3400—3050, 2750—2150, 1630, 1520, 1160, 1115, 1030

Example 18

1.3 g of sulfodehydroabietic acid monohydrate and 0.994 g of phenethylamine are treated in the same manner as described in Example 12, whereby 1.42 g of sulfodehydroabietic acid di(phenethylamine) salt are obtained as needles.

M.p. 281—284°C (decomp.) (recrystallized from methanol)

IRv_{max}^{nujol} (cm^{-1}): 3400—3000, 2800—2100, 1630, 1480, 1360, 1190, 1170, 1030

Example 19

1.3 g of sulfodehydroabietic acid monohydrate and 0.21 g of ethylenediamine are treated in the same manner as described in Example 12, whereby 0.6 g of sulfodehydroabietic acid ethylenediamine salt hemihydrate are obtained as small needles.

M.p. 279—280°C (decomp.) (recrystallized from ethanol-tetrahydrofuran)

IRv_{max}^{nujol} (cm^{-1}): 3450, 2750—2300, 1650, 1585, 1180, 1150, 1025

Example 20

1.3 g of sulfodehydroabietic acid monohydrate and 0.298 g of tetramethylenediamine are treated in the same manner as described in Example 12, whereby 1.06 g of sulfodehydroabietic acid tetramethylenediamine salt hemihydrate are obtained.

M.p. 284—287°C (decomp.) (recrystallized from methanol-aqueous tetrahydrofuran)

IRv_{max}^{nujol} (cm^{-1}): 3550—3400, 2800—2100, 1610, 1500, 1360, 1160, 1025

Example 21

1.3 g of sulfodehydroabietic acid monohydrate and 0.4 g of hexamethylenediamine are treated in the same manner as described in Example 12, whereby 0.77 g of sulfodehydroabietic acid hexamethylenediamine salt hemihydrate is obtained.

M.p. 290°C (decomp.) (recrystallized from water-acetone)

IRv_{max}^{nujol} (cm^{-1}): 3530, 3490, 2750—2300, 1615, 1510, 1375, 1190, 1160, 1020

Example 22

2.6 g of sulfodehydroabietic acid monohydrate are dissolved in 20 ml of methanol, and a solution of 0.94 g of L-lysine in 10 ml of water is added thereto. The mixture is concentrated under reduced pressure to dryness. The residue is recrystallized from a mixture of methanol and water, whereby 3 g of sulfodehydroabietic acid L-lysine salt monohydrate are obtained as a crystalline solid.

M.p. 236°C (decomp.)

IRv_{max}^{nujol} (cm^{-1}): 3400, 1680, 1590, 1165

Example 23

1.3 g of sulfodehydroabietic acid monohydrate and 0.45 g of L-ornithine are treated in the same manner as described in Example 22, whereby 1.4 g of sulfodehydroabietic acid L-ornithine salt monohydrate are obtained as a crystalline solid.

M.p. 213—215°C (recrystallized from methanol)

IRv_{max}^{nujol} (cm^{-1}): 3400, 3160—3100, 2750—2200, 1700, 1650, 1190, 1150

Example 24

2.85 g of sulfodehydroabietic acid monohydrate and 1.75 g of L-arginine acetate are treated in the same manner as described in Example 22, whereby 2.9 g of sulfodehydroabietic acid L-arginine salt hemihydrate are obtained as colourless prisms.

M.p. 230°C (decomp.) (recrystallized from methanol-water)

IRv_{max}^{nujol} (cm^{-1}): 3350, 3200, 3100, 1680—1630 (br), 1180

Example 25

1.3 g of sulfodehydroabietic acid monohydrate and 0.513 g of L-asparagine are treated in the same manner as described in Example 22, whereby 1.5 g of sulfodehydroabietic acid L-asparagine salt monohydrate are obtained as a crystalline solid.

M.p. >300°C (recrystallized from water)

IRv_{max}^{nujol} (cm^{-1}): 3400—3200, 2750—2300, 1740, 1680, 1270, 1170

Example 26

1.3 g of sulfodehydroabietic acid monohydrate and 0.5 g of L-glutamine are treated in the same manner as described in Example 22, whereby 1.1 g of sulfodehydroabietic acid L-glutamine salt hemihydrate are obtained as a crystalline solid.

M.p. >240°C (recrystallized from methanol-acetone)

IRv_{max}^{nujol} (cm^{-1}): 3400—3100, 2750—2300, 1750, 1690, 1670, 1590, 1240, 1200, 1170, 1140

Example 27

1.3 g of sulfodehydroabietic acid monohydrate and 0.51 g of L-methionine are treated in the same manner as described in Example 22, whereby 1.4 g of sulfodehydroabietic acid L-methionine salt are obtained as a crystalline solid.

M.p. 250—252°C (decomp.) (recrystallized from methanol-ethyl acetate)

IRv_{max}^{nujol} (cm^{-1}): 3450—3050, 2800—2300, 1750, 1690, 1280, 1200, 1190, 1160

Example 28

1.3 g of sulfodehydroabietic acid monohydrate and 0.64 g of L-histidine are treated in the same manner as described in Example 22, whereby 1.0 g of sulfodehydroabietic acid L-histidine salt monohydrate is obtained as a crystalline solid.

M.p. 225°C (decomp.) (recrystallized from methanol-water)

IRv_{max}^{nujol} (cm^{-1}): 3400—3100, 2750—2300, 1690, 1610, 1160

Example 29

1.3 g of sulfodehydroabietic acid are dissolved in 15 ml of ethanol, and 0.472 mg of silver carbonate and 20 ml of water are added thereto. 0.635 g of ethyl L-cysteinate hydrochloride are added to the mixture, and the mixture is stirred at room temperature. The precipitates are filtered off, and the filtrate is concentrated to dryness under reduced pressure. The residue is recrystallized from a mixture of methanol and ethyl acetate, whereby 1.5 g of sulfodehydroabietic acid ethyl L-cysteinate salt hemihydrate are obtained.

M.p. 239—241°C (decomp.)

IRv_{max}^{nujol} (cm^{-1}): 3400—3100, 2750—2400, 1750, 1690, 1210, 1150, 1030

Example 30

1.3 g of sulfodehydroabietic acid, 0.472 g of silver carbonate and 0.672 g of ethyl L-asparaginate hydrochloride are treated in the same manner as described in Example 29, whereby 0.9 g of salt of sulfodehydroabietic acid ethyl L-asparaginate salt is obtained.

M.p. >260°C (decomp.) (recrystallized from ethanol-ethyl acetate)

IRv_{max}^{nujol} (cm^{-1}): 3450, 3300, 3200, 2800—2400, 1760, 1710, 1690, 1610, 1250, 1190, 1160

Example 31

1.31 g of sulfodehydroabietic acid, 0.472 g of silver carbonate and 0.93 g of ethyl L-glutaminate hydrochloride are treated in the same manner as described in Example 29, whereby 0.8 g of sulfodehydroabietic acid ethyl L-glutaminate salt monohydrate is obtained.

M.p. 254°C (decomp.) (recrystallized from water-ethanol)

IRv_{max}^{nujol} (cm^{-1}): 3500—3050, 2750—2300, 1740, 1690—1640, 1200, 1180, 1160, 1140

Example 32

1.3 g of sulfodehydroabietic acid, 0.472 g of silver carbonate and 0.526 g of L-homocysteine thiolactone hydrochloride are treated in the same manner as described in Example 29, whereby 1.4 g of sulfodehydroabietic acid L-homocysteine thiolactone salt are obtained.

M.p. 289—291°C (decomp.) (recrystallized from methanol-ethyl acetate)

IRv_{max}^{nujol} (cm^{-1}): 3400, 3150, 2750—2400, 1710, 1505, 1185, 1150, 1030

Example 33

1.3 g of sulfodehydroabietic acid, 0.5 g of silver carbonate and 0.573 g of L-asparagine amide hydrochloride are treated in the same manner as described in Example 29, whereby 0.9 g of sulfodehydroabietic acid L-asparagine amide salt is obtained.

M.p. >300°C (recrystallized from ethanol)

IRv_{max}^{nujol} (cm^{-1}): 3400—3200, 2750—2300, 1690, 1650, 1605, 1195, 1155

Example 34

1.3 g of sulfodehydroabietic acid, 0.5 g of silver carbonate and 0.621 g of L-glutamine amide hydrochloride are treated in the same manner as described in Example 29, whereby 1.14 g of sulfodehydroabietic acid L-glutamine amide salt hemihydrate are obtained.

M.p. >300°C (recrystallized from methanol-ethyl acetate

IRv_{max}^{nujol} (cm^{-1}): 3370, 3200, 2800—2300, 1690, 1650, 1530, 1200, 1165, 1100

Example 35

1.52 g of sulfodehydroabietic acid monohydrate are dissolved in 5 ml of methanol, and a solution of 0.907 g of L-glutamine cyclohexylamide in 20 ml of methanol is added thereto. The mixture is concentrated under reduced pressure to remove solvent until the volume of the mixture is 5 ml. Ether is added to the residue and the precipitates (white crystalline) are collected therefrom. 1.35 g of sulfodehydroabietic acid L-glutamine cyclohexylamide salt hemihydrate are thereby obtained.

M.p. >190°C (decomp.)

IRν_{max}^{nujol} (cm^{-1}): 3400, 3210, 3070, 2750—2300, 1695, 1670, 1650, 1570, 1255, 1180, 1160

Example 36

1.14 g of sulfodehydroabietic acid monohydrate and 0.435 g of L-asparagine methylamide are treated in the same manner as described in Example 35, whereby 1.3 g of sulfodehydroabietic acid L-asparagine methylamide salt are obtained.

M.p. 240°C (decomp.) (recrystallized from ethanol-ether)

IRν_{max}^{nujol} (cm^{-1}): 3430—3050, 2750—2300, 1710, 1680, 1630, 1560, 1180, 1170, 1140

Example 37

1.14 g of sulfodehydroabietic acid monohydrate and 0.73 g of L-asparagine n-octylamide are treated in the same manner as described in Example 35, whereby 1.2 g of sulfodehydroabietic acid L-asparagine n-octylamide salt hemihydrate are obtained as a crystalline powder.

M.p. >87°C (decomp.)

IRν_{max}^{nujol} (cm^{-1}): 3400—3100, 2750—2300, 1700, 1680, 1655, 1620, 1560, 1180, 1160, 1140

Example 38

1.14 g of sulfodehydroabietic acid monohydrate and 0.525 g of L-asparagine isopropylamide are treated in the same manner as described in Example 35, whereby 1.42 g of sulfodehydroabietic acid L-asparagine isopropylamide salt are obtained.

M.p. 141°C (decomp.) (recrystallized from ethanol-acetone)

Example 39

1.14 g of sulfodehydroabietic acid monohydrate and 0.639 g of L-asparagine cyclohexylamide are treated in the same manner as described in Example 35, whereby 1.4 g of sulfodehydroabietic acid L-asparagine cyclohexylamide salt monohydrate are obtained.

M.p. 228°C (decomp.) (recrystallized from ethanol-acetone)

IRν_{max}^{nujol} (cm^{-1}): 3430—3100, 2800—2300, 1690, 1680, 1660, 1620, 1560, 1215, 1160, 1140

Example 40

1.12 g sulfodehydroabietic acid monohydrate and 0.7 g of L-asparagine p-methoxyanilide are treated in the same manner as described in Example 35, whereby 1.4 of sulfodehydroabietic acid L-asparagine p-methoxyanilide salt hemihydrate are obtained as a powder.

M.p. >170°C (decomp.)

IRν_{max}^{nujol} (cm^{-1}): 3450—3050, 2750—2300, 1690, 1655, 1620, 1610, 1550, 1510, 1240, 1170,

Example 41

1.14 g of sulfodehydroabietic acid monohydrate and 0.771 g of L-glutamine n-octylamide are treated in the same manner as described in Example 35, whereby 1.42 g of sulfodehydroabietic acid L-glutamine n-octylamide salt monohydrate are obtained.

M.p. 141°C (decomp.)

IRν_{max}^{nujol} (cm^{-1}): 3450—3100, 2750—2250, 1690, 1660, 1570, 1510, 1200, 1180, 1130

Example 42

1.14 g of sulfodehydroabietic acid monohydrate and 0.567 g of L-glutamine isopropylamide are treated in the same manner as described in Example 35, whereby 1.62 g of sulfodehydroabietic acid L-glutamine isopropylamide salt hemihydrate are obtained.

M.p. >190°C (decomp.) (recrystallized from ethanol-acetone)

IRν_{max}^{nujol} (cm^{-1}): 3500—3050, 2750—2300, 1700, 1670, 1610, 1550, 1520, 1255, 1210, 1160, 1140, 1100

Example 43

1.04 g of sulfodehydroabietic acid monohydrate and 0.63 g of L-glutamine di-n-propylamide are treated in the same manner as described in Example 35, whereby 0.6 g of sulfodehydroabietic acid L-glutamine di-n-propylamide salt monohydrate is obtained.

M.p. >139°C (decomp.) (recrystallized from methanol-ether)

IRν_{max}^{nujol} (cm^{-1}): 3400—3100, 2750—2300, 1700, 1660, 1240, 1200, 1160

Example 44

11.6 g of S-methyl-L-methionine iodide are dissolved in 50 ml of water, and the solution is passed through a column packed with 100 ml of a weakly basic ion exchange resin (manufactured by Rohm & Haas Co. under the trade name "Amberlite IR 45"). Then, the column is washed with about 200 ml of water. The effluent and washings are combined, and a solution of 15.2 g of sulfodehydroabietic acid monohydrate in 150 ml of methanol is added to the combined solution. The mixture is concentrated to dryness at a temperature below 50°C under reduced pressure. The residue is dissolved in 200 ml of a 50% aqueous ethanol solution, and 800 ml of acetone are added thereto. The mixture is allowed to stand at room temperature. The precipitates are collected, whereby 18 g of sulfodehydroabietic acid S - methyl - L - methionine salt dihydrate are obtained as crystals.

M.p. 268°C (decomp.)
IRv_{max}^{nujol} (cm^{-1}): 3460, 3340, 1695, 1680, 1630, 1520, 1230, 1210, 1170, 1140, 1035

Example 45

1.53 g of sulfodehydroabietic acid monohydrate are suspended in 17.6 ml of water, and a solution of 0.85 g of carnosine in 3.3 ml of water is added thereto under stirring. The mixture is heated to make a solution, and the hot solution is filtered with charcoal. The filtrate is allowed to stand at room temperature, whereby 2.2 g of sulfodehydroabietic acid carnosine salt monohydrate are obtained as needles.

M.p. 190—224°C (decomp).
IRv_{max}^{nujol} (cm^{-1}): 3600—3100, 2800—2300, 1700, 1660, 1630, 1230, 1200, 1170

Example 46

1.3 g of sulfodehydroabietic acid monohydrate and 0.448 g of 6-aminocaproic acid are treated in the same manner as described in Example 22, whereby 1.1 g of sulfodehydroabietic acid 6-aminocaproic acid salt are obtained.

M.p. 220—222°C (decomp.) (recrystallized from methanol-water)
IRv_{max}^{nujol} (cm^{-1}): 3300, 3070, 2750—2300, 1710, 1670, 1210, 1160

Example 47

1.14 g of sulfodehydroabietic acid monohydrate and 0.87 g of ethyl N - piperidinoacetyl - p - aminobenzoate are treated in the same manner as described in Example 12, whereby 1.4 g of the salt (monohydrate) of sulfodehydroabietic acid with ethyl N - piperidinoacetyl - p - aminobenzoate are obtained.

M.p. 171°C (recrystallized from ethanol-water)
IRv_{max}^{nujol} (cm^{-1}): 3500—3080, 2750—2300, 1700, 1680, 1605, 1550, 1280, 1210, 1150, 1115

Example 48

1.3 g of sulfodehydroabietic acid monohydrate and 0.862 g of ethyl N - L - prolyl - p - aminobenzoate are treated in the same manner as described in Example 12, whereby 1.1 g of the salt of sulfodehydroabietic acid with ethyl N - L - prolyl - p - aminobenzoate are obtained.

M.p. 273—275°C (recrystallized from methanol)
IRv_{max}^{nujol} (cm^{-1}): 3430, 3300—3100, 1715—1705, 1605, 1550, 1280, 1210, 1180, 1150

Example 49

1.2 g of sulfodehydroabietic acid monohydrate and 0.83 g of ethyl N - pipecolyl - p - aminobenzoate are treated in the same manner as described in Example 12, whereby 0.8 g of the salt (monohydrate) of sulfodehydroabietic acid with ethyl N - pipecolyl - p - aminobenzoate is obtained.

M.p. 230°C (decomp.) (recrystallized from ethanol-ether)
IRv_{max}^{nujol} (cm^{-1}): 3430—3050, 2750—2300, 1700, 1675, 1600, 1545, 1270, 1200, 1180, 1150, 1100

Example 50

1.14 g of sulfodehydroabietic acid monohydrate, 0.4 g of silver carbonate and 0.66 g of 2 - (3,4 - dihydroxyphenyl) - 8,8 - dimethyl - 5,8 - diazoniaspiro[4.5]decane dibromide are treated in the same manner as described in Example 29, whereby 0.8 g of the salt of sulfodehydroabietic acid with 1/2 2 - (3,4 - dihydroxyphenyl) - 8,8 - dimethyl - 5,8 - diazoniaspiro[4.5]decane is obtained as a crystalline powder.

M.p. 265°C (decomp.) (recrystallized from methanol-ethylacetate)
IRv_{max}^{nujol} (cm^{-1}): 3500—3200, 1700, 1600, 1520, 1250, 1200, 1150, 1130, 1030,

Example 51

1.14 g of sulfodehydroabietic acid monohydrate, 0.7 g of 1 - (2 - dimethylaminoethyl) - 4 - phenyl - 2 - pyrrolidone are treated in the same manner as described in Example 12, whereby 1.30 g of the salt of sulfodehydroabietic acid with 1 - (2 - dimethylaminoethyl) - 4 - phenyl - 2 - pyrrolidone are obtained.

M.p. 216—218°C (decomp.) (recrystallized from ethanol-ether)
IRv_{max}^{nujol} (cm^{-1}): 3400, 2750—2400, 1720, 1690, 1600, 1260, 1200, 1130, 1030

Example 52

1.14 g of sulfodehydroabietic acid monohydrate, 0.58 g of methyl 4 - amino - 3 - phenylbutylate are treated in the same manner as described in Example 12, whereby 0.7 g of the salt of sulfodehydroabietic acid with methyl 4 - amino - 3 - phenylbutylate is obtained.

M.p. 242°C (decomp.) (recrystallized from a mixture of methanol and ether)

IRν_{max}^{nujol} (cm^{-1}): 3300—3050, 1720, 1700, 1630, 1520, 1240, 1180, 1160, 1030

Example 53
(Tablets)

Sulfodehydroabietic acid monosodium salt	250 g
Corn starch	25 g

The mixture of these ingredients is granulated with the aid of 10 g of hydroxypropyl cellulose (a binding agent). 12 g of crystalline cellulose and 3 g of magnesium stearate are added to the resultant granules, and the mixture is then compressed into tablets of suitable concaved form (10 mm in diameter, weight 300 mg).

Example 54
(Granules)

Sulfodehydroabietic acid monosodium salt	100 g
Corn starch	5 g

The mixture of these ingredients is granulated with the aid of 5 g of polyvinylpyrrolidone (a binding agent), and the resultant granules are passed through a standard sieve (840 µ aperture) to give granules containing 1000 mg of the monosodium salt per 1100 mg of granules.

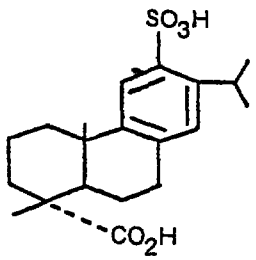
Example 55
(Capsules)

Sulfodehydroabietic acid monosodium salt	500 g
Corn starch	50 g
Crystalline cellulose	47 g
Magnesium stearate	3 g

The above-mentioned ingredients are thoroughly mixed and the mixture is encapsulated to give capsules containing 600 mg of the mixture per capsule.

Claims

1. A pharmaceutically acceptable salt of sulfodehydroabietic acid of the formula:—



for use as an active therapeutic substance.

2. A pharmaceutically acceptable salt of sulfodehydroabietic acid of the formula:

Example 52

1.14 g of sulfodehydroabietic acid monohydrate, 0.58 g of methyl 4 - amino - 3 - phenylbutylate are treated in the same manner as described in Example 12, whereby 0.7 g of the salt of sulfodehydroabietic acid with methyl 4 - amino - 3 - phenylbutylate is obtained.

M.p. 242°C (decomp.) (recrystallized from a mixture of methanol and ether)

IRν_{max}^{nujol} (cm^{-1}): 3300—3050, 1720, 1700, 1630, 1520, 1240, 1180, 1160, 1030

Example 53
(Tablets)

Sulfodehydroabietic acid monosodium salt	250 g
Corn starch	25 g

The mixture of these ingredients is granulated with the aid of 10 g of hydroxypropyl cellulose (a binding agent). 12 g of crystalline cellulose and 3 g of magnesium stearate are added to the resultant granules, and the mixture is then compressed into tablets of suitable concaved form (10 mm in diameter, weight 300 mg).

Example 54
(Granules)

Sulfodehydroabietic acid monosodium salt	100 g
Corn starch	5 g

The mixture of these ingredients is granulated with the aid of 5 g of polyvinylpyrrolidone (a binding agent), and the resultant granules are passed through a standard sieve (840 µ aperture) to give granules containing 1000 mg of the monosodium salt per 1100 mg of granules.

Example 55
(Capsules)

Sulfodehydroabietic acid monosodium salt	500 g
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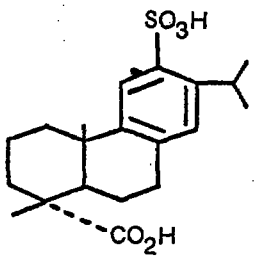
Crystalline cellulose	47 g
Magnesium stearate	3 g

The above-mentioned ingredients are thoroughly mixed and the mixture is encapsulated to give capsules containing 600 mg of the mixture per capsule.

Claims

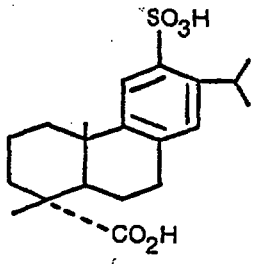
1. A pharmaceutically acceptable salt of sulfodehydroabietic acid of the formula:—



for use as an active therapeutic substance.

2. A pharmaceutically acceptable salt of sulfodehydroabietic acid of the formula:

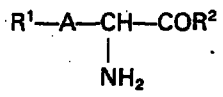
* C L M S *



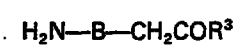
for use in the therapeutic treatment of prophylaxis of a gastro-intestinal disease.

3. A salt of sulfodehydroabietic acid as claimed in claim 1, for use in the therapeutic treatment or prophylaxis of a peptic ulcer disease or gastritis.

4. A salt of sulfodehydroabietic acid as claimed in claim 1, 2 or 3 which is a salt of sulfodehydroabietic acid with an alkali metal; an alkali earth metal; aluminium, aluminium hydroxide, an alkyl (C_{1-5})amine, di - alkyl(C_{1-5})amine, tri - alkyl(C_{1-5})amine, cycloalkyl(C_{3-6})amine, di - alkyl(C_{1-5}) - amino, -alkyl(C_{1-5})amine, alkoxy(C_{1-5}) - alkyl(C_{1-5})amine, alkylene(C_{2-6})diamine, aralkyl - (C_{7-8})amine, alkyl(C_{1-5}) N - piperidinoacetyl - p - aminobenzoate, alkyl(C_{1-5}) N - prolyl - p - aminobenzoate, alkyl(C_{1-5}) N - pipecolyl - p - aminobenzoate, morpholine, piperazine, 2 - (3,4 - dihydroxyphenyl) - 8,8 - dimethyl - 5,8 - diazoniaspiro[4.5]decane, 1 - (2 - dimethylaminoethyl) - 4 - phenyl - 2 - pyrrolidone, homocysteine thiolactone, an α-amino acid of the formula:



wherein R^1 is amino, guanidino, carbamoyl, dimethyl - sulfonio - 4 - imidazolyl, mercapto or methylthio, R^2 is hydroxy, alkoxy(C_{1-5}), amino, alkyl(C_{1-8})amino, di - alkyl(C_{1-5})amino, cycloalkyl(C_{3-6})amino or p - alkoxy(C_{1-5})anilino, and A is straight alkylene(C_{1-5}), an ω-amino acid of the formula:



wherein R^3 is hydroxy or alkoxy(C_{1-5}) and B is straight alkylene(C_{1-5}) (the alkylene being optionally substituted with phenyl), or carnosine.

5. A salt of sulfodehydroabietic acid as claimed in claim 1, 2 or 3 which is a salt of sulfodehydroabietic acid with lithium, potassium, sodium, magnesium, calcium, aluminium; aluminium hydroxide, an alkyl(C_{1-5})amine, cycloalkyl(C_{3-6})amine, di - alkyl(C_{1-5})amino - alkyl(C_{1-5})amine, alkoxy(C_{1-5}) - alkyl(C_{1-5}) - amine, alkylene(C_{2-6})diamine, morpholine, arginine, glutamine, asparagine, lysine, S - methyl - methionine or carnosine.

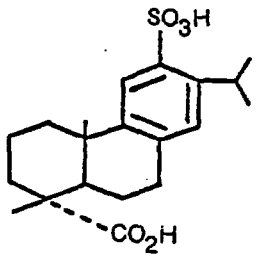
6. A salt of sulfodehydroabietic acid as claimed in claim 1, 2 or 3 which is a salt of sulfodehydroabietic acid with sodium, calcium, aluminium, aluminium hydroxide (2-dimethylaminoethyl)amine, cyclohexylamine, isopropylamine, morpholine, (2-methoxyethyl)amine, ethylenediamine, tetramethylenediamine, hexamethylenediamine, arginine, glutamine, asparagine, lysine, S-methylmethionine or carnosine.

7. A salt of sulfodehydroabietic acid as claimed in claim 1, 2 or 3 which is sulfodehydroabietic acid monosodium salt.

8. A salt of sulfodehydroabietic acid as claimed in claim 1, 2 or 3 which is sulfodehydroabietic acid disodium salt.

9. A salt of sulfodehydroabietic acid as claimed in claim 1, 2 or 3 which is sulfodehydroabietic acid calcium salt.

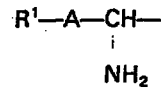
10. A salt of sulfodehydroabietic acid of the formula:—



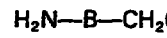
with lithium, potassium, magnesium, calcium, aluminium, aluminium hydroxide, an alkyl(C_{1-5})amine, di - alkyl(C_{1-5})amine, tri - alkyl(C_{1-5})amine, cycloalkyl(C_{3-6})amine, di - alkyl(C_{1-5})amino - alkyl(C_{1-5})amine, alkoxy(C_{1-5}) - alkyl(C_{1-5})amine, alkylene(C_{2-6})diamine, aralkyl(C_{7-8})amine, alkyl(C_{1-5}) N -

* C L M S *

piperidinoacetyl - p - aminobenzoate, alkyl(C_{1-5})N - prolyl - p - aminobenzoate, alkyl(C_{1-5}) N - pipecolyl - p - amino - benzoate, morpholine, piperazine, 2 - (3,4 - dihydroxyphenyl) - 8,8 - dimethyl - 5,8 - diazoniaspiro[4.5]decane, 1 - (2 - dimethylaminoethyl) - 4 - phenyl - 2 - pyrrolidone, homocysteine thiolactone, an α-amino acid of the formula:



wherein R^1 is amino, guanidino, carbamoyl, dimethylsulfonio, 4-imidazolyl, mercapto or methylthio, R^2 is hydroxy, alkoxy(C_{1-5}), amino, alkyl(C_{1-8})amino, dialkyl(C_{1-5})amino, cycloalkyl - (C_{3-6})amino or p - alkoxy(C_{1-5})anilino, and A is straight alkylene(C_{1-5}), an ω-amino acid of the formula:



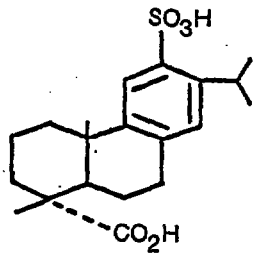
wherein R^3 is hydroxy or alkoxy(C_{1-5}) and B is straight alkylene(C_{1-5}) (the alkylene being optionally substituted with phenyl), or carnosine.

11. A salt of sulfodehydroabietic acid as claimed in claim 10, which is a salt of sulfodehydroabietic acid with lithium, potassium, magnesium, calcium, aluminium, aluminium hydroxide an alkyl(C_{1-5})amine, cycloalkyl(C_{3-6})amine, di - alkyl(C_{1-5})amino - alkyl(C_{1-5})amine, alkoxy(C_{1-5}) - alkyl(C_{1-5}) - amine, alkylene(C_{2-6})diamine, morpholine, arginine, glutamine, asparagine, lysine, S-methylmethionine or carnosine.

12. A salt of sulfodehydroabietic acid as claimed in claim 10, which is a salt of sulfodehydroabietic with with calcium, aluminium, aluminium hydroxide, (2 - dimethylaminoethyl)amine, cyclohexylamine, isopropylamine, morpholine, (2-methoxyethyl)amine, ethylenediamine, tetramethylenediamine, hexamethylenediamine, arginine, glutamine, asparagine, lysine, S-methylmethionine or carnosine.

13. A salt of sulfodehydroabietic acid as claimed in claim 10, which is sulfodehydroabietic acid calcium salt.

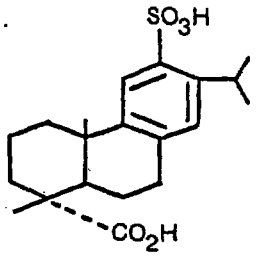
14. A pharmaceutical composition comprising a therapeutically effective amount of a pharmaceutically acceptable salt of sulfodehydroabietic acid of the formula:—



and a pharmaceutically acceptable carrier.

Patentansprüche

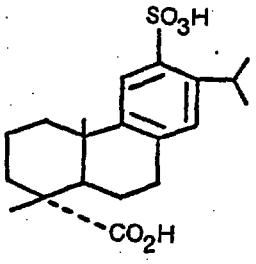
1. Pharmazeutisch annehmbares Salz der Sulfodehydroabietinsäure der Formel



für die Verwendung als aktive therapeutische Substanz.

2. Pharmazeutisch annehmbares Salz der Sulfodehydroabietinsäure der Formel

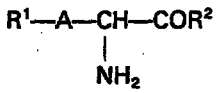
* C L M S *



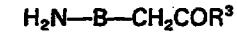
für die Verwendung bei der therapeutischen Behandlung oder Prophylaxe von gastrointestinalen Erkrankungen.

3. Salz der Sulfodehydroabietinsäure gemäss Anspruch 1 für die Verwendung bei der therapeutischen Behandlung oder Prophylaxe bei Magengeschwürerkrankungen oder Gastritis.

4. Salz der Sulfodehydroabietinsäure gemäss Ansprüchen 1, 2 oder 3, welches ein Salz von Sulfodehydroabietinsäure mit einem Alkalimetall, einem Erdalkalimetall, Aluminium, Aluminiumhydroxid, einem Alkyl(C_{1-5})amin, einem Di - alkyl(C_{1-5})amin, einem Tri - alkyl(C_{1-5})amin, einem Cycloalkyl(C_{3-6})amin, einem Di - alkyl(C_{1-5}) - amino - alkyl(C_{1-5})amin, einem Alkoxy(C_{1-5}) - alkyl(C_{1-5})amin, einem Alkylen(C_{2-6}) - diamin, einem Aralkyl(C_{7-8})amin, einem Alkyl(C_{1-5}) - N - piperidinoacetyl - p - aminobenzoat, einem Alkyl - (C_{1-5})N - prolyl - p - aminobenzoat, einem Alkyl(C_{1-5}) - N - pipecolyl - p - aminobenzoat, einem Morpholin, einem Piperazin, einem 2 - (3,4 - Dihydroxyphenyl) - 8,8 - dimethyl - 5,8 - diazoniaspiro[4,5]decan, einem 1 - (2 - Dimethylaminoethyl) - 4 - phenyl - 2 - pyrrolidon, einem Homocysteinthiolacton, einer α-Aminosäure der Formel



worin R^1 Amino, Guanidino, Carbamoyl, Dimethyl - sulfonio - 4 - imidazolyl, Mercapto oder Methylthio bedeutet, R^2 Hydroxy, Alkoxy(C_{1-5})amino, Alkyl - (C_{1-8})amino, Dialkyl(C_{1-5})amino, Cycloalkyl(C_{3-6})amino oder p - Alkoxy(C_{1-5})anilino bedeutet und A ein geradkettiges Alkylen(C_{1-5}), eine ω-Aminosäure der Formel



bedeutet, worin R^3 Hydroxy oder Alkoxy(C_{1-5}) und B geradkettiges Alkylen(C_{1-5}) (wobei das Alkylen gewünschtenfalls mit Phenyl substituiert sein kann) oder Carnosin ist.

5. Salz der Sulfodehydroabietinsäure gemäss Ansprüchen 1, 2 oder 3, worin das Salz der Sulfodehydroabietinsäure ein Salz mit Lithium, Kalium, Natrium, Magnesium, Calcium, Aluminium, Aluminiumhydroxid, einem Alkyl(C_{1-5})amin, Cycloalkyl(C_{3-6})amin, Dialkyl(C_{1-5})amino - alkyl(C_{1-5})amin, Alkoxy(C_{1-5}) - alkyl(C_{1-5})amin, Alkylen(C_{2-6})diamin, Morpholin, Arginin, Glutamin, Asparagin, Lysin, S - Methyl - methionin oder Carnosin ist.

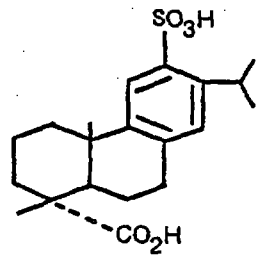
6. Salz der Sulfodehydroabietinsäure gemäss Ansprüchen 1, 2 oder 3, welches ein Salz der Sulfodehydroabietinsäure mit Natrium, Calcium, Aluminium, Aluminiumhydroxid(2 - dimethylamino-ethyl)amin, Cyclohexylamin, Isopropylamin, Morpholin, (2 - Methoxyethyl)amin, Ethylendiamin, Tetramethylendiamin, Hexamethylendiamin, Arginin, Glutamin, Asparagin, Lysin, S - Methyl - methionin oder Carnosin ist.

7. Salz der Sulfodehydroabietinsäure gemäss Ansprüchen 1, 2 oder 3, welches das Sulfodehydroabietinsäure - mononatriumsalz ist.

8. Salz der Sulfodehydroabietinsäure gemäss Ansprüchen 1, 2 oder 3, welches das Sulfodehydroabietinsäure - dinatriumsalz ist.

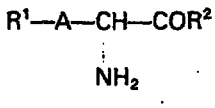
9. Salz der Sulfodehydroabietinsäure gemäss Ansprüchen 1, 2 oder 3, welches das Sulfodehydroabietinsäure - calciumsalz ist.

10. Salz der Sulfodehydroabietinsäure der Formel

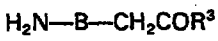


* C L M S *

mit Lithium, Kalium, Magnesium, Calcium, Aluminium, Aluminiumhydroxid, einem Alkyl(C_{1-5})amin, Di - alkyl - (C_{1-5})amin, Tri - alkyl(C_{1-5})amin, Cycloalkyl(C_{3-6})amin, Di - alkyl(C_{1-5})amino - alkyl(C_{1-5})amin, Alkoxy - (C_{1-5})alkyl(C_{1-5})amin, Alkylen(C_{2-6})diamin, Aralkyl - (C_{7-8})amin, Alkyl(C_{1-5}) - N - piperidinoacetyl - p - aminobenzoat, Alkyl(C_{1-5}) - N - prolyl - p - aminobenzoat, Alkyl(C_{1-5}) - N - pipercolyl - p - aminobenzoat, Morpholin, Piperazin, 2 - (3,4 - Dihydroxyphenyl) - 8,8 - dimethyl - 5,8 - diazaniaspiro[4,5]decan, 1 - (2 - Dimethylaminoethyl) - 4 - phenyl - 2 - pyrrolidon, Homocysteinthiolacton, einer α-Aminosäure der Formel



worin R^1 Amino, Guanidino, Carbamoyl, Dimethylsulfonio, 4 - Imidazolyl, Mercapto oder Methylthio bedeutet, R^2 Hydroxy, Alkoxy(C_{1-5})amino, Alkyl(C_{1-8})amino, Dialkyl(C_{1-5})amino, Cycloalkyl(C_{3-6})amino der p - Alkoxy(C_{1-5})anilino bedeutet und A ein geradkettiges Alkylen(C_{1-5}), eine ω-Aminosäure der Formel



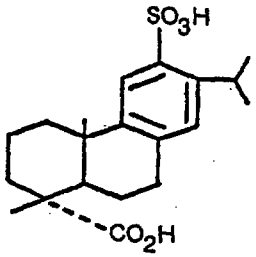
ist, worin R^3 Hydroxy oder Alkoxy(C_{1-5}) bedeutet und B geradkettiges Alkylen(C_{1-5}) (wobei das Alkylen gewünschtenfalls mit Phenyl substituiert ist) oder Carnosin ist.

11. Salz der Sulfodehydroabietinsäure gemäss Anspruch 10, welches ein Salz der Sulfodehydroabietinsäure mit Lithium, Kalium, Magnesium, Calcium, Aluminium, Aluminiumhydroxid, einem Alkyl(C_{1-5})amin, Cycloalkyl(C_{3-6})amin, Di - alkyl(C_{1-5})amino - alkyl(C_{1-5})amin, Alkoxy(C_{1-5}) - alkyl(C_{1-5})amin, Alkylen(C_{2-6})diamin, Morpholin, Arginin, Glutamin, Asparagin, Lysin, S - Methyl - methionin oder Carnosin ist.

12. Salz der Sulfodehydroabietinsäure gemäss Anspruch 10, welches ein Salz der Sulfodehydroabietinsäure mit Calcium, Aluminium, Aluminiumhydroxid, (2 - Dimethylaminoethyl)amin, Cyclohexylamin, Isopropylamin, Morpholin, (2 - Methoxyethyl)amin, Ethylendiamin, Tetramethylendiamin, Hexamethylendiamin, Arginin, Glutamin, Asparagin, Lysin, S - Methyl - methionin oder Carnosin ist.

13. Salz der Sulfodehydroabietinsäure gemäss Anspruch 10, welches Sulfodehydroabietinsäure - calciumsalz ist.

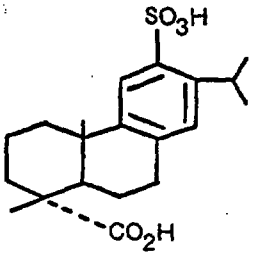
14. Pharmazeutische Zusammensetzung, umfassend eine therapeutisch wirksame Menge eines pharmazeutisch annehmbaren Salzes der Sulfodehydroabietinsäure der Formel



und einen pharmazeutisch annehmbaren Träger.

Revendications

1. Sel pharmaceutiquement tolérable de l'acide sulfodéhydroabiétique répondant à la formule générale:



destiné à l'utilisation comme substance thérapeutiquement active.

2. Sel pharmaceutiquement tolérable de l'acide sulfodéhydroabiétique répondant à la formule générale:

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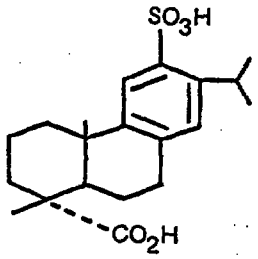
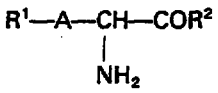


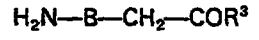
destiné à être utilisé pour le traitement thérapeutique ou la prophylaxie des affections gastro-intestinales.

3. Sel de l'acide sulfodéhydroabiétique suivant la revendication 1, destiné à être utilisé dans le traitement thérapeutique ou la prophylaxie des affections causées par l'ulcère peptique ou la gastrite.

4. Sel de l'acide sulfodéhydroabiétique suivant les revendications 1, 2 ou 3, caractérisé en ce qu'il est constitué par un sel de l'acide sulfodéhydroabiétique avec un métal alcalin, un métal alcalino-terreux, l'aluminium, l'hydroxyde d'aluminium, les alcoyl(C_{1-5})amine, di - alcoyl(C_{1-5})amine, tri - alcoyl(C_{1-5})amine, cycloalcoyl(C_{3-6}), di - alcoyl(C_{1-5})amino - alcoyl(C_{1-5})amine, alcoxy(C_{1-5}) - alcoyl(C_{1-5})amine, alkylène(C_{2-6})diamine, aralcoyl - (C_{7-8})amine, alcoyl (C_{1-5}) N - pipéridinoacétyl - p - aminobenzoate, alcoyl(C_{1-5}) N - propyl - p - aminobenzoate, alcoyl(C_{1-5}) N - pipécolyl - p - aminobenzoate, morpholine, pipérazine, 2 - (3,4 - dihydroxy - phényl) - 8,8 - diméthyl - 5,8 - diazoniaspiro[4,5]décane, 1 - (2 - diméthylamino - éthyl) - 4 - phényl - 2 - pyrrolidone, homocystéine thiolactone, un α-amino acide répondant à la formule:



où R^1 est un groupe amino, guanidino, carbamoyl, diméthylsulfonio - 4 - imidazolyl, mercapto ou méthylthio, R^2 un groupe hydroxy, alcoxy(C_{1-5}), amino, alcoyl(C_{1-8})amino, di - alcoyl - (C_{1-5})amino, cycloalcoyl(C_{3-6})amino ou p - alcoxy(C_{1-5})anilino et A est un alkylène(C_{1-5})linéaire, un ω-amino-acide répondant à la formule:



où R^3 est un hydroxy ou alcoxy(C_{1-5}) et B est un alkylène linéaire, (cet alkylène pouvant être au besoin substitué par un phényl), ou la carnosine.

5. Sel de l'acide sulfodéhydroabiétique suivant les revendications 1, 2 ou 3, caractérisé en ce qu'il est constitué par un sel de l'acide sulfodéhydroabiétique avec les lithium, potassium, sodium, magnésium, calcium et aluminium; l'hydroxyde d'aluminium; alcoyl(C_{1-5})amine, cycloalcoyl(C_{3-6})amine, di - alcoyl(C_{1-5})amino - alcoyl(C_{1-5})amine, alcoxy(C_{1-5}) - alcoyl(C_{1-5})amine, alkylène(C_{2-6})diamine, morpholine, arginine, glutamine, asparagine, lysine, S - méthyl - méthionine ou carnosine.

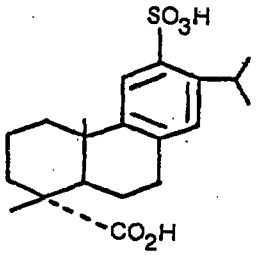
6. Sel de l'acide sulfodéhydroabiétique selon les revendications 1, 2 ou 3, caractérisé en ce qu'il est constitué par un sel de l'acide sulfodéhydroabiétique avec les sodium, calcium, aluminium, hydroxyde d'aluminium, (2 - diméthylaminoéthyl)amine, cyclohexylamine, isopropylamine, morpholine, (2 - méthoxyéthyl)amine, éthylènediamine, tétraméthylènediamine, hexaméthylènediamine, arginine, glutamine, asparagine, lysine, S - méthyl - méthionine ou carnosine.

7. Sel suivant les revendications 1, 2 ou 3, caractérisé en ce qu'il est constitué par le sel monosodique de l'acide sulfodéhydroabiétique.

8. Sel suivant l'une des revendications 1, 2 ou 3, caractérisé en ce qu'il est constitué par le sel disodique de l'acide sulfodéhydroabiétique.

9. Sel suivant l'une des revendications 1, 2 ou 3, caractérisé en ce qu'il est constitué par le sel de calcium de l'acide sulfodéhydroabiétique.

10. Sel caractérisé en ce qu'il est constitué par un sel de l'acide sulfodéhydroabiétique répondant à la formule:



avec les lithium, potassium, magnésium, calcium, aluminium, hydroxyde d'aluminium, une

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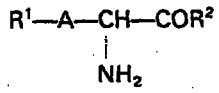
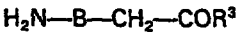
alcoyl(C_{1-5})amine, di - alcoyl(C_{1-5})amine, tri - alcoyl(C_{1-5})amine, cycloalcoyl(C_{3-6})amine, di - alcoyl(C_{1-5})amino - alcoyl(C_{1-5})amine, alcoxy(C_{1-5}) - alcoyl(C_{1-5})amine, alkylène(C_{2-6})diamine, aralcoyl(C_{7-8})amine, alcoyl(C_{1-5})N - pipéridino - acétyl - p - aminobenzoate, alcoyl(C_{1-5})N - prolyl - p - aminobenzoate, alcoyl(C_{1-5})N - pipécolyl - p - aminobenzoate, morpholine, pipérazine, 2 - (3,4 - dihydroxyphényl) - 8,8 - diméthyl - 5,8 - diazoniaspiro[4,5]décane, 1 - (2 - diméthylamino - éthyl) - 4 - phényl - 2 - pyrrolidone, homocystéine thiolactone, un α - aminoacide répondant à la formule:



où R^1 est un groupe amino, guanidino, carbamoyl, diméthyl - sulfonio - 4 - imdazolyl, mercapto ou méthylthio, R^2 est un groupe hydroxy, alcoxy(C_{1-5}), amino, alcoyl(C_{1-8})amino, di - alcoyl - (C_{1-5})amino, cycloalcoyl(C_{3-6})amino ou p - alcoxy(C_{1-3})anilino et A est un alkylène (C_{1-5}) linéaire, un ω - amino - acide répondant à la formule:



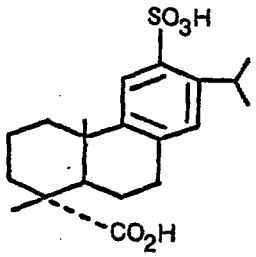
où R^3 est un hydroxy ou alcoxy(C_{1-5}) et B est un alkylène linéaire (C_{1-5}), (cet alkylène pouvant être au besoin substitué par un phényl), ou la carnosine.

11. Sel de l'acide sulfodéhydroabiétique suivant la revendication 10, caractérisé en ce qu'il est constitué par un sel de l'acide sulfodéhydroabiétique avec les lithium, potassium, magnésium, calcium, aluminium, hydroxyde d'aluminium, alcoyl(C_{1-5})amine, cycloalcoyl(C_{3-6})amine, di - alcoyl(C_{1-5})amino - alcoyl (C_{1-5})amine, alcoxy(C_{1-5})alcoyl (C_{1-5})amine, alkylène (C_{2-6})diamine, morpholine, arginine, glutamine, asparagine, lysine, S - méthylméthionine ou carnosine.

12. Sel de l'acide sulfodéhydroabiétique suivant la revendication 10, caractérisé en ce qu'il est constitué par un sel de l'acide sulfodéhydroabiétique avec les calcium, aluminium, hydroxyde d'aluminium, (2 - dyméthylaminoéthyl)amine, cyclohexylamine, isopropylamine, morpholine, (2 - méthoxyéthyl)amine, éthylènediamine, tétraméthylènediamine, hexaméthylènediamine, arginine, glutamine, asparagine, lysine, S - méthylméthionine ou carnosine.

13. Sel de l'acide sulfodéhydroabiétique suivant la revendication 10, caractérisé en ce qu'il est constitué par le sel de calcium de l'acide sulfodéhydroabiétique.

14. Composition pharmaceutique comprenant une quantité efficace thérapeutiquement d'un sel pharmaceutiquement acceptable de l'acide sulfodéhydroabiétique répondant à la formule:



et un véhicule pharmaceutiquement acceptable.

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