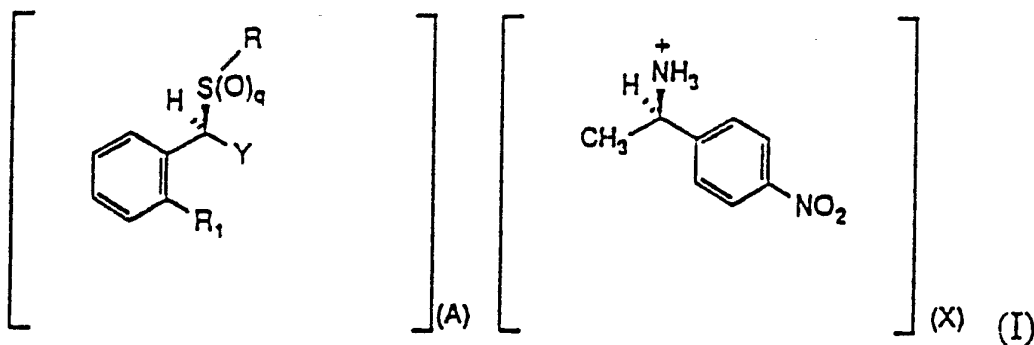




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(21) International Application Number: PCT/US91/06862 (22) International Filing Date: 20 September 1991 (20.09.91) (30) Priority data: 586,124 21 September 1990 (21.09.90) US (71) Applicant (for all designated States except US): SMITH-KLINE BEECHAM CORPORATION [US/US]; Corporate Patents - U.S., 709 Swedeland Road, King of Prussia, PA 19406 (US). (72) Inventors; and (75) Inventors/Applicants (for US only) : LAIRD, Trevor [GB/GB]; 2 Richmead Gardens, Mayfield, East Sussex TN20 6DE (GB). MILLS, Robert, John [GB/US]; 441 Rittenhouse Boulevard, Norristown, PA 19403 (US).		(74) Agents: KANAGY, James, M. et al.; SmithKline Beecham Corporation, Corporate Patents - U.S., 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406 (US). (81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), CS, DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, KR, LU (European patent), NL (European patent), PL, SE (European patent), US. Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: CRYSTALLIZATION OF OPTICAL ISOMERS OF LEUKOTRIENE ANTAGONISTS



(57) Abstract

This invention relates to salts of formula (I) where, A is 1 and X is 1 or 2; R₁ is C₈ to C₁₃ alkyl, C₇ to C₁₂ alkoxy, C₇ to C₁₂ alkylthio, C₁₀ to C₁₂ 1-alkynyl, 10-undecynyloxy, 11-dodecynyl, phenyl-C₄ to C₁₀ alkyl, phenyl-C₃ to C₉ alkoxy, phenylthio-C₃ to C₉ alkyl with the phenyl unsubstituted or monosubstituted with bromo, chloro, trifluoromethyl, C₁ to C₄ alkoxy, methylthio or trifluoromethylthio, furyl-C₄ to C₁₀ alkyl, trifluoromethyl-C₇ to C₁₂ alkyl or cyclohexyl-C₄ to C₁₀ alkyl; q is 0, 1 or 2, with the proviso that R₁ is not alkylthio or phenylthioalkyl when q is 1 or 2; Y is COR₃, C(R₄)H(CH₂)_mCOR₃, or (CH₂)_{0.1}-C-tetrazolyl; R₃ is 0-, amino, or C₁ to C₆ alkoxy, R₄ is hydrogen, methyl, C₁ to C₄-alkoxy, fluoro or hydroxy; m is 0, 1, or 2; R is (CH₂)_nCOR₆; n is 0 to 6; R₆ is 0-, amino, or C₁ to C₆-alkoxy; with the proviso that at least one of Y or R must have an R₃ or R₆ group respectively which is 0- and the use of certain amines to form these salts as a means for selectively crystallizing optical isomers of the leukotriene antagonists recited herein.

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CRYSTALLIZATION OF OPTICAL ISOMERS OF LEUKOTRIENE ANTAGONISTS

SCOPE OF THE INVENTION

5 This invention relates to certain amine salts of leukotriene antagonists and the use of certain amines to form these salts as a means for crystallizing selectively optical isomers of the leukotriene antagonists recited herein.

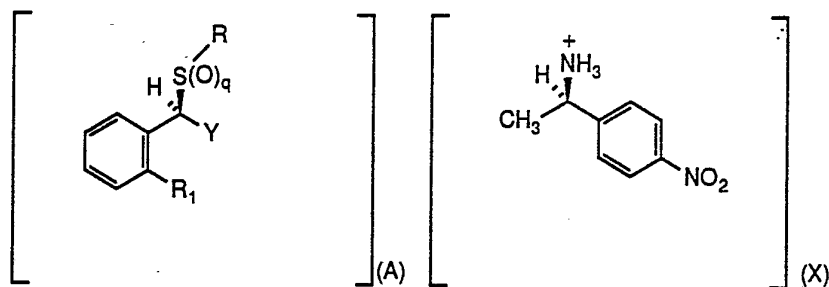
10 BACKGROUND OF THE INVENTION

 "Slow Reacting Substance of Anaphylaxis" (SRS-A) has been shown to be a highly potent bronchoconstricting substance which is released primarily from mast cells and basophils on antigenic challenge. SRS-A has been proposed as a primary mediator in human
15 asthma. SRS-A, in addition to its pronounced effects on lung tissue, also produces permeability changes in skin and may be involved in acute cutaneous allergic reactions. Further, SRS-A has been shown to effect depression of ventricular contraction and potentiation of the cardiovascular effects of histamine.

20 Antagonists to SRS substances have been developed in an attempt to provide relief from the disease conditions giving rise to or resulting from these compounds. A number of the compounds developed are normally prepared as a racemic mixture, though activity lies primarily or completely in just one of the optical isomers.
25 Resolving these mixtures is a useful, if not necessary step in preparing a useful formulation for treating these diseases. It has now been found that for certain compounds, the ones set out below, this can be accomplished most readily and inexpensively by means of (R)-4-nitro- α -methylbenzenemethanamine. This amine is uniquely suited
30 to resolving certain enantiomers of the compounds given below so that the most active isomer can be obtained for use in treating SRS-related diseases.

DETAILED DESCRIPTION OF THE INVENTION

35 The compounds of this invention are (R)-4-nitro- α -methylbenzenemethanamine salts of formula I

Formula I

5 where:

A is 1 and X is 1 or 2;

R₁ is C₈ to C₁₃ alkyl, C₇ to C₁₂ alkoxy, C₇ to C₁₂ alkylthio, C₁₀ to C₁₂ 1-alkynyl, 10-undecynyloxy, 11-dodecynyl, phenyl-C₄ to C₁₀ alkyl, phenyl-C₃ to C₉ alkoxy, phenylthio-C₃ to C₉ alkyl with the
 10 phenyl optionally mono substituted with bromo, chloro, trifluoromethyl, C₁ to C₄ alkoxy, methylthio or trifluoromethylthio, furyl-C₄ to C₁₀ alkyl, trifluoromethyl-C₇ to C₁₂ alkyl or cyclohexyl-C₄ to C₁₀ alkyl;

q is 0, 1 or 2, with the proviso that R₁ is not alkylthio or
 15 phenylthioalkyl when q is 1 or 2;

Y is COR₃, C(R₄)H(CH₂)_mCOR₃, or (CH₂)₀₋₁-C-tetrazolyl;

R₃ is O⁻, amino, or C₁ to C₆ alkoxy,

R₄ is hydrogen, methyl, C₁ to C₄-alkoxy, fluoro or hydroxy;

m is 0, 1, or 2;

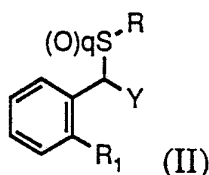
20 R is (CH₂)_nCOR₆;

n is 0 to 6;

R₆ is O⁻, amino, or C₁ to C₆-alkoxy;

with the proviso that at least one of Y or R must have an R₃ or R₆ group respectively which is O⁻.

25 This invention also relates to a process for separating a single isomer, either the R or S form, from a racemic mixture of a compound of formula II

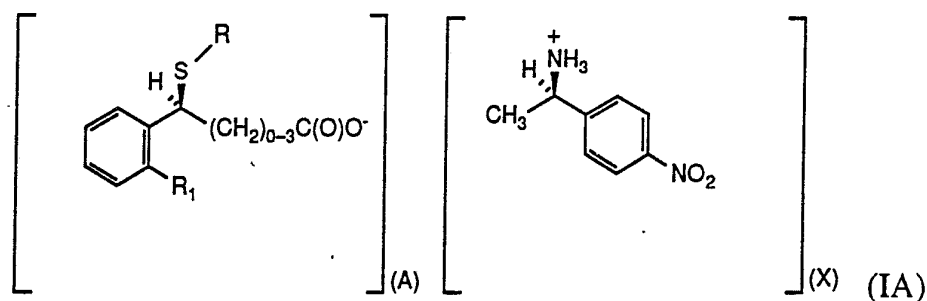


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where R, R₁, q and Y are defined above with the proviso that R₃ and R₆ are R₃' and R₆' where R₃' and R₆' are independently -OH, amino, or

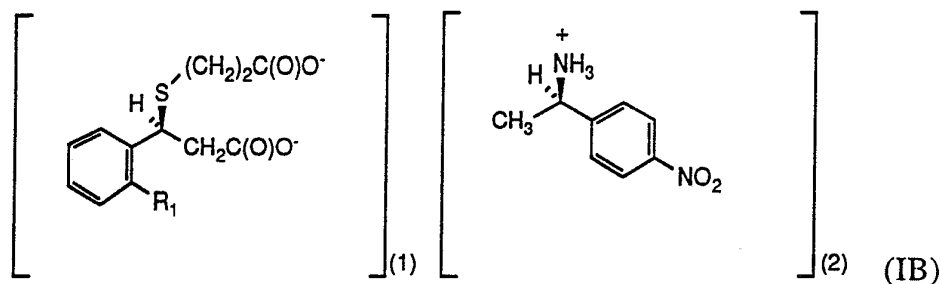
C₁ to C₆ alkoxy, with the further proviso that at least one of R₃' or R₆' must be -OH or a salt thereof, which process comprises treating a racemic mixture of formula II with about 0.5 to 2.5 equivalents, relative to the number of carboxylic acid groups in the formula, of either (R)-4-nitro- α -methylbenzenemethanamine or (S)-4-nitro- α -methylbenzenemethanamine, recovering a crystalline salt, and converting the salt to an acid or a pharmaceutically acceptable salt. It is preferred to use 0.5 to 1.5 equivalents of the nitro compound per carboxylic acid group in formula II. This process yields a substantially pure single enantiomer from a racemic mixture.

A preferred class of salts are those of formula (IA)



wherein A is 1, X is 1 or 2, and R₁ and R are described above.

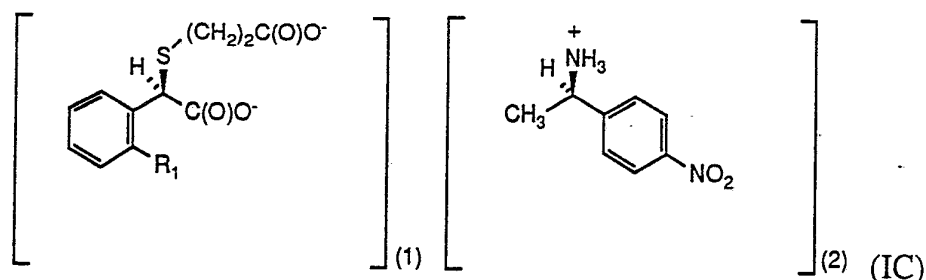
Another preferred group of these salts are 3-aryl-propionates of formula (IB)



wherein R₁ is defined above, particularly where R₁ is phenylalkyl. Most preferred among the salts of this group are:

the bis-(R)-4-nitro- α -methylbenzenemethanamine salt of (S)- β -[(2-carboxyethyl)thio]-2-(1-dodecyl)benzenepropanoic acid; and the bis-(R)-4-nitro- α -methylbenzenemethanamine salt of (S)- β -[(2-carboxyethyl)thio]-2-(8-phenyloctyl)benzenepropanoic acid.

Another preferred group of salts are the aryl-acetates of formula (IC).



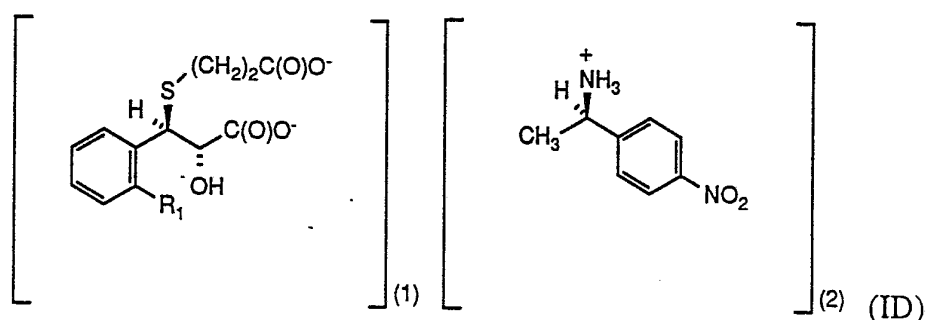
where R_1 is described above, particularly where R_1 is phenylalkyl.

The salts of the formula (IC) are exemplified by the following
5 compounds:

the bis-(R)-4-nitro- α -methylbenzenemethanamine salt of (R)- α -
[(2-carboxyethyl)thio]-2-(1-dodecyl)benzeneacetic acid; and the

bis-(R)-4-nitro- α -methylbenzenemethanamine salt of (R)- α -[(2-
carboxyethyl)thio]-2-(8-phenyloctyl)benzeneacetic acid.

10 Another preferred group of salts are 3-aryl-
2-hydroxypropionates of formula (ID)



15 where R_1 is defined above, particularly where R_1 is phenylalkyl.

The compounds of formula (ID) are exemplified by the following
compounds:

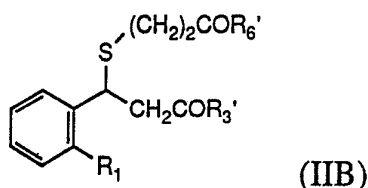
the bis-(R)-4-nitro- α -methylbenzenemethanamine salt of [R-
(R*,S*)]- β -[(2-carboxyethyl)thio]- α -hydroxy-2-(8-phenyloctyl)-

20 benzenepropanoic acid; and the

bis-(R)-4-nitro- α -methylbenzenemethanamine salt of
[R-(R*,S*)]- β -[(2-carboxyethyl)thio]- α -hydroxy-2-(1-dodecyl)-
benzenepropanoic acid.

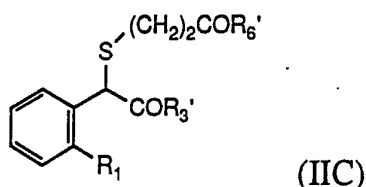
25 In a process for resolving racemates of formula II, the following
sets of general and specific compounds are preferred.

A set of preferred racemates are those of formula (IIB),



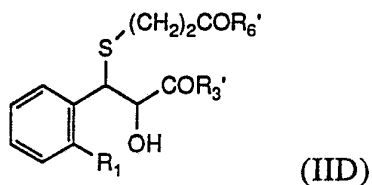
5 more particularly those where R_1 is a phenyl- C_4 to C_{10} -alkyl. Most particularly racemates of formula (IIB) can be treated with the (R)-4-nitro- α -methylbenzenemethanamine to obtain, after further manipulation, the isomers (S)- β -[(2-carboxyethyl)thio]-2-(1-dodecyl)benzenepropanoic acid and (S)- β -[(2-carboxyethyl)thio]-2-(8-phenyloctyl)benzenepropanoic acid.

Another set of preferred racemates are those of formula IIC



15 particularly those where R_1 is a phenyl- C_4 to C_{10} alkyl. Most particularly racemates of formula (IIC) can be treated with (R)-4-nitro- α -methylbenzenemethanamine to obtain, after further manipulation, the isomers (R)- α -[(2-carboxyethyl)thio]-2-(1-dodecyl)benzeneacetic acid and (R)- α -[(2-carboxyethyl)thio]-2-(8-phenyloctyl)benzeneacetic acid.

20 Yet another preferred set of racemates are the 2S*,3R*-isomers represented by formula (IID),



25 particularly those where R_1 is a phenyl- C_4 to C_{10} -alkyl. Most particularly the racemate of formula (IID) can be treated with (R)-4-nitro- α -methylbenzenemethanamine to obtain, after further manipulation, the isomer [R-(R*,S*)]- β -[(2-carboxyethyl)thio]- α -hydroxy-2-(8-phenyloctyl)benzenepropanoic acid.

30 The racemates of this invention can be prepared according to the disclosure set out in United States Patent number 4,820,719

issued April 11, 1989. That disclosure, in full, is incorporated herein by reference as if set out herein.

The amine, (R)-4-nitro- α -methylbenzenemethanamine, can be purchased as a hydrochloride salt from a commercial source such as Chiron, a Norwegian company. Or the hydrochloride salt may be made by the process of Baker, J. W. & Ingold, C.K., J. Chem. Soc., 261-264, 1927, and the R and S isomers fractionally crystallized by the method of Nerdel, F. and Liebeg, H., Ann 621:42-50, 1959. A more recent process for making the hydrochloride salt of this amine is given in Perry, C.W. et al, Synthesis 492-494, 1977. The amine can be prepared by treating the hydrochloride salt with a strong base and extracting the amine into an organic solvent, for example methylene chloride or toluene. Amine prepared in this manner may be stored prior to use. Alternatively, the amine can be liberated *in-situ* by treating the hydrochloride salt with a strong base in an aqueous alcoholic solvent, and then used immediately.

This amine is a particularly effective resolving agent for separating out a particular isomer from a racemic mixture of compounds denoted by formula II. A salt is formed between the amine and the carboxylate function. This salt can be fractionally crystallized, giving a salt comprising the amine and just one isomer of the acid. An alcohol is the preferred solvent for crystallization. This method provides excellent selectivity for the desired isomer.

These salts may be converted to the corresponding acid by means of a dilute acid. Or they may be converted to another salt, such as an alkali metal salt, by treating a solution of the isolated salt with a base. For example, the salt can be converted to the free acid by treating a solution of that salt with dilute mineral acid, for example 0.5N HCl at room temperature or thereabouts. The mixture is then extracted with an appropriate organic solvent, or subjected to other convenient separatory means, and the pure isomer obtained as the free acid after removing the solvent.

The following examples illustrate the process for making and preparing the compounds of this invention. Being examples they are not to be considered as limiting the invention set forth in the claims appended hereto.

Example 1Preparation of (S)- β -[(2-Carboxyethyl)thio]-2-(8-phenyloctyl)benzenepropanoic acid, compound with (R)-4-Nitro- α -methylbenzenemethanamine (1:2)

5 Racemic β -[(2-carboxyethyl)thio]-2-(8-phenyloctyl)-benzenepropanoic acid [6.05 g (60.7% assay, 8.3 mmol)] was dissolved in 80 mL of 2-propanol and treated with a solution of 1.48 g (8.9 mmol) of (R)-4-nitro- α -methylbenzenemethanamine in 2-propanol.

10 The mixture was heated to reflux, then allowed to cool to 0°C. The resulting solids were isolated by filtration to afford, after drying, 2.33 g of crude product. Chiral HPLC analysis indicated 97.7% of the desired S-enantiomer. After recrystallizing from 2-propanol, the content of S-enantiomer was enhanced to >99.5%. The salt contained 2

15 moles of amine per mole of diacid: Mp 239-240°C; $[\alpha]_D^{25} = -8.9^\circ$ (c=1.0, methanol); Chiral HPLC (Bakerbond Chiralcel OD, 4.6 mm x 250 mm, 3.5/96.5/0.1 isopropanol/n-hexane/trifluoroacetic acid, 2.0 mL/min, ambient temperature, UV detection at 215 nm): Retention Time = 15.9 min (minor peak; R-enantiomer), Retention Time = 19.4 min (major

20 peak; S-enantiomer); Anal. Calcd for $C_{42}H_{54}N_4O_8S$: C, 65.09; H, 7.02; N, 7.23; S, 4.14. Found: C, 65.11; H, 7.00; N, 7.39; S, 4.09; 1H NMR ($CDCl_3/CD_3OD$, 270 MHz) δ 8.21-8.24 (m, 4H), 7.57-7.60 (m, 4H), 7.14-7.39 (m, 9H), 4.47-4.53 (t, 1H), 4.30-4.38 (q, 2H, J=6.6 Hz), 2.32-2.91 (m, 10H), 1.32-1.60 (br, 18H).

Example 2Preparation of [R-(R*,S*)]- β -[(2-Carboxyethyl)thio]- α -hydroxy-2-(8-phenyloctyl)benzenepropanoic acid, compound with (R)-4-Nitro- α -methylbenzenemethanamine.(1:2)

25 A solution of racemic (R*,S*)- β -[(2-carboxyethyl)thio]- α -hydroxy-2-(8-phenyloctyl)benzenepropanoic acid (2.32g, 6.6 mmol) was prepared by warming the acid in 40 mL of 2-propanol. The resulting solution was treated with 2.32 g (13.9 mmol) of (R)-4-nitro- α -methylbenzenemethanamine in 50 mL of absolute ethanol. The solution was heated to reflux, then cooled to room temperature. The

30 resulting solids were isolated by filtration to afford, after drying, 1.95 g of crude product. Chiral HPLC analysis indicated 95.2% of the desired 2S,3R-enantiomer. After recrystallizing from absolute ethanol, the content of 2S,3R-enantiomer was enhanced to >99.5%. The salt contained 2 moles of amine per mole of diacid: Mp 141.5-

35

142.5°C; $[\alpha]_D^{25} = -20.0^\circ$ (c=1.0, methanol); Chiral HPLC (Bakerbond Chiralcel OD, 4.6 mm x 250 mm, 10.0/90.0/0.1 isopropanol/n-hexane/trifluoroacetic acid, 2.0 mL/min, ambient temperature, UV detection at 215 nm): Retention Time = 6.1 min (minor peak; 2R,3S-enantiomer), Retention Time = 9.5 min (major peak; 2S,3R-enantiomer); Anal. Calcd for $C_{42}H_{54}N_4O_9S$: C, 63.78; H, 6.88; N, 7.08; S, 4.05. Found: C, 63.80; H, 6.93; N, 7.12; S, 3.94; 1H NMR (DMSO- d_6 , 270 MHz) δ 8.22-8.16 (m, 4H), 7.70-7.65 (m, 4H), 7.28-7.01 (m, 9H), 4.53 (d, 1H, J=3.4 Hz), 4.33-4.26 (q, 2H, J=6.7 Hz), 4.05 (d, 1H, 3.4 Hz), 2.90-2.84 (m, 1H), 2.66-2.34 (m, 7H), 1.53 (m, 4H), 1.37 (d, 6H, J=6.8 Hz), 1.29 (s, 8H).

Example 3

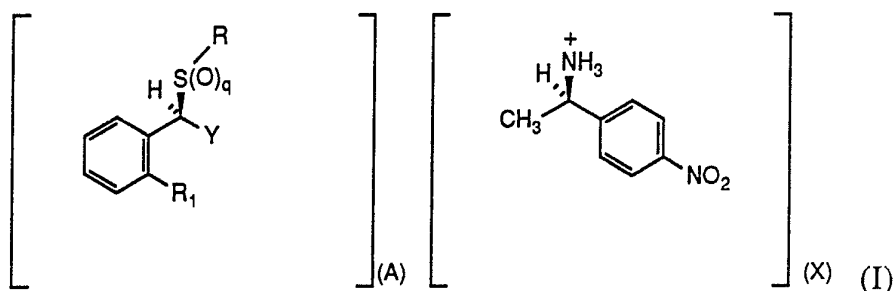
Determination and Confirmation of Absolute Configuration

Both (S)- β -[(2-carboxyethyl)thio]-2-(8-phenyloctyl)-benzenepropanoic acid and [R-(R*,S*)]- β -[(2-carboxyethyl)thio]- α -hydroxy-2-(8-phenyloctyl)benzenepropanoic acid react with two molar equivalents of (R)-4-iodo- α -methylbenzenemethanamine to produce highly crystalline salts. In each of these salts, the absolute configuration of the diacid portion was determined unambiguously by single crystal x-ray analysis.

In order to correlate this information to the salts obtained in Examples 1 and 2, each salt was treated with aqueous acid and extracted with ethyl acetate. By analyzing the extracts on an HPLC column (cellulose tris-3,5-dimethylphenylcarbamate chiral stationary phase, coated on silica gel) and comparing retention times to authentic samples of the racemates, it was determined that the diacid portion of the salt from Example 1 possessed the S-configuration, and the diacid portion of the salt from Example 2 possessed the 2S,3R-configuration.

Claims:

1. A salt of formula I



5

where:

A is 1 and X is 1 or 2;

R₁ is C₈ to C₁₃ alkyl, C₇ to C₁₂ alkoxy, C₇ to C₁₂ alkylthio, C₁₀ to C₁₂ 1-alkynyl, 10-undecyloxy, 11-dodecynyl, phenyl-C₄ to C₁₀ alkyl, phenyl-C₃ to C₉ alkoxy, phenylthio-C₃ to C₉ alkyl with the phenyl unsubstituted or monosubstituted with bromo, chloro, trifluoromethyl, C₁ to C₄ alkoxy, methylthio or trifluoromethylthio, furyl-C₄ to C₁₀ alkyl, trifluoromethyl-C₇ to C₁₂ alkyl or cyclohexyl-C₄ to C₁₀ alkyl;

15 q is 0, 1 or 2, with the proviso that R₁ is not alkylthio or phenylthioalkyl when q is 1 or 2;

Y is COR₃, C(R₄)H(CH₂)_mCOR₃, or (CH₂)₀₋₁-C-tetrazolyl;R₃ is O⁻, amino, or C₁ to C₆ alkoxy,R₄ is hydrogen, methyl, C₁ to C₄-alkoxy, fluoro or hydroxy;

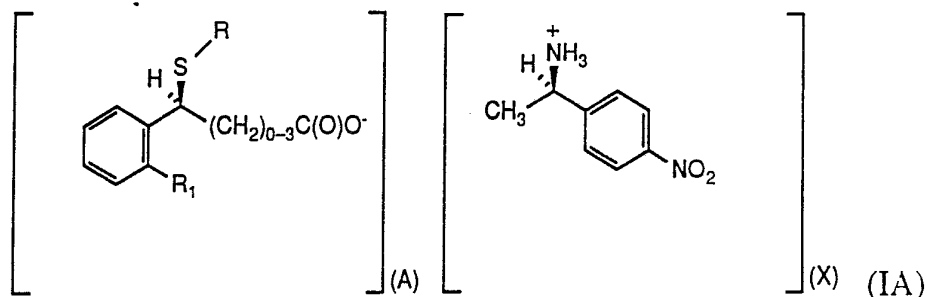
20 m is 0, 1, or 2;

R is (CH₂)_nCOR₆;

n is 0 to 6;

R₆ is O⁻, amino, or C₁ to C₆-alkoxy;with the proviso that at least one of Y or R must have an R₃ or25 R₆ group respectively which is O⁻.

2. A salt of claim 1 represented by formula (IA).

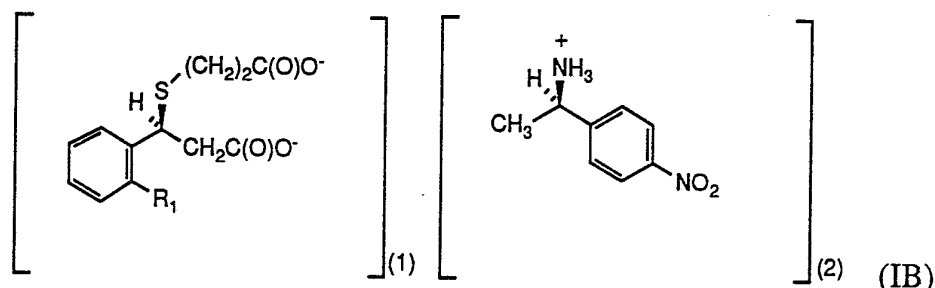


where R_1 is phenylalkyl.

3. A salt of claim 2 where R is $(CH_2)_{1-3} COR_6$.

4. A salt of claim 3 represented by the 3-arylpropionate of formula (IB).

5

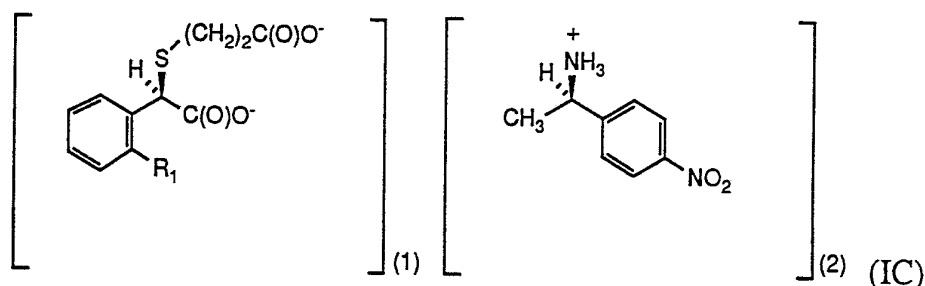


5. A salt of claim 4 where R_1 is phenyl- C_4 to C_{10} alkyl or C_8 to C_{13} alkyl.

10 6. A salt of claim 5 which is the bis-(R)-4-nitro- α -methylbenzenemethanamine salt of (S)- β -[(2-carboxyethyl)thio]-2-(1-dodecyl)benzenepropanoic acid.

7. A salt of claim 5 which is the bis-(R)-4-nitro- α -methylbenzenemethanamine salt of (S)- β -[(2-carboxyethyl)thio]-2-(8-phenyloctyl)benzenepropanoic acid.

15 8. A salt of claim 3 represented by formula (IC).

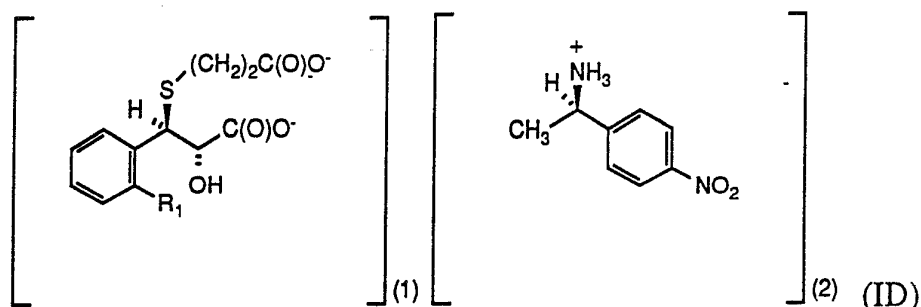


20 9. A salt of claim 8 where R_1 is a phenyl- C_4 to C_{10} alkyl or C_8 to C_{13} alkyl.

10. A salt of claim 9 which is the bis-(R)-4-nitro- α -methylbenzenemethanamine salt of (R)- α -[(2-carboxyethyl)thio]-2-(1-dodecyl)benzeneacetic acid.

25 11. A salt of claim 9 which is the bis-(R)-4-nitro- α -methylbenzenemethanamine salt of (R)- α -[(2-carboxyethyl)thio]-2-(8-phenyloctyl)benzeneacetic acid.

12. A salt of claim 1 represented by formula (ID).

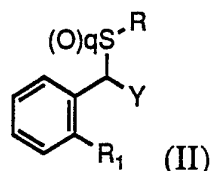


13. A salt of claim 12 where R_1 is a phenyl- C_4 to C_{10} -alkyl.

14. A salt of claim 13 which is the bis-(R)-4-nitro- α -methylbenzenemethanamine salt of [R-(R^* , S^*)]- β -[(2-carboxyethyl)thio]- α -hydroxy-2-(8-phenyloctyl)benzenepropanoic acid.

15. A process for separating a single isomer from a racemic mixture of a compound of formula II

10



where:

R_1 is C_8 to C_{13} alkyl, C_7 to C_{12} alkoxy, C_7 to C_{12} alkylthio, C_{10} to C_{12} 1-alkynyl, 10-undecynyloxy, 11-dodecynyl, phenyl- C_4 to C_{10} alkyl, phenyl- C_3 to C_9 alkoxy, phenylthio- C_3 to C_9 alkyl with the phenyl optionally mono substituted with bromo, chloro, trifluoromethyl, C_1 to C_4 alkoxy, methylthio or trifluoromethylthio, furyl- C_4 to C_{10} alkyl, trifluoromethyl- C_7 to C_{12} alkyl or cyclohexyl- C_4 to C_{10} alkyl;

q is 0, 1 or 2, with the proviso that R_1 is not alkylthio or phenylthioalkyl when q is 1 or 2;

Y is COR_3 , $C(R_4)H(CH_2)_mCOR_3$, or $(CH_2)_{0-1}$ -C-tetrazolyl;

R_3 is OH, amino, or C_1 to C_6 alkoxy,

R_4 is hydrogen, methyl, C_1 to C_4 -alkoxy, fluoro or hydroxy;

m is 0, 1, or 2;

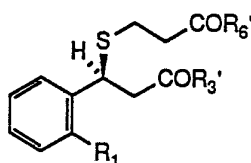
R is $(CH_2)_nCOR_6$;

n is 0 to 6;

R_6 is OH, amino, or C_1 to C_6 -alkoxy;

with the proviso that at least one of R_3 or R_6 is -OH or a salt thereof, which process comprises:

- (i). treating a racemic mixture of formula II with between about 0.5 to 2.5 equivalents, relative to the number of carboxylic acid groups in formula (II), of (R)-4-nitro- α -methylbenzenemethanamine;
- (ii). recovering a crystalline salt; and
- (iii). converting the salt to an acid or a pharmaceutically acceptable salt.
16. The process of claim 15 where the separated isomer is a compound of formula

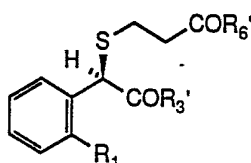


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17. The process of claim 16 where R_1 is a phenyl- C_4 to C_{10} -alkyl or C_8 to C_{13} alkyl.

18. The process of claim 17 which gives the isomer (S)- β -[(2-carboxyethyl)thio]-2-(1-dodecyl)benzenepropanoic acid, or (S)- β -[(2-carboxyethyl)thio]-2-(8-phenyloctyl)benzenepropanoic acid.

19. The method of claim 15 where the separated isomer is that of formula

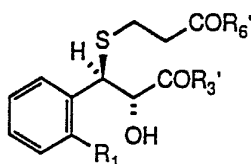


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20. The process of claim 19 where R_1 is a phenyl- C_4 to C_{10} alkyl or C_8 to C_{13} alkyl.

21. The process of claim 20 which gives the isomer (R)- α -[(2-carboxyethyl)thio]-2-(1-dodecyl)benzeneacetic acid or (R)- α -[(2-carboxyethyl)thio]-2-(8-phenyloctyl)benzeneacetic acid.

22. The process of claim 15 where the separated isomer is represented by the formula



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23. The process of claim 22 where R_1 is a phenyl- C_4 to C_{10} -alkyl.

24. The process of claim 23 which gives the isomer [R-(R*,S*)]-[(2-carboxyethyl)thio]- α -hydroxy-2-(8-phenyloctyl)benzenepropanoic acid.

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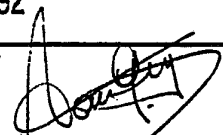
INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 91/06862

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int.Cl. 5 C07C323/56; C07C319/28		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl. 5	C07C	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	EP,A,0 365 149 (SMITHKLINE BEECHAM) 25 April 1990	

A	EP,A,0 313 697 (SMITHKLINE BECKMAN) 3 May 1989	

¹⁰ Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
15 JANUARY 1992	- 3. 02. 92	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE	J. VAN GEYT 	

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. US 9106862
SA 52775**

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 15/01/92

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		AU-A- 4156989	29-03-90
		JP-A- 2124869	14-05-90
		US-A- 5034537	23-07-91

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		JP-A- 1135762	29-05-89
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