

(12) PATENT
(19) AUSTRALIAN PATENT OFFICE

(11) Application No. **AU 199886670 B2**
(10) Patent No. **733236**

(54) Title
Use of selective RXR agonists to prevent surgical adhesions

(51)⁶ International Patent Classification(s)
A61K 031/07 A61K 031/38
A61K 031/335

(21) Application No: 199886670 (22) Application Date: 1998.07.28

(87) WIPO No: WO99/06036

(30) Priority Data

(31) Number (32) Date (33) Country
60/054017 1997.07.29 US

(43) Publication Date : 1999.02.22
(43) Publication Journal Date : 1999.04.22
(44) Accepted Journal Date : 2001.05.10

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(56) Related Art
US 5534261

CPI DATE 22/02/99 APPLN. ID 86670/98
AOJP DATE 22/04/99 PCT NUMBER PCT/US98/15625



AU9886670

1)

(51) International Patent Classification ⁶ : A61K 31/07, 31/38, 31/335		(11) International Publication Number: WO 99/06036
A1		(43) International Publication Date: 11 February 1999 (11.02.99)
(21) International Application Number: PCT/US98/15625		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, GA, GN, GW, ML, MR, NE, SN, TD, TG).
(22) International Filing Date: 28 July 1998 (28.07.98)		
(30) Priority Data: 60/054,017 29 July 1997 (29.07.97) US		
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(54) Title: USE OF SELECTIVE RXR AGONISTS TO PREVENT SURGICAL ADHESIONS		
(57) Abstract Certain retinoid derivatives, most or all of which are selective RXR retinoid agonists, have been found to be useful in the prevention or minimization of surgical adhesion formation.		

5 USE OF SELECTIVE RXR AGONISTS
 TO PREVENT SURGICAL ADHESIONS

FIELD OF THE INVENTION

10 The present invention is directed to methods for the minimization
or prevention of post-surgical adhesion formation using agonists of the
RXR retinoid receptors.

BACKGROUND OF THE INVENTION

15 Retinoic acid and its natural and synthetic analogs exert a wide
array of biological effects. They have been shown to affect cellular growth
and differentiation and are useful in a variety of dermatological and
malignant conditions.

20 U.S. Patent 5,534,261 discloses that retinoids, particularly all-trans
retinoic acid, can be used to minimize or prevent adhesion formation
following surgery. There is no disclosure, however, that selective RXR
agonists would have this same utility and there is no disclosure of the
25 particular retinoid derivatives of the present invention.

 Selective agonists of RXR retinoid receptors are disclosed in the
literature along with suitable assays for determining if a given retinoid-
like compound is considered to be a selective RXR agonist. For example,
30 U.S. Patents 5,455,265 and 5,399,586 disclose a wide variety of such
compounds and their utility in the same diseases or conditions against
which retinoids are useful. U.S. Patent 5,455,265 states that RXR selective



5 agonists are useful as regulators of cell proliferation and differentiation, and are particularly useful as agents for treating dermatoses such as acne, Darier's disease, psoriasis, ichthyosis, eczema and atopic dermatitis, and for treating and preventing malignant hyperproliferative diseases such as epithelial cancer, breast cancer, prostatic cancer, head and neck cancer and
10 myeloid leukemias, for reversing and preventing atherosclerosis and restenosis resulting from neointimal hyperproliferation, for treating and preventing other non-malignant hyperproliferative diseases such as endometrial hyperplasia, benign prostatic hypertrophy, proliferative vitreal retinopathy and dysplasias, for treating autoimmune diseases and
15 immunological disorders (e.g. lupus erythematoses), for treating chronic inflammatory diseases such as pulmonary fibrosis, for treating and preventing diseases associated with lipid metabolism and transport such as dyslipidemias, for promoting wound healing, for treating dry eye syndrome and for reversing and preventing the effects of sun damage to
20 skin. U.S. Patent 5,399,586 discloses that RXR agonists, particularly selective RXR agonists, induce apoptosis of tumor cells.

The prior art also indicates that selective RXR agonists surprisingly lack substantial teratogenic activity and have substantially reduced skin
25 toxicity, properties which have been serious disadvantages with other classes of retinoid compounds.

U.S. Patent 5,455,265 discloses a suitable assay for determining the potency of a retinoid or retinoid-like compound as an agonist at the RXR
30 receptor sites and RAR receptor sites. For purposes of defining the term "selective" RXR agonist in this application, applicant adopts the definition of this term as used in U.S. Patent 5,455,265, i.e. a "selective" RXR agonist

is one which is at least approximately ten times as potent as an agonist at the RXR receptor sites then at the RAR receptor sites.

5

The above discussion of documents, acts, materials, devices, articles and the like is included in this specification solely for the purpose of providing a context for the present invention. It is not suggested or represented that any or all of these matters formed part of the prior art base or were common general knowledge in the field relevant to the present invention as it existed in Australia before the priority date of each claim of this application.

10 The present invention involves the finding that certain retinoid derivatives, most or all of which are selective RXR agonist compounds, have utility in preventing or minimizing post-surgical adhesion formation.

Throughout the description and claims of this specification, the word "comprise" and variations of the word, such as "comprising" and "comprises", is not intended to exclude other additives, components, integers or steps.

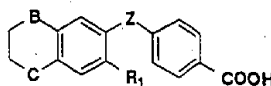
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SUMMARY OF THE INVENTION

The present invention provides a method for the minimization or prevention of post-surgical adhesion formation between organ surfaces comprising administering an effective amount of a retinoid derivative of general formula I below, most or all of which are selective RXR agonists, to a site of surgical activity on an organ surface for a period of time sufficient to permit tissue repair.

25

The retinoid derivatives which are the subject of the present invention have the general formula



35



5 wherein Z is $\begin{array}{c} \text{Q} \\ \parallel \\ -\text{C}- \end{array}$ or $\begin{array}{c} \text{A} \\ \diagup \quad \diagdown \\ \text{X} \quad \text{Y} \end{array}$ in which Q, X and Y are each independently O, S or CH₂;

A is -(CR₂)_n- wherein n is an integer of from 1 to 3;

10 B and C are each independently O, S, CH₂ or C(CH₃)₂; and

R₁ is hydrogen or (C₁-C₆) alkyl; or a pharmaceutically acceptable salt thereof.

15 DETAILED DESCRIPTION OF THE INVENTION

Adhesion formation, particularly following peritoneal surgery, is a major source of postoperative morbidity and mortality. Appendectomy and gynecologic surgery are the most frequent surgical procedures
20 implicated in clinically significant adhesion formation. The most serious complication of intraperitoneal adhesions is intestinal obstruction. In addition, adhesions are associated with chronic or recurrent pelvic pain and infertility in females.

25 Various approaches for the prevention of adhesion formation have been explored, but an effective therapeutic approach has not been discovered to date.

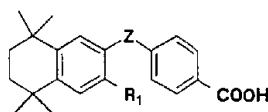
The use of retinoids for prevention of adhesion formation is
30 described in U.S. Patent 5,534,261. While the term "retinoid" as used in

5 this patent is defined in several ways, no mention is made of selective RXR agonists and there is no indication that such agonists would possess this property.

Applicant has unexpectedly found that certain retinoid derivatives,
10 most or all of which are selective RXR agonists, possess surprisingly potent activity in preventing or minimizing adhesion formation. The reduction or absence of teratogenicity and skin irritation described for selective RXR agonists in the prior art (See, for example, H Jiang et al, *Biochemical Pharmacology* Vol 50, 669-676 (1995); DM Kochhar et al,
15 *Chemico-Biological Interactions* Vol 100, 1-12 (1996); C Willhite et al, *Drug Metabolism Reviews* Vol 28, 105-119 (1996); SM Thatcher et al, *J Pharmacology and Experimental Therapeutics* Vol 282, 528-534 (1997); RL Beard et al, *J Medicinal Chemistry* Vol 39, 3556-63 (1996)) would also make such agonists more advantageous for this use than the retinoids
20 described in U.S. Patent 5,534,261.

Thus, the present invention provides a method for the minimization or prevention of post-surgical adhesion formation between organ surfaces comprising administering an effective amount of a
25 retinoid derivative of general formula I above to a site of surgical activity for a period of time sufficient to permit tissue repair.

Preferred compounds of general formula I are those wherein B and C are both $C(CH_3)_2$, i.e.



IA

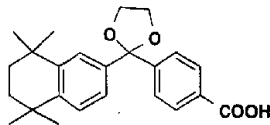
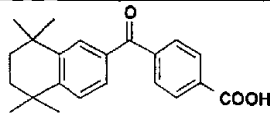
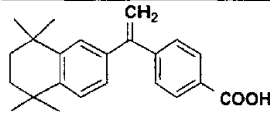
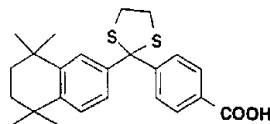
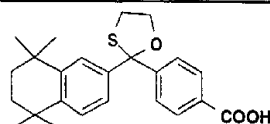
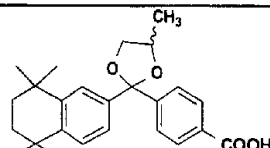
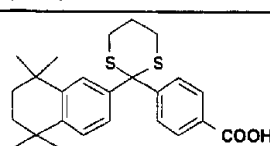
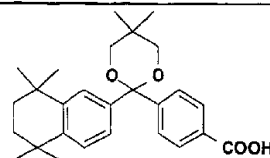
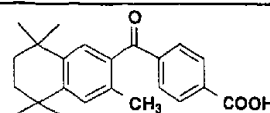
in which Z and R₁ are as defined above for the formula I compounds.

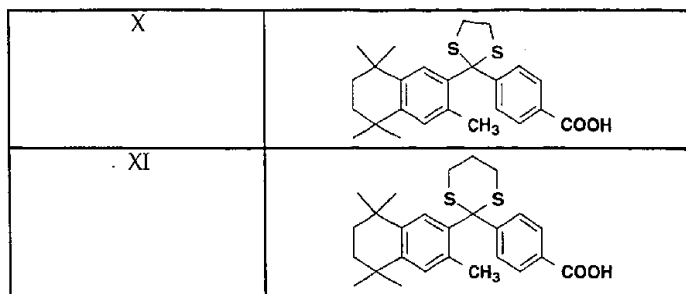
The most preferred compounds of formula I and IA are those in which R₁ is hydrogen.

The compounds of the present invention have a carboxylic acid functional group and can, therefore, form salts with suitable bases. It is intended that the present invention encompass pharmaceutically acceptable salts of the compounds of formula I formed with conventional bases, i.e. both inorganic and organic bases. Examples of suitable salts include ammonium, alkali metal salts, particularly sodium and potassium, alkaline earth metal salts such as calcium and magnesium, and salts with suitable organic bases such as lower alkylamines (methylamine, ethylamine, cyclohexylamine, and the like) or with substituted lower alkylamines (e.g. hydroxyl-substituted alkylamines such as diethanolamine, triethanolamine or tris (hydroxymethyl) aminomethane, or with bases such as piperidine or morpholine.

Examples of the compounds of the present invention are given in the table below:

5

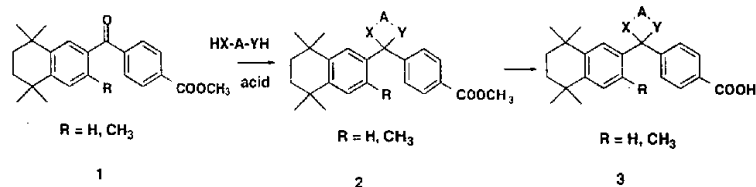
COMPOUND	STRUCTURE
I	
II	
III	
IV	
V	
VI	
VII	
VIII	
IX	



5

Compounds I-V, VII, and IX have been reported in MI Dawson et al; *J Medicinal Chemistry* **1995**, 38, 3368-3383, where they are described as selective RXR agonists. Compounds VI, VIII, X, and XI may be prepared using the following scheme:

10



A diaryl ketone-ester, **1**, is condensed with a diol, dithiol, or mixed alcohol/thiol under acidic conditions to generate a cyclic ketal-ester, **2**, whose ester group is then hydrolyzed to yield the final compound, **3**.

15

Example 1: 4-[4-Methyl-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-[1,3]dioxolan-2-yl]-benzoic acid, Compound VI

20

750 mg (2.1 mmol) keto-ester **1** (R = H, from MI Dawson et al; *J Medicinal Chemistry* **1995**, 38, 3368-3383) and 1.6 ml (1.66 g; 21.9 mmol) 1,2-propanediol were dissolved in 40 ml benzene and then 50 mg

5 p-toluenesulfonic acid monohydrate was added. The resulting mixture was heated at reflux under a Dean-Stark trap for 24 hours. The reaction mixture was then cooled to room temperature, washed with 5% aq. NaHCO_3 , water (2x), and brine. The organic layer was dried over MgSO_4 , filtered, and then evaporated *in vacuo* directly onto silica. Flash
10 chromatography through silica gel using 5% EtOAc/hexane afforded 870 mg (99%) product as a colorless, viscous oil. NMR revealed the presence of the desired compound plus its isomer: 4-[5-methyl-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-[1,3]dioxolan-2-yl]-benzoic acid methyl ester. Each isomer exists as a pair of enantiomers.

15

^1H NMR (300 MHz, CDCl_3): 1.24 (d, 12H), 1.37 (dd, 3H), 1.65 (d, 4H), 3.55-3.65 (m, 1H), 3.9 (d, 3H) 4.05-4.35 (m, 2H), 7.15-7.25 (m, 2H), 7.42 (dd, 1H), 7.65 (m, 2H), 8.05 (m, 2H); IR: 2959, 1727, 1277, 1110 cm^{-1} ; MS (ESI): 409 (M+H) $^+$.

20

870 mg (2.1 mmol) 4-[5-methyl-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-[1,3]dioxolan-2-yl]-benzoic acid methyl ester was dissolved in 10 ml MeOH plus 10 ml THF. 8.0 ml 1.0 N NaOH (8.0 mmol) was added and the resulting mixture was stirred at room temperature for 24
25 hours. The reaction mixture was neutralized with 8.0 ml 1.0 N HCl (8.0 mmol), diluted with water, and extracted several times with EtOAc. The combined organic extracts were washed with water (2x), brine, dried over MgSO_4 , filtered, and then evaporated *in vacuo* to give 775 mg (92%) dioxolane-acid as a white solid. The product was recrystallized from
30 hexanes/ CH_2Cl_2 to afford 570 mg of a white solid VI. NMR revealed the presence of the desired compound plus its isomer: 4-[5-methyl-2-(5,5,8,8-

- 5 tetramethyl-5,6,7,8-tetrahydro-napthalen-2-yl)-[1,3]dioxolan-2-yl]-benzoic acid (compound VI). Each isomer exists as a pair of enantiomers.

¹H NMR (300 MHz, CDCl₃): 1.24 (d, 12H, J = 4.8 Hz), 1.36 (dd, 3H, J = 14.7 Hz, 6.0 Hz), 1.65 (d, 4H, J = 3.3 Hz), 3.55-3.65 (m, 1H), 4.05-4.35 (m, 2H), 7.15-
10 7.25 (m, 2H), 7.43 (dd, 1H, J = 7.5 Hz, 2.1 Hz), 7.65 (m, 2H), 8.07 (m, 2H); IR: 2962, 1689, 1423, 1291, 1084, 1020 cm⁻¹; MS (ESI): 393 (M-H)⁺; Anal. calc. for C₂₅H₃₀O₄: C, 76.11; H, 7.66. Found: C, 76.01; H, 7.71.

- 15 Example 2: 4-[5,5-Dimethyl-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-napthalen-2-yl)-[1,3]dioxan-2-yl]-benzoic acid, Compound VIII

750 mg (2.1 mmol) keto-ester 1 (R = H, from MI Dawson et al; *J Medicinal Chemistry* 1995, 38, 3368-3383) and 2.2 g (21.1 mmol) 2,2-dimethyl-1,3-propanediol were dissolved in 40 ml benzene and then 50 mg p-
20 toluenesulfonic acid monohydrate was added. The resulting mixture was heated at reflux under a Dean-Stark trap for 24 hours. The reaction mixture was cooled to room temperature, washed with 5% aq. NaHCO₃ (2x), water, and brine. The organic layer was dried over MgSO₄, filtered, and then evaporated *in vacuo* directly onto silica. Flash chromatography
25 through silica using a 3% to 5% EtOAc/hexane gradient afforded 890 mg (95%) 4-[5,5-dimethyl-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-napthalen-2-yl)-[1,3]dioxan-2-yl]-benzoic acid methyl ester as a colorless oil.

¹H NMR (300 MHz, CDCl₃): 1.0 (d, 6H), 1.21 (s, 6H), 1.22 (s, 6H), 1.63 (s, 4H),
30 3.6 (q, 4H), 3.9 (s, 3H), 7.19 (dd, 1H), 7.21 (s, 1H), 7.4 (d, 1H), 7.6 (d, 2H), 8.0 (d, 2H); IR: 2956, 1727, 1277, 1101 cm⁻¹; MS (ESI): 437 (M+H)⁺.
890 mg (2.0 mmol) 4-[5,5-dimethyl-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-napthalen-2-yl)-[1,3]dioxan-2-yl]-benzoic acid methyl ester was dissolved

5 in 25 ml MeOH plus 25 ml THF. 8.0 ml 1.0 N NaOH (8.0 mmol) was added and the resulting mixture was stirred at room temperature for 24 hours. The reaction mixture was neutralized with 8.0 ml 1.0 N HCl (8.0 mmol), diluted with water, and extracted several times with EtOAc. The combined organic extracts were washed with water (2x), brine, dried over
10 MgSO_4 , filtered, and then evaporated *in vacuo* to give 790 mg (92%) dioxane-acid as a white solid. The product was recrystallized from hexanes/ CH_2Cl_2 to afford 705 mg 4-[5,5-dimethyl-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-[1,3]dioxan-2-yl]-benzoic acid, Compound VIII.

15

^1H NMR (300 MHz, d_6 -DMSO): 0.88 (s, 3H), 0.93 (s, 3H), 1.19 (s, 12H), 1.61 (s, 4H), 3.55 (s, 4H), 7.16 (dd, 2H, $J = 8.3$ Hz, 1.8 Hz), 7.28 (d, 1H, $J = 8.3$ Hz), 7.39 (d, 1H, $J = 1.8$ Hz), 7.58 (d, 2H, $J = 8.5$ Hz), 7.92 (d, 2H, $J = 8.5$ Hz); IR: 2961, 2868, 1685, 1290, 1099 cm^{-1} ; MS (ESI): 423 ($\text{M}+\text{H}$) $^+$; Anal. calc. for
20 $\text{C}_{27}\text{H}_{34}\text{O}_4$: C, 76.75; H, 8.11. Found: C, 76.53; H, 8.22.

Example 3: 4-[2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-[1,3]dithiolan-2-yl]-benzoic acid, Compound X

25

750 mg (2.05 mmol) keto ester 1 ($\text{R} = \text{CH}_3$, from MI Dawson et al; *J Medicinal Chemistry* 1995, 38, 3368-3383) and 0.52 ml (0.58 g; 6.2 mmol) 1,2-ethanedithiol were dissolved in 3 ml CH_2Cl_2 under a dry nitrogen atmosphere. The mixture was cooled to 0-5°C in an ice bath and then 1.0
30 ml (1.15 g; 8.1 mmol) $\text{BF}_3 \cdot \text{Et}_2\text{O}$ was added via syringe. The reaction mixture was warmed to room temperature and stirred for 2 days. The mixture was diluted with EtOAc and then washed with 5% aq. Na_2CO_3 , 5% aq. NaHCO_3 , water, and brine. The organic layer was dried over MgSO_4 ,

5 filtered and evaporated *in vacuo* directly onto silica. Flash chromatography through silica using 5% EtOAc/hexane then afforded 855 mg (94%) white solid, 4-[2-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-[1,3]dithiolan-2-yl]-benzoic acid methyl ester.

10 ¹H NMR (300 MHz, CDCl₃): 1.24 (s, 6H), 1.36 (s, 6H), 1.7 (s, 4H), 1.84 (s, 3H), 3.35-3.55 (m, 4H), 7.0 (s, 1H), 7.58 (d, 2H), 7.93 (d, 2H), 8.1 (s, 1H); IR: 2959, 1724, 1277 cm⁻¹; MS (DCI): 441 (M+H)⁺.

855 mg (1.9 mmol) 4-[2-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-[1,3]dithiolan-2-yl]-benzoic acid methyl ester was dissolved
15 in 10 ml MeOH plus 25 ml THF. 8.0 ml 1.0 N NaOH (8.0 mmol) was added and the resulting mixture was stirred at room temperature for 24 hours. The reaction mixture was neutralized with 8.0 ml 1.0 N HCl (8.0 mmol) and left to stir at room temperature. After about 5 minutes, white
20 crystals came out of solution. The mixture was further cooled in the freezer for 1 hour, and the resulting crystals were filtered off, washed with copious amounts of water, and dried under high vacuum (< 1mm Hg) to give 820 mg (99%) 4-[2-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-[1,3]dithiolan-2-yl]-benzoic acid, Compound X.

25 ¹H NMR (300 MHz, d₆-DMSO): 1.23 (s, 6H), 1.31 (s, 6H), 1.67 (s, 4H), 1.76 (s, 3H), 3.35-3.55 (m, 4H), 7.06 (s, 1H), 7.49 (d, 2H, J = 8.4 Hz), 7.88 (d, 2H, J = 8.4 Hz), 8.05 (s, 1H); IR: 2956, 1718, 1682, 1604, 1259 cm⁻¹; MS (ESI): 425 (M-H)⁺; Anal. calc. for C₂₅H₃₀S₂O₂: C, 70.38; H, 7.09; S, 15.03. Found: C, 69.65; H,
30 7.45; S, 12.83.

5 Example 4, 4-[2-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-[1,3]dithian-2-yl]-benzoic acid, Compound XI

750 mg (2.05 mmol) keto ester 1 (R = CH₃, from MI Dawson et al; *J Medicinal Chemistry* **1995**, 38, 3368-3383) and 0.62 ml (0.67 g; 6.2 mmol)
10 1,3-propanedithiol were dissolved in 3 ml CH₂Cl₂ under a dry nitrogen atmosphere. The mixture was cooled to 0-5°C in an ice bath and then 1.0 ml (1.15 g; 8.1 mmol) BF₃·Et₂O was added via syringe. The reaction mixture was warmed to room temperature and stirred for 2 days. The mixture was diluted with EtOAc and then washed with 5% aq. Na₂CO₃, 5%
15 aq. NaHCO₃, water, and brine. The organic layer was dried over MgSO₄, filtered and evaporated *in vacuo* directly onto silica. Isolation of the less polar fraction by flash chromatography through silica using 5% EtOAc/hexane then afforded 490 mg (52%) 4-[2-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-[1,3]dithian-2-yl]-benzoic acid methyl
20 ester as a colorless, viscous oil.

¹H NMR (300 MHz, CDCl₃): 1.20 (s, 6H), 1.25 (s, 6H), 1.64 (s, 4H), 2.0 (m, 2H), 2.9 (4H, q), 3.9 (s, 3H), 7.2 (s, 2H), 7.55 (s, 1H), 7.9 (d, 2H), 8.05 (d, 2H); IR: 2926, 1720, 1282, 1113 cm⁻¹; MS (DCI): 441 (M+H)⁺.

25

490 mg (1.1 mmol) 4-[2-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-[1,3]dithian-2-yl]-benzoic acid methyl ester was dissolved in 10 ml MeOH plus 25 ml THF. 5.0 ml 1.0 N NaOH (5.0 mmol) was added and the resulting mixture was stirred at room temperature for 24
30 hours. The reaction mixture was neutralized with 5.0 ml 1.0 N HCl (5.0 mmol), diluted with water, and extracted several times with EtOAc. The combined organic extracts were washed with water (2x), brine, dried over MgSO₄, filtered, and then evaporated *in vacuo* to give 465 mg (98%)

5 dithiane-acid as a white solid. The product was recrystallized from hexanes/ CH_2Cl_2 to afford 300 mg white solid, 4-[2-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-yl)-[1,3]dithian-2-yl]-benzoic acid, Compound XI.

10 ^1H NMR (300 MHz, d_6 -DMSO): 1.22 (d, 12H), 1.61 (s, 4H), 1.95 (br s, 5H), 2.75-2.95 (m, 4H), 7.05 (s, 1H), 7.6 (d, 2H, $J = 8.4$ Hz), 7.78 (s, 1H), 7.95 (d, 2H, $J = 8.4$ Hz); IR: 2960, 2918, 1688, 1422, 1287 cm^{-1} ; MS (ESI): 439 (M-H) $^+$; Anal. calc. for $\text{C}_{26}\text{H}_{32}\text{S}_2\text{O}_2$: C, 70.87; H, 7.32; S, 14.55. Found: C, 69.89; H, 7.29; S, 13.88.

15

Biological Activity

For prevention of surgical adhesions, the retinoid derivative of the present invention may be administered by a variety of systemic and local
20 methods. The compounds may be administered orally, by intravenous injection, by intramuscular injection or by intracavity instillation. The general range of doses will depend on the efficacy of the compound and the intended route but is expected to be from about 0.1 mg/kg to about 100 mg/kg with a preferred range of about 1 to about 25 mg/kg.

25

The term of administration may vary depending upon a number of factors which would be readily appreciated by those skilled in the art. In general, administration of a retinoid derivative of the present invention should be effected 12-48 hours prior to the time of surgery and for at least
30 24-48 hours post-surgery. In general the retinoid derivative may be

- 5 administered from 72 hours prior to surgery and continue up to 2 weeks after surgery and preferably for a period 12 hours prior to surgery and continuing 48 hours after surgery.

- For intracavity administration the retinoid derivative of the
- 10 present invention can be administered in a suitable vehicle such as 5% dextrose in water adjusted to a pH to assure complete salt formation. However it is understood that many other single dose delivery systems could be contemplated by those skilled in the art including microcapsules, microspheres, liposomes, viscous instillates, and polymeric delivery
- 15 materials.

- The method of the present invention may be used in the prevention of surgical adhesions in any animal (mammalian) host, but is particularly preferred for use in human hosts.

20

- Models of peritoneal adhesions induced by surgical trauma have been used to predict the clinical activity of a number of marketed anti-adhesion barrier devices. One such model is the trauma-induced caecal adhesion model in rats. Representative retinoid derivatives of the
- 25 present invention as disclosed in the table above were used in this model to demonstrate efficacy.

5 Adult female Wistar rats were used in our studies. The trauma
induction was carried out using aseptic conditions in animals
anesthetized with a mixture of Ketamine (100 mg/kg) and Rompun (10
mg/kg) given IP. A 2 cm midline abdominal incision was made and the
caecum was exteriorized. Both sides of the caecum were abraded with a
10 dry gauze until there was evidence of punctate bleeding. After replacing
the organ in the abdominal cavity, the incision was closed. Trauma to the
caecum produces fibrous scar tissue or adhesions to adjacent organs,
peritoneal wall, or the omentum. Animals were treated with test
compound orally or by intravenous injection or intra-abdominally by
15 direct instillation into the peritoneal cavity. Oral treatments were
administered once daily for up to 7 days. Intra-abdominal treatments
were applied once post-trauma and just prior to wound closure.

On the seventh postoperative day, the animals were sacrificed and
20 the peritoneal cavity was exposed and examined for adhesions.
Three criteria that were used to evaluate the adhesions are: severity of the
adhesions, extent or area of the caecum involved with adhesions and the
number of adhesions formed in each animal. Statistical analysis of the
data was performed using students' T test. The following scoring system
25 was used:

5	<u>Grade</u>		<u>Description</u>
	0	=	no adhesions;
10	1.0	=	easily separable, filmy, non-vascularized adhesions covering 25% of the caecum;
	2.0	=	dense adhesions separated by blunt dissection and involving 50% of the caecum;
15	3.0	=	dense, fibrous, vascularized adhesions requiring sharp dissection and covering 75% of the caecum;
20	4.0	=	severe, dense, vascularized adhesions unable to separate without tearing the adjacent membranes and covering greater than 75% of the caecum.

Data on the test compounds are given in the following tables:

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30

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**Dose Dependent Effect of Orally Dosed Test Compound I on
Surgical Adhesions in Rat Cecum**

Compound	Dose	Mean number of adhesions/rat +/-SD	Mean Adhesion Severity/Rat +/- SD
Vehicle		13 ± 3.1	33 ± 10.3
Compound I	15 mg/kg	6.8 ± 1.3	14.2 ± 4.14*
Compound I	30 mg/kg	5.4 ± 2.3	12.2 ± 4.32

*p = 0.04 at N=5/group

10

**Dose Dependent Effect of Orally Dosed Test Compound II
on Surgical Adhesions in Rat Cecum**

Compound	Dose mg/kg (orally)	Mean Number of Adhesions/rat ± S.D. (% Inhibition)	Mean Adhesion Severity/Rat ± S.D. (% Inhibition)
Vehicle		14.3 ± 3.6	29 ± 9.8
Compound II	1	8.4 ± 1.7	18.3 ± 4.5
Compound II	3	5.9 ± 2.7*	12.2 ± 5.6*
Compound II	10	3.9 ± 1.1*	8.0 ± 2.1*

*p < 0.05

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**Effect of Orally Dosed Test Compounds
on Surgical Adhesions in Rat Cecum**

Compound	Dose mg/kg (orally)	Mean Number of Adhesions/rat $\pm$ S.D. (% Inhibition)	Mean Adhesion Severity/Rat $\pm$ S.D. (% Inhibition)
Vehicle		7.5 $\pm$ 2	15.3 $\pm$ 4.9
Compound VI	10	Not active	Not active
Compound VII	10	3.1 $\pm$ 1.2 (58)*	6.7 $\pm$ 2.4 (56)*
Compound VIII	10	4.1 $\pm$ 1.7 (37)	8.7 $\pm$ 4.2 (43)
Compound V	10	4.7 $\pm$ 1.4 (37)	9.9 $\pm$ 3.4 (36)

*p < 0.05

10

**Effect of Orally Dosed Test Compounds
on Surgical Adhesions in Rat Cecum**

15

Compound	Dose mg/kg (orally)	Mean Number of Adhesions/rat $\pm$ S.D. (% Inhibition)	Mean Adhesion Severity/Rat $\pm$ S.D. (% Inhibition)
Vehicle		8.9 $\pm$ 3.2	17.7 $\pm$ 6.2
Compound IV	10	2.9 $\pm$ 0.7 (68)*	5.7 $\pm$ 2.3 (68)*
Compound X	10	6.7 $\pm$ 2.9 (24)	13.1 $\pm$ 5.0 (26)
Compound III	10	4.3 $\pm$ 1.5 (52)*	8.7 $\pm$ 3.6 (51)*
Compound XI	10	4.3 $\pm$ 2.1 (52)*	8.6 $\pm$ 4.0 (52)*

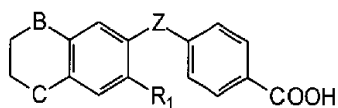
*p < 0.05

As demonstrated above, the retinoid derivatives of formula I are
useful in the prevention of surgical adhesions.

20

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A method for the minimization or prevention of post-surgical adhesion formation between organ surfaces comprising administering to an animal host an effective amount of a retinoid derivative to a site of surgical activity on an organ surface for a period of time sufficient to permit tissue repair, said retinoid derivative being a compound of the formula



- 10 wherein Z is $\text{—}\overset{\text{Q}}{\underset{\text{||}}{\text{C}}}\text{—}$ or  in which Q, X and Y are each independently O, S or CH₂;

A is $\text{—}(\text{CR}_2)_n\text{—}$ wherein n is 1-3;

B and C are each independently O, S, CH₂ or C(CH₃)₂;

R₁ is hydrogen or (C₁-C₆) alkyl; and

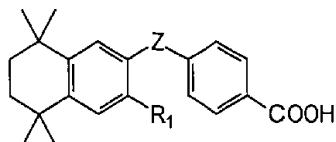
- 15 R₂ is hydrogen or CH₃; or a pharmaceutically acceptable salt thereof;

with the proviso that when Z is , R₁ cannot be (C₁-C₆)alkyl.

2. A method for the minimization or prevention of post-surgical adhesion formation between organ surfaces comprising administering to an animal host an effective amount of a retinoid derivative to a site of surgical activity on an organ



surface for a period of time sufficient to permit tissue repair, said retinoid derivative being a compound of the formula



5 wherein Z is $\text{—}\overset{\text{Q}}{\underset{\text{||}}{\text{C}}}\text{—}$ or  in which Q, X and Y are each independently O, S or CH₂;

A is $\text{—}(\text{CR}_2)_n\text{—}$ wherein n is 1-3;

R₁ is hydrogen or (C₁-C₆) alkyl; and

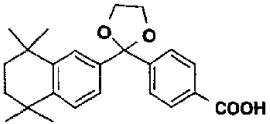
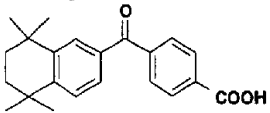
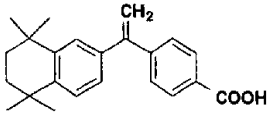
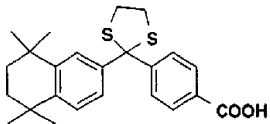
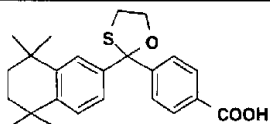
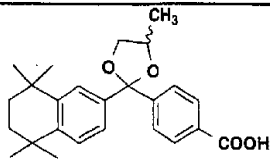
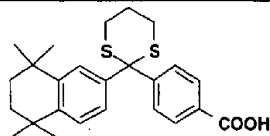
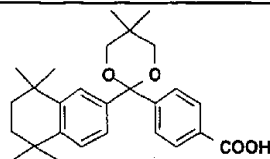
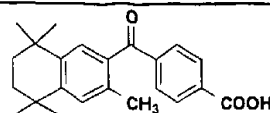
R₂ is hydrogen or CH₃; or a pharmaceutically acceptable salt thereof;

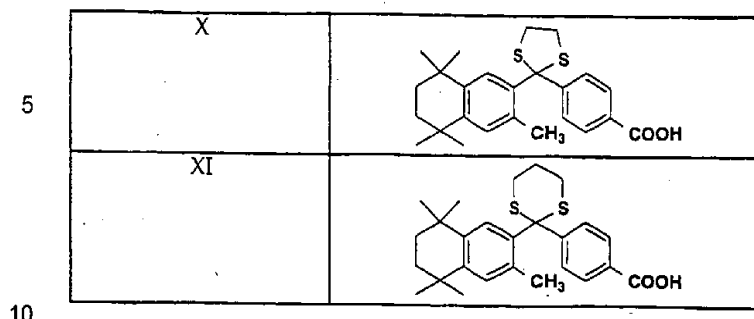
10 with the proviso that when Z is , R₁ cannot be (C₁-C₆)alkyl.

3. A method for the minimization or prevention of post-surgical adhesion formation between organ surfaces comprising administering to an animal host an effective amount of a retinoid derivative to a site of surgical activity on an organ
15 surface for a period of time sufficient to permit tissue repair, said retinoid derivative being a compound of the formula



5

COMPOUND	STRUCTURE
I	
II	
III	
IV	
V	
VI	
VII	
VIII	
IX	



or a pharmaceutically acceptable salt thereof.

4. Use of a retinoid derivative being a compound of the formula I as defined in claim 1 in the manufacture of a medicament for use in minimizing or preventing post-surgical adhesion formation between organ surfaces by administering to an animal host an effective amount of the medicament to a site of surgical activity or an organ surface for a period of time sufficient to permit tissue repair.

5. Use of a retinoid derivative being a compound of the formula IA as defined in claim 2 in the manufacture of a medicament for use in minimizing or preventing post-surgical adhesion formation between organ surfaces by administering to an animal host an effective amount of the medicament to a site of surgical activity or an organ surface for a period of time sufficient to permit tissue repair.

6. Use of a retinoid derivative as defined in claim 3 in the manufacture of a medicament for use in minimizing or preventing post-surgical adhesion formation between organ surfaces by administering to an animal host an effective amount of the medicament to a site of surgical activity or an organ surface for a period of time sufficient to permit tissue repair.

DATED: 15 June 2000
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 BRISTOL-MYERS SQUIBB COMPANY

David B Fitzpatrick

