



ENANTIOMERICALLY PURE (-)-LIARAZOLE

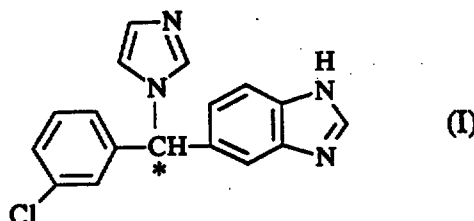
5

10 This invention relates to novel enantiomerically pure compounds of formula (I) useful in treating disorders which are characterized by an increased proliferation and/or abnormal differentiation of normal, preneoplastic or neoplastic epithelial cells. These compounds are particularly useful in the field of oncology. Also disclosed are compositions containing said novel compounds, as well as methods of using the mentioned compounds to treat the mentioned disorders. The laevorotatory compounds of formula 15 (I) are useful for the manufacture of a medicament for treating epithelial disorders. Further the present invention provides methods of preparing the present novel compounds.

20 The novel compounds subject to the present invention are the laevorotatory isomer of the compound liarozole and the pharmaceutically acceptable acid addition salts thereof.

Liarozole is a racemic mixture, i.e. a mixture of its optical isomers, and is specifically mentioned as compound 28 in EP-0,371,559. Said patent application mentions the use of compounds like liarozole in the treatment of epithelial disorders. EP-0,260,744 25 describes the use of compounds like liarozole for inhibiting or lowering androgen formation. Whereas EP-0,371,559 and EP-0,260,744 recognize that compounds like liarozole have stereochemically isomeric forms, no example of an enantiomerically pure form is given of liarozole.

30 Chemically liarozole is $(\pm)$ -5-[3-chlorophenyl]-1H-imidazol-1-ylmethyl]-1H-benzimidazole, and is represented by formula (I). As can be seen from the chemical structure, liarozole has one stereogenic center (indicated with an asterisk in formula (I)).



35

The subject of this invention is the enantiomerically pure laevorotatory isomer or

8-438888E



(-)-isomer of liarozole. Said isomer will hereinafter be referred to as (-)-liarozole.

Many organic compounds exist in optically active forms, i.e. they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L or R and S are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes (+) and (-) or d and l are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or l meaning that the compound is laevorotatory and with (+) or d meaning that the compound is dextrorotatory. For a given chemical structure the optically active isomers having an opposite sign of optical rotation are called enantiomers. Said enantiomers are identical except that they are mirror images of one another. A 1:1-mixture of such enantiomers is called a racemic mixture.

Stereochemical purity is of importance in the field of pharmaceuticals since the respective enantiomers may have a different potency or may have a different activity. The enantiomer of a beneficial isomer may even be deleterious rather than simply inert. Several examples of such differences are known in the art.

The term "enantiomerically pure" as used herein means that the product contains at least 90% by weight of one enantiomer and 10% by weight or less of the other enantiomer. In the most preferred embodiment the term "enantiomerically pure" means that the composition contains at least 99% by weight of one enantiomer and 1% or less of the other enantiomer.

It should be noted that optical rotation of chemical substances is dependent upon experimental parameters. The values shown in the experimental part hereinunder are specific rotations and the experimental conditions such as temperature, the wavelength of the plane polarized light used, the solvent as well as the concentration of the sample are indicated in the conventional way. The optical rotation may vary (it may even change sign!) when for instance an acid addition salt is formed. When reference is made to the laevorotatory isomer of liarozole or (-)-liarozole then the sign of the optical rotation of the base form is intended under the given experimental conditions shown hereinunder.

It should also be noted that when a chemical reaction does not involve the stereocenter then the absolute configuration of said stereocenter remains the same, although the optical rotation of the compound which results from said chemical reaction may be different or even have an opposite sign. Hence, in order to avoid confusion, the



intermediate with the same absolute configuration of the stereocenter as the desired enantiomer of the final product will be designated with the prefix (A) before the reference number.

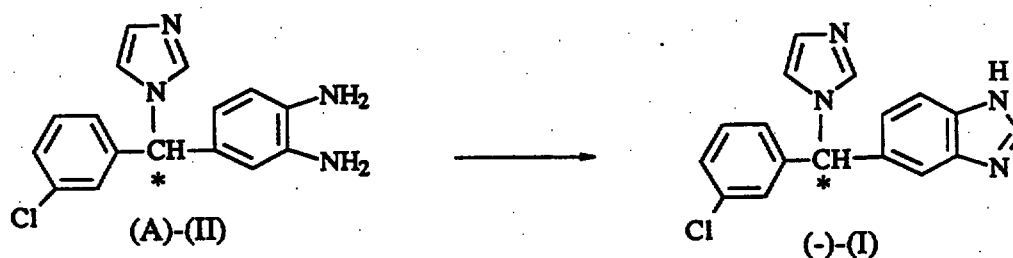
- 5 The pharmaceutically acceptable acid addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid addition salt forms which the compounds of formula (I) are able to form. The latter can conveniently be obtained by treating the base form with such appropriate acids as inorganic acids, for example, hydrohalic acids, e.g. hydrochloric, hydrobromic and the like; sulfuric acid; nitric acid; phosphoric acid and the like; or organic acids, for example, acetic, propanoic, hydroxyacetic, 2-hydroxypropanoic, 10 2-oxopropanoic, ethanedioic, propanedioic, butanedioic, (Z)-2-butenedioic, (E)-2-butenedioic, 2-hydroxybutanedioic, 2,3-dihydroxybutanedioic, 2-hydroxy-1,2,3-propanetricarboxylic, methanesulfonic, ethanesulfonic, benzenesulfonic, 4-methylbenzenesulfonic, cyclohexanesulfamic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic and the like acids.
- 15 Conversely the salt form can be converted by treatment with alkali into the free base form. The term addition salt also comprises the hydrates and solvent addition forms which the compounds of formula (I) are able to form. Examples of such forms are e.g. hydrates, alcoholates and the like.
- 20 Preferred pharmaceutically acceptable acids are hydrochloric acid and (E)-2-butenedioic acid.

General preparation of structures including liarozole have been extensively described in EP-0,371,559 and EP-0,260,744.

25

Enantiomerically pure (-)-liarozole may be prepared by reacting an enantiomerically pure intermediate diamine of formula (A)-(II) with formic acid or a functional derivative thereof.

30



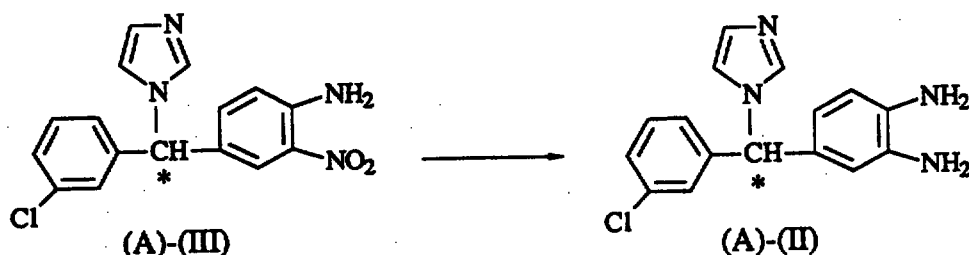
Said functional derivative of formic acid is meant to comprise the halide, anhydride, amide and ester, including the ortho and imino ester form thereof. Also



methanimidamide or an acid addition salt thereof can be used as cyclizing agent.

The general reaction conditions, work-up procedures and conventional isolation techniques for carrying out the above and following reactions are described in the prior art. When more specific conditions are required they are mentioned hereinunder.

The enantiomerically pure intermediate diamine of formula (A)-(II) may be prepared by reducing an intermediate of formula (A)-(III) by a standard nitro-to-amine reduction reaction.



The desired enantiomer of the intermediate of formula (A)-(III) can be prepared by fractional crystallization of a racemic mixture of the intermediate of formula (III) with an enantiomerically pure chiral acid. Preferred chiral acid for the above fractional crystallization is 7,7-dimethyl-2-oxobicyclo[2.2.1]heptane-1-methanesulfonic acid (i.e. 10-camphorsulfonic acid).

Appropriate solvents for carrying out said fractional crystallization are water, ketones, e.g. 2-propanone, 2-butanone; alcohols, e.g. methanol, ethanol, 2-propanol. Mixtures of ketones and water are very suitable for the above fractional crystallization. Preferably a mixture of 2-propanone and water is used.

The ratio of water/2-propanone by volume may vary from 1/10 to 1/2. Preferred range of said ratio is 1/5 to 1/3.

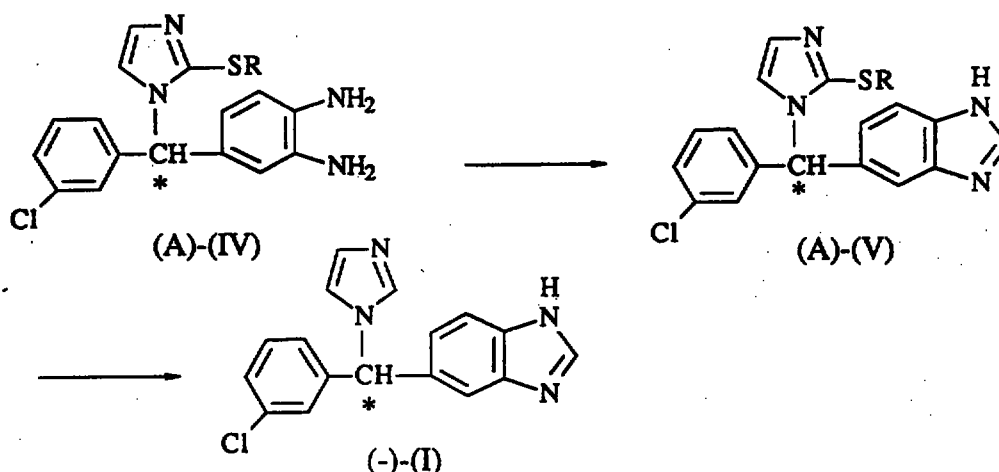
The fractional crystallizations are suitably carried out below room temperature, preferably below 5°C.

It was also found that the subsequent reaction step can be carried out without any appreciable racemization.

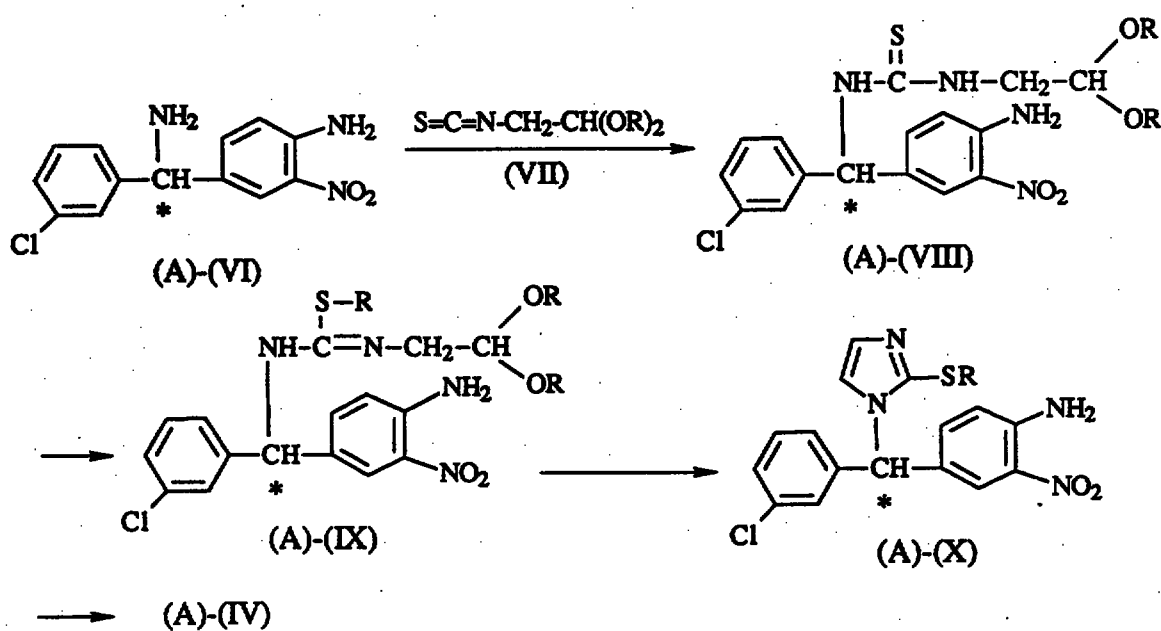
Alternatively the (-)-isomer of the compound of formula (I) may be prepared by cyclizing an intermediate of formula (A)-(IV) following procedures as described above for the



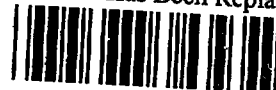
- cyclization of intermediates of formula (A)-(II) and desulfurating the thus obtained intermediate of formula (A)-(V). In formulas (A)-(IV) and (A)-(V) R represents C₁₋₆alkyl, wherein C₁₋₆alkyl is a straight or branch chained saturated hydrocarbon radicals having to 1 to 6 carbon atoms such as, for example, methyl, ethyl, propyl, butyl, pentyl, hexyl. Preferably R is methyl.
- 5



- The intermediates of formula (A)-(IV) may be prepared by reacting an intermediate of formula (A)-(VI) with a reagent of formula (VII), alkylating the thus formed thiourea derivative of formula (A)-(VIII) subsequently cyclizing the intermediate of formula (A)-(IX), and reducing the nitro group of the intermediate (A)-(X). In the formulas (VII), (A)-(VIII), (A)-(IX) and (A)-(X) R represents C₁₋₆alkyl as defined hereinabove.
- 10



The enantiomerically pure intermediate of formula (A)-(VI) can be prepared by art-known resolution techniques, e.g. by chromatography using chiral stationary phases or



by forming diastereomeric compounds such as forming an amide with an enantiomerically pure chiral acid, e.g. α -hydroxybenzeneacetic acid (mandelic acid), or by forming diastereomeric salt forms using enantiomerically pure chiral acid.

- 5 Liarozole has retinoid mimetic effects *in vivo* and *in vitro*. This means that the compound is thought to inhibit retinoic acid (RA) catabolism, so that increased retinoic acid (RA) levels lead to pronounced RA effects at the tissue or cell level. Liarozole has also been shown to be a potent inhibitor of androgen biosynthesis. Preclinical and clinical studies are ongoing showing the utility of liarozole in the field of oncology and dermatology.

- 10 (-)-Liarozole has unexpectedly shown a higher activity in certain tumor models than (+)-liarozole or the racemic liarozole. It has been shown that a more "targeted" therapy is possible in the field of oncology by administering enantiomerically pure (-)-liarozole.
- 15 Especially (-)-liarozole may be used to treat prostate cancers.

- The use of (-)-liarozole and its pharmaceutically acceptable acid addition salts in the method of the present invention is based on their useful property to delay the catabolism of retinoids, such as, all-*trans*-retinoic acid, 13-*cis*-retinoic acid and their derivatives.
- 20 The latter results in more sustained / higher tissue concentrations of retinoids and improved control of differentiation and growth of various cell types. This action of (-)-liarozole is also called retinoic mimetic activity because administering (-)-liarozole causes the same effect as if retinoid would be administered. As such, (-)-liarozole can be used to control the rate of growth and differentiation of normal, preneoplastic and
- 25 neoplastic epithelial cells.

- (-)-Liarozole and its pharmaceutically acceptable acid addition salts is therefore useful in a method of treating disorders which are characterized by an increased proliferation and/or abnormal differentiation of epithelial cells. (-)-Liarozole shows activity on cells of
- 30 which the growth and differentiation is not substantially mediated by or insensitive to the actions of androgens or estrogens, in particular on cells of which the growth and differentiation is sensitive to the actions of retinoids. (-)-Liarozole is particularly useful in the treatment of tumors like head- and neck tumors, lung tumors, breast tumors, uterine cervix tumors, gastrointestinal tract tumors, skin tumors, bladder tumors and
- 35 prostate tumors. (-)-Liarozole and its pharmaceutically acceptable acid addition salts is useful for the manufacture of a medicament for treating epithelial tumors.



In general it is contemplated than an effective amount to treat disorders which are characterized by an excessive proliferation and/or abnormal differentiation of tissues, would be from 0.001 mg/kg to 20 mg/kg body weight and more preferably from 0.01 mg/kg to 10 mg/kg body weight.

5

The compounds of formula (I) used in the method of the invention are most preferably applied in the form of appropriate compositions. As appropriate compositions there may be cited all compositions usually employed for systemically or topically administering drugs. To prepare the pharmaceutical compositions of this invention, an effective
10 amount of the particular compound, optionally in acid-addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirable in unitary dosage form suitable, particularly, for administration orally, rectally, percutaneously, or
15 by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders,
20 pills, capsules, and tablets. Because of their ease in administration, tablets and capsules represents the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be
25 prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations. In the compositions suitable for percutaneous
30 administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not introduce a significant deleterious effect on the skin. As appropriate compositions for topical application there may be cited all compositions usually employed for topically administering drugs, e.g., creams, gellies, dressings,
35 shampoos, tinctures, pastes, ointments, salves, powders, liquid or semi-liquid formulation and the like. Application of said compositions may be by aerosol e.g. with a propellant such as nitrogen carbon dioxide, a freon, or without a propellant such as a



pump spray, drops, lotions, or a semisolid such as a thickened composition which can be applied by a swab. In particular compositions, semisolid compositions such as salves, creams, pastes, gellies, ointments and the like will conveniently be used.

- 5 It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with
- 10 the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powders packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.
- 15 Other compositions are preparations of the cosmetic type, such as toilet waters, packs, lotions, skin milks or milky lotions. Said preparations contain, besides the active ingredient, components usually employed in such preparations. Examples of such components are oils, fats, waxes, surfactants, humectants, thickening agents, antioxidants, viscosity stabilizers, chelating agents, buffers, preservatives, perfumes,
- 20 dyestuffs, lower alkanols, and the like. If desired, further ingredients may be incorporated in the compositions, e.g. antiinflammatory agents, antibacterials, antifungals, disinfectants, vitamins, sunscreens, antibiotics, or other anti-acne agents.

25 In a further aspect of the invention there are provided particular pharmaceutical or cosmetical compositions which comprise an inert carrier, an effective amount of (-)-liarozole or an acid addition salt form thereof and an effective amount of a retinoic acid, a derivative thereof or a stereochemically isomeric form thereof.

30 It can be demonstrated that the retinoic acids and the derivatives thereof, in particular retinol, and (-)-liarozole act in a synergistic manner. Indeed, the combined effect of both substances is greater than the sum of their respective effects when administered separately. The above described retinoic acid containing compositions are particularly useful for treating acne or for retarding the effects of aging of the skin and generally improve the quality of the skin, particularly human facial skin. A pharmaceutical or

35 cosmetical composition containing retinoic acid or a derivative thereof as the active ingredient in intimate admixture with a dermatologically acceptable carrier can be prepared according to conventional compounding techniques, such as those known for



topical application of retinoic acid and its derivatives, optionally in admixture with cyclodextrines or derivatives thereof known in the art. Preferred composition for topical application are in form of a cream, ointment or lotion comprising from 0.001 to 0.5% (particularly from 0.01 to 0.1%) all-*trans*-retinoic acid, 13-*cis*-retinoic acid or a derivative thereof, in particular retinol, and from 0.1 to 5% of a (-)-liarozole or a dermatologically acceptable acid addition salt thereof, in a semi-solid or liquid diluent or carrier.

These preferred compositions should preferably be non-irritating and as far as possible they should be odorless and non-toxic. For convenience in applying to the skin, the composition usually contain, besides water or an organic solvent, several of certain organic emollients, emulsifiers for the aqueous and/or non aqueous phases of the compositions, wetting agents preservatives and agents that facilitate the penetration and remainence of the active agents in the skin.

15 Experimental part

A. Preparation of the intermediates

Example 1

a) A mixture of (4-amino-3-nitrophenyl) (3-chlorophenyl)methanone (50 g), formamide (375 ml) and formic acid (63 ml) was stirred and refluxed for 17 hours. After cooling, the mixture was poured on ice. The precipitate was filtered off and dried, yielding 55 g (99.4%) of ($\pm$)-N-[(4-amino-3-nitrophenyl) (3-chlorophenyl)methyl]formamide (interm. 1).

b) A mixture of intermediate (1) (50.7 g), hydrochloric acid 6N (350 ml) and 2-propanol (70 ml) was stirred and refluxed for 17 hours. The resulting precipitate was filtered off and dried in vacuo, yielding 51 g (97.8%) of ($\pm$)-4-amino- α -(3-chlorophenyl)-3-nitrobenzenemethanamine monohydrochloride; mp. 263°C (interm. 2).

c) N,N-diethylethanamine (13.8 g) was added to a solution of intermediate (2) (43 g) in tetrahydrofuran (400 ml) and stirred at room temperature. (R)-(-)- α -hydroxybenzeneacetic acid (20.8 g) was added. A solution of 1-hydroxybenzotriazole (22.2 g) in tetrahydrofuran (200 ml) was added, followed by a solution of N,N'-methanetetrayl-biscyclohexanamine (33.9 g) in dichloromethane (300 ml). The reaction mixture was stirred for 2 hours at room temperature. Dichloromethane (400 ml) was added and N,N'-dicyclohexylurea was filtered off. The filtrate was washed with a 10% aqueous potassium carbonate solution and the organic layer was dried (MgSO_4), filtered and the solvent was evaporated, yielding 60 g (I) (mixture of diastereomers). The same experiment starting from intermediate (2) (16 g) resulted in a yield of 26 g (II) (mixture of diastereomers). Fractions (I) and (II) were combined and purified by high-



performance liquid chromatography (eluent: CH₂Cl₂/ethyl acetate 90/10). Two fraction groups were collected. The solvent of the fraction group with higher R_f value was evaporated, yielding 27 g of (-)-(R,A)-N-[(4-amino-3-nitrophenyl)(3-chlorophenyl)methyl]-α-hydroxybenzeneacetamide (interm. 3)

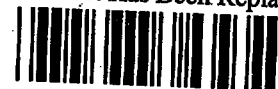
- 5 d) A mixture of intermediate (3) (27 g) in hydrochloric acid 12N (300 ml) and 1-propanol (100 ml) was stirred and refluxed for 18 hours. The cooled reaction mixture was poured on ice. This mixture was alkalized with ammonium hydroxide and extracted with dichloromethane. The separated organic layer was dried (MgSO₄), filtered and the solvent was evaporated. The residue (19 g) was purified by column chromatography
10 over silica gel (eluent: CH₂Cl₂/CH₃OH 98/2). The pure fractions were collected and the solvent was evaporated, yielding 6 g (33%) of (-)-(A)-4-amino-α-(3-chlorophenyl)-3-nitrobenzenemethanamine; $[\alpha]_D^{20} = -27.00^\circ$ (c = 1% in methanol) (interm. 4).

- e) A mixture of intermediate (4) (11.6 g) and 1,1-dimethoxy-2-isothiocyanato-ethane (7.3 g) in methanol (120 ml) was stirred and refluxed for 2 hours. The solvent was
15 evaporated, yielding theoretically 17.8 g of (-)-(A)-N-[(4-amino-3-nitrophenyl)(3-chlorophenyl)methyl]-N'-(2,2-dimethoxyethyl)thiourea (interm. 5).

- f) Potassium carbonate (6.95 g) was added to a solution of intermediate (5) (17.8 g) in 2-propanone (200 ml). Iodomethane (3.1 ml) was added and the reaction mixture was stirred for 48 hours at room temperature. The solvent was evaporated and the residue
20 was stirred in dichloromethane. The organic layer was separated, washed with water, dried (MgSO₄), filtered and the solvent was evaporated, yielding 17 g (92%) (-)-S-methyl (A)-N-[(4-amino-3-nitrophenyl)(3-chlorophenyl)methyl]-N'-(2,2-dimethoxyethyl)carbamidodithioate (interm. 6).

- g) Intermediate (6) (16 g) was cooled to 0 °C and sulfuric acid (cooled to 5 °C) was
25 added. The mixture was stirred at 5 °C to complete dissolution. The solution was warmed to room temperature, then stirred for 2 hours. The solution was poured on ice and alkalized with ammonium hydroxide. The aqueous solution was extracted with ethyl acetate. The separated organic layer was dried (MgSO₄), filtered and the solvent was evaporated. The residue (16 g) was purified by column chromatography over silica gel
30 (eluent: CH₂Cl₂/CH₃OH 98/2). The pure fractions were collected and the solvent was evaporated, yielding 10 g (74%) (-)-(A)-4-[(3-chlorophenyl)[2-(methylthio)-1H-imidazol-1-yl]methyl]-2-nitrobenzenamine (interm. 7).

- h) A mixture of intermediate (7) (10 g) in methanol (200 ml) was hydrogenated for 2 hours at room temperature (2-bar pressure; Parr apparatus) with Raney nickel (10 g) as a
35 catalyst. After uptake of hydrogen (3 eq.), the catalyst was filtered off and the filtrate was evaporated, yielding theoretically 9.3 g of (-)-(A)-4-[(3-chlorophenyl)[2-(methylthio)-1H-imidazol-1-yl]methyl]-1,2-benzenediamine (interm. 8).



- i) A mixture of intermediate (8) (9.3 g) and methanimidamide acetate (8.4 g) in methanol (200 ml) was stirred and refluxed for 3 hours. The solvent was evaporated and the residue was dissolved in dichloromethane. The organic solution was washed with a 10% NaHCO_3 solution, dried (MgSO_4), filtered and the solvent was evaporated. The oily residue (10 g) was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 95/5). The pure fractions were collected and the solvent was evaporated, yielding 6.2 g (65%) of (-)-(A)-5-[(3-chlorophenyl)[2-(methylthio)-1H-imidazol-1-yl]methyl]-1H-benzimidazole (interm. 9).

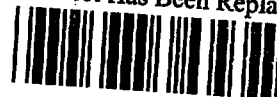
10 Example 2

- a) A mixture of ($\pm$)-4-[(3-chlorophenyl)-1H-imidazol-1-ylmethyl]-2-nitrobenzenamine (500 g) and (+)-(1S)-7,7-dimethyl-2-oxo-bicyclo[2.2.1]heptane-1-methanesulfonic acid (353.3 g) in 2-propanone (2000 ml) was stirred at 20 °C until it became homogeneous. Crystallization rapidly resulted. Water (100 ml) was added and the mixture was warmed to 38 °C. The mixture became homogeneous and was seeded with crystals. The compound was allowed to crystallize out during a 20-hour stirring at 20 °C, followed by a 2-hour stirring at 0 °C. The precipitate was filtered off, washed with 2-propanone/water 95/5 (250 ml), then dried (50 °C), yielding 288.90 g (33.86%; 67.7% in relation with the enantiomer) of (-)-(A)-4-[(3-chlorophenyl)-1H-imidazol-1-ylmethyl]-2-nitrobenzenamine (1S)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptane-1-methanesulfonate; mp. 158.8°C; $[\alpha]_D^{20} = -22.70^\circ$ (c = 0.5% in methanol) (interm. 10).
- b) A mixture of intermediate (10) (167.7 g) in methanol (615 ml) and methanol/ammonia (30.7 ml) was hydrogenated at 20-25 °C with platinum on activated carbon (5%) (12.3 g) as a catalyst in the presence of thiophene (0.5 g). After uptake of hydrogen (3 eq.); the catalyst was filtered off and washed with 2-propanol (30 ml). Hydrochloric acid in 2-propanol (487 ml) was added to the filtrate at < 30 °C. The mixture was stirred for 18 hours at 20 °C, then for 3 hours at 0 °C. The resulting precipitate was filtered off, washed with methanol (100 ml) and dried (50 °C), yielding 180.40 g of product (86.7%). The mother layer was evaporated, yielding 25.12 g (12.1%) of product. The total yield was 205.52g (98.8%) of (-)-(A)-4-[(3-chlorophenyl)-1H-imidazol-1-ylmethyl]-1,2-benzenediamine trihydrochloride (interm. 11).

B. Preparation of the final compounds

Example 3

- 35 A mixture of intermediate (9) (6.2 g) in ethanol (100 ml) was stirred and refluxed for 24 hours with Raney nickel (6 g) as a catalyst. The mixture was stirred and refluxed for 5 days and every day an additional amount of Raney nickel (6 g/addition) was added.



Then, the catalyst was filtered off and the filter residue was rinsed with dichloromethane. The filtrate was evaporated. The residue (4 g) was purified by column chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 95/5 and $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/\text{NH}_4\text{OH}$ 80/20/3). The pure fractions were collected and the solvent was evaporated. The residue (2.58 g free base) was dissolved in 2-propanol and converted into the hydrochloric acid salt (1:1) with HCl /ethanol. Crystallization was induced by addition of methyl ethyl ketone. The precipitate was filtered off and dried, yielding 2.3 g (38%) of (-)-(A)-5-[(3-chlorophenyl)-1H-imidazol-1-ylmethyl]-1H-benzimidazole monohydrochloride; mp. 207.7°C ; $[\alpha]_{\text{D}}^{20} = -42.43^\circ$ (c = 1% in methanol) (comp. 1).

Example 4

A mixture of intermediate (11) (177.35 g) in water (491 ml), hydrochloric acid (277 ml) and formic acid (70.6 ml) was heated to $50-55^\circ\text{C}$. The reaction mixture was stirred for 3 hours at 55°C . The mixture was cooled to 20°C . Dichloromethane (1173 ml) was added. Ammonium hydroxide (700 ml) was added ($\text{pH} > 9$) while cooling. The mixture was stirred for 30 minutes at 20°C . The organic layer was separated, washed with water (500 ml), dried, filtered and the solvent was evaporated at $45-50^\circ\text{C}$, yielding 134.16 g (100%) of (-)-(A)-5-[(3-chlorophenyl)-1H-imidazol-1-ylmethyl]-1H-benzimidazole; mp. 132.7°C ; $[\alpha]_{\text{D}}^{20} = -45.30^\circ$ (c = 1% in methanol) (comp. 2)

Example 5

A mixture of compound (2) (2.66 g) in ethanol (28.5 ml) was stirred at 20°C until it became homogeneous. (E)-2-butenedioic acid (2 g) was added and the mixture became homogeneous after 10 minutes. The product was allowed to crystallize out over a 20-hour period. The precipitate was filtered off, washed with ethanol (5 ml) and dried, yielding 1.72 g (41.4%) of (-)-(A)-5-[(3-chlorophenyl)-1H-imidazol-1-ylmethyl]-1H-benzimidazole (E)-2-butenedioate(2:3); mp. 116.7°C ; $[\alpha]_{\text{D}}^{20} = -29.20^\circ$ (c = 0.5% in methanol) (comp. 3).

Example 6

Compound (2) (114.5 g) was dissolved in 2-butanone (1854 ml). A mixture of hydrochloric acid in 2-propanol (68.5 ml) in 2-butanone (556 ml) was added over a 2-hour period at 20°C . The reaction mixture was stirred for 16 hours at 20°C . The precipitate was filtered off, washed with 2-butanone (185 ml) and dried (vacuum; 80°C), yielding 122.6 g (99.5%) of (-)-(A)-5-[(3-chlorophenyl)-1H-imidazol-1-ylmethyl]-1H-benzimidazole monohydrochloride; mp. 216.4°C ; $[\alpha]_{\text{D}}^{20} = -37.90^\circ$ (c = 1% in methanol) (comp. 1).



C. Composition Examples

The following formulations exemplify typical pharmaceutical compositions suitable for systemic or topical administration to animal and human subjects in accordance with the present invention.

"Active ingredient" (A.I.) as used throughout these examples relates to a compound of formula (I) or a pharmaceutically acceptable acid addition salt form thereof.

Example 7 : Oral drops

500 g of the A.I. was dissolved in 0.5 l of 2-hydroxypropanoic acid and 1.5 l of the polyethylene glycol at 60~80°C. After cooling to 30~40°C there were added 35 l of polyethylene glycol and the mixture was stirred well. Then there was added a solution of 1750 g of sodium saccharin in 2.5 l of purified water and while stirring there were added 2.5 l of cocoa flavor and polyethylene glycol q.s. to a volume of 50 l, providing an oral drop solution comprising 10 mg/ml of A.I. The resulting solution was filled into suitable containers.

Example 8 : Oral solution

9 g of methyl 4-hydroxybenzoate and 1 g of propyl 4-hydroxybenzoate were dissolved in 4 l of boiling purified water. In 3 l of this solution were dissolved first 10 g of 2,3-dihydroxybutanedioic acid and thereafter 20 g of the A.I. The latter solution was combined with the remaining part of the former solution and 12 l 1,2,3-propanetriol and 3 l of sorbitol 70% solution were added thereto. 40 g of sodium saccharin were dissolved in 0.5 l of water and 2 ml of raspberry and 2 ml of gooseberry essence were added. The latter solution was combined with the former, water was added q.s. to a volume of 20 l providing an oral solution comprising 5 mg of the A.I. per teaspoonful (5 ml). The resulting solution was filled in suitable containers.

Example 9: Capsules

20 g of the A.I., 6 g sodium lauryl sulfate, 56 g starch, 56 g lactose, 0.8 g colloidal silicon dioxide, and 1.2 g magnesium stearate were vigorously stirred together. The resulting mixture was subsequently filled into 1000 suitable hardened gelatin capsules, each comprising 20 mg of the A.I.

Example 10 : Film-coated tablets

Preparation of tablet core

A mixture of 100 g of the A.I., 570 g lactose and 200 g starch was mixed well and



thereafter humidified with a solution of 5 g sodium dodecyl sulfate and 10 g polyvinylpyrrolidone (Kollidon-K 90 ®) in about 200 ml of water. The wet powder mixture was sieved, dried and sieved again. Then there was added 100 g microcrystalline cellulose (Avicel ®) and 15 g hydrogenated vegetable oil (Sterotex ®). The whole was
5 mixed well and compressed into tablets, giving 10.000 tablets, each comprising 10 mg of the active ingredient.

Coating

To a solution of 10 g methyl cellulose (Methocel 60 HG ®) in 75 ml of denaturated ethanol there was added a solution of 5 g of ethyl cellulose (Ethocel 22 cps ®) in 150 ml
10 of dichloromethane. Then there were added 75 ml of dichloromethane and 2.5 ml 1,2,3-propanetriol. 10 g of polyethylene glycol was molten and dissolved in 75 ml of dichloromethane. The latter solution was added to the former and then there were added 2.5 g of magnesium octadecanoate, 5 g of polyvinylpyrrolidone and 30 ml of concentrated color suspension (Opaspray K-1-2109 ®) and the whole was homogenated.
15 The tablet cores were coated with the thus obtained mixture in a coating apparatus.

Example 11 : Injectable solution

1.8 g methyl 4-hydroxybenzoate and 0.2 g propyl 4-hydroxybenzoate were dissolved in about 0.5 l of boiling water for injection. After cooling to about 50°C there were added
20 while stirring 4 g lactic acid, 0.05 g propylene glycol and 4 g of the A.I. The solution was cooled to room temperature and supplemented with water for injection q.s. ad 1 l volume, giving a solution of 4 mg/ml of A.I. The solution was sterilized by filtration (U.S.P. XVII p. 811) and filled in sterile containers.

Example 12 : Suppositories

3 g A.I. was dissolved in a solution of 3 g 2,3-dihydroxy-butanedioic acid in 25 ml polyethylene glycol 400. 12 G surfactant (SPAN ®) and triglycerides (Witepsol 555 ®) q.s. ad 300 g were molten together. The latter mixture was mixed well with the former
30 solution. The thus obtained mixture was poured into moulds at a temperature of 37~38°C to form 100 suppositories each containing 30 mg of the active ingredient.

Example 13 : 2% topical gel

To a solution of 200 mg hydroxypropyl β -cyclodextrine in purified water is added 20 mg of A.I. while stirring. Hydrochloric acid is added until complete dissolution and then
35 sodium hydroxide is added until pH 6.0. This solution is added to a dispersion of 10 mg carrageenan PJ in 50 mg propylene glycol while mixing. While mixing slowly, the mixture is heated to 50°C and allowed to cool to about 35°C whereupon 50 mg ethyl



alcohol 95% (v/v) is added. The rest of the purified water q.s. ad 1 g is added and the mixture is mixed to homogenous.

Example 15 : Aerosols

- 5 a) To a solution of 0.1 g of hydroxypropyl β -cyclodextrin (MS = 0.43) in 0.7 ml of distilled water were added 730 μ g of a 0.1 N hydrochloric acid solution and 2.5 mg A.I.. After stirring for 10 minutes at room temperature, the pH of the thus obtained solution was adjusted to pH 5.5 by adding a 0.1 N sodium hydroxide solution. Then there were added successively 4 mg of sodium chloride and 0.15 mg of phenyl mercuri
- 10 acetate and the whole was stirred to produce complete dissolution. Distilled water was then added to a volume of 1.0 ml. The whole was filled in a glass bottle closed with a mechanical pump delivering 0.1 ml per puff upon administration.
- 15 b) To a solution of 0.1 g of dimethyl β -cyclodextrin in 0.7 ml of distilled water were added 600 μ g of a 0.1 N hydrochloric acid solution and 2 mg A.I.. After stirring for 10 minutes at room temperature, 10 mg of polyvinylalcohol was dissolved in the mixture and the pH of the thus obtained solution was adjusted to pH 5.5 by adding a 0.1 N sodium hydroxide solution. Then there were added successively 4 mg of sodium chloride and 2 mg of phenylethyl alcohol and the whole was stirred to produce complete
- 20 dissolution. Distilled water was added to produce a volume of 1.0 ml which was filled in a glass bottle closed with a mechanical pump delivering 0.1 ml per puff upon administration.

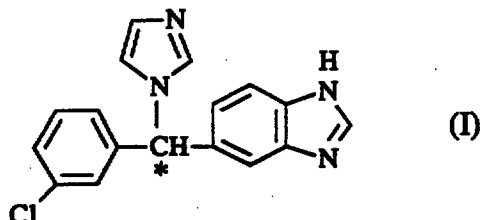


This Sheet Has Been Replaced



Claims

1. The laevorotatory compound of formula (I)



or a pharmaceutically acceptable acid addition salt thereof.

- 10 2. A compound according to claim 1, wherein the compound is (-)-5-[3-chlorophenyl]-1H-imidazol-1-ylmethyl]-1H-benzimidazole hydrochloride (1:1).

3. A compound according to claim 1, wherein the compound is (-)-5-[3-chlorophenyl]-1H-imidazol-1-ylmethyl]-1H-benzimidazole (E)-2-butenedioate (3:2).

15

4. A composition for treating epithelial tumors comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound as claimed in any of claims 1 to 3.

- 20 5. A composition as claimed in claim 4 wherein said composition is in a form suitable for systemic administration.

6. A composition according to claim 5 wherein said composition also comprises an effective amount of a retinoic acid, a derivative thereof or a stereochemically isomeric form thereof.

25

7. Use of a compound as claimed in any of claims 1 to 3 as a medicine.

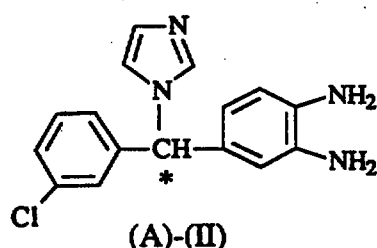
8. Use of a compound for the manufacture of a medicament for treating epithelial tumors.

30

9. Use of a compound for the manufacture of a medicament for treating prostatic tumors.



10. An enantiomerically pure intermediate of formula (A)-(II)



This Sheet Has Been Replaced

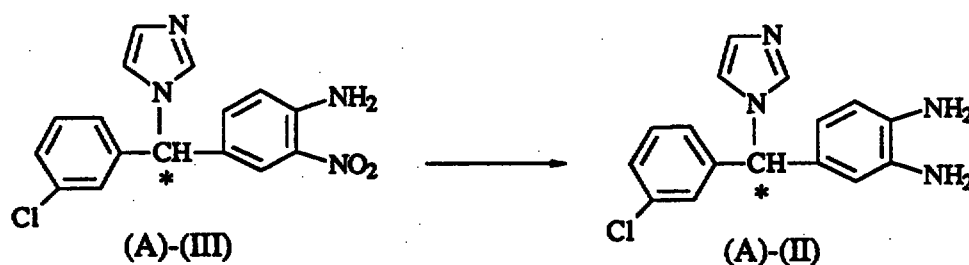


5 or an acid addition salt thereof.

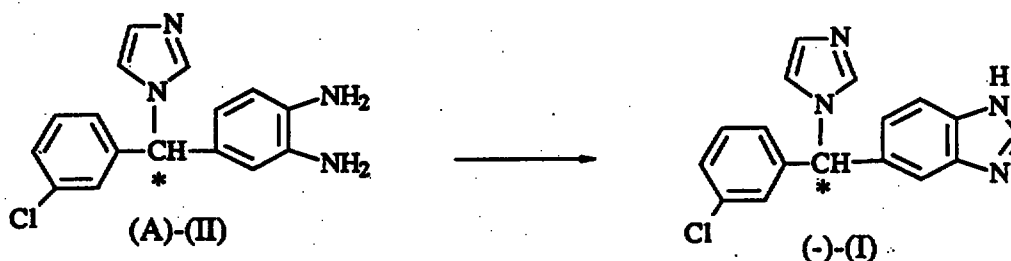
11. A process for preparing a compound as claimed in claim 1, characterized by

10 a) resolving an intermediate of formula (III) with an enantiomerically pure chiral acid, such as 7,7-dimethyl-2-oxobicyclo[2.2.1]heptane-1-methanesulphonic acid, in an appropriate solvent;

b) reducing the thus obtained enantiomerically pure intermediate of formula (A)-(III);



15 c) cyclizing the enantiomerically pure intermediate of formula (A)-(II), with methanimidamide, formic acid; functional derivatives thereof, yielding an enantiomerically pure compound of formula (I);



20 and if desired, converting the compound of formula (I) into a pharmaceutically acceptable acid addition salt form thereof by treatment with an appropriate acid or, conversely, converting the acid-addition salt into the free base form with alkali.

25