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(71) Applicant(s)
SmithKline Beecham Corporation

(72) Inventor(s)
Willette, Robert N

(74) Agent/Attorney
Davies Collison Cave, Level 15 1 Nicholson Street, MELBOURNE, VIC, 3000

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(71) Applicant *(for all designated States except US)*: **SMITHKLINE BEECHAM CORPORATION** [US/US]; One Franklin Plaza, Philadelphia, PA 19103 (US).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **WILLETTE, Robert, N.** [US/US]; 709 Swedeland Road, King of Prussia, PA 19406 (US).

(74) Agents: **MCCARTHY, Mary, E.** et al.; SmithKline Beecham Corporation, Corporate Intellectual Property, UW2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939 (US).

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(54) Title: METHOD OF INHIBITING ADHESION FORMATION

(57) Abstract: This invention relates to the use of a vitronectin receptor antagonist to inhibit adhesion formation.

Method of Inhibiting Adhesion Formation

Field of the Invention

This invention relates to the use of antagonists of the vitronectin receptor to inhibit adhesion formation.

Background of the Invention

Integrins are a superfamily of cell adhesion receptors that couple intracellular cytoskeletal elements with extracellular matrix molecules. These cell surface adhesion receptors include $\alpha_v\beta_3$ (the vitronectin receptor). The vitronectin receptor $\alpha_v\beta_3$ is expressed on a number of cells, including endothelial, smooth muscle, osteoclast, and tumor cells, and, thus, it has a variety of functions. The $\alpha_v\beta_3$ receptor expressed on the membrane of osteoclast cells mediates the adhesion of osteoclasts to the bone matrix, a key step in the bone resorption process. Ross, et al., *J. Biol. Chem.*, **1987**, *262*, 7703. The $\alpha_v\beta_3$ receptor expressed on human aortic smooth muscle cells mediates their migration into neointima, a process which can lead to restenosis after percutaneous coronary angioplasty. Brown, et al., *Cardiovascular Res.*, **1994**, *28*, 1815. Additionally, Okada, et al., *Am. J. Pathol.*, **1996**, *149(1)*, 37 suggest that $\alpha_v\beta_3$ plays a role in vascular integrity and remodeling following focal ischemia within an infarcted area.

Surprisingly, it has been found that vitronectin receptor antagonists would be useful in inhibiting adhesion formation. In particular, the compounds of this invention are useful in the treatment of post-surgical adhesions.

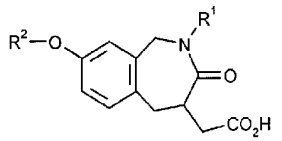
Summary of the Invention

The present invention provides a new method of inhibiting adhesion formation in a mammal, in particular a man, which comprises administering to a subject in need thereof an effective amount of a vitronectin receptor antagonist.

Detailed Description of the Invention

The present invention is a therapeutic method for inhibiting adhesion formation and a method for treating post-surgical adhesions. The method utilizes a class of antagonists which have been prepared and evaluated as effective vitronectin receptor antagonists. Examples of suitable vitronectin receptor antagonists include, but are not limited to, the following:

Benzazepine ethers of the formula (I), which are described in PCT Application No. PCT/US97/18001, filed October 1, 1997, published as WO 98/14192 on April 9, 1998:



(I)

wherein:

R^1 is R^7, or A-C_{0-4}alkyl, A-C_{2-4}alkenyl, A-C_{2-4}alkynyl, A-C_{3-4}oxoalkenyl, A-C_{3-4}oxoalkynyl, A-C_{1-4}aminoalkyl, A-C_{3-4}aminoalkenyl, A-C_{3-4}aminoalkynyl, optionally substituted by any accessible combination of one or more of R^{10} or R^7;

A is H, C_{3-6}cycloalkyl, Het or Ar;

R^7 is -COR^8, -$COCR'_2R^9$, -$C(S)R^8$, -$S(O)_mOR'$, -$S(O)_mNR'R''$, -$PO(OR')$, -$PO(OR')_2$, -NO_2, or tetrazolyl;

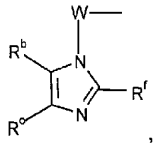
each R^8 independently is -OR', -NR'R", -$NR'SO_2R'$, -NR'OR', or -$OCR'_2CO(O)R'$;

R^9 is -OR', -CN, -$S(O)_rR'$, -$S(O)_mNR'_2$, -C(O)R', C(O)NR'_2, or -CO_2R';

R^{10} is H, halo, -OR^{11}, -CN, -$NR'R^{11}$, -NO_2, -CF_3, $CF_3S(O)_r$-, -CO_2R', -$CONR'_2$, A-C_{0-6}alkyl-, A-C_{1-6}oxoalkyl-, A-C_{2-6}alkenyl-, A-C_{2-6}alkynyl-, A-C_{0-6}alkyloxy-, A-C_{0-6}alkylamino- or A-C_{0-6}alkyl-$S(O)_r$-;

R^{11} is R', -C(O)R', -C(O)NR'_2, -C(O)OR', -$S(O)_mR'$, or -$S(O)_mNR'_2$;

R^2 is



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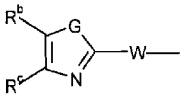

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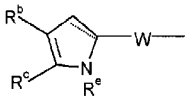

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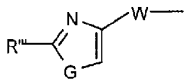

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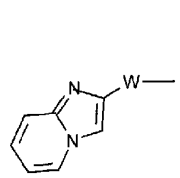
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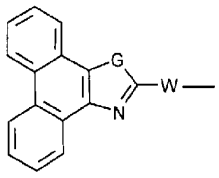
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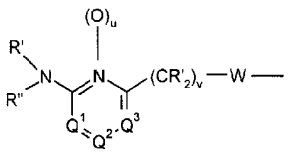
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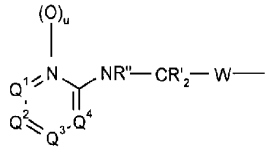
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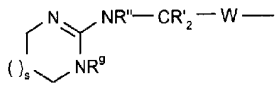

;

W is -$(CHR^g)_a$-U- $(CHR^g)_b$-;

U is absent or CO, CR^g_2, $C(=CR^g_2)$, $S(O)_k$, O, NR^g, CR^gOR^g, $CR^g(OR^k)CR^g_2$, $CR^g_2CR^g(OR^k)$, $C(O)CR^g_2$, $CR^g_2C(O)$, $CONR^i$, NR^iCO, OC(O), C(O)O, C(S)O, OC(S), C(S)NR^g, $NR^gC(S)$, $S(O)_2NR^g$, $NR^gS(O)_2$ N=N, NR^gNR^g, $NR^gCR^g_2$, $CR^g_2NR^g$, CR^g_2O, OCR^g_2, C≡C or CR^g=CR^g;

G is NR^e, S or O;

R^g is H, C_{1-6}alkyl, Het-C_{0-6}alkyl, C_{3-7}cycloalkyl-C_{0-6}alkyl or Ar-C_{0-6}alkyl;

R^k is R^g, -C(O)R^g, or -C(O)OR^f;

R^i is H, C_{1-6}alkyl, Het-C_{0-6}alkyl, C_{3-7}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, or C_{1-6}alkyl substituted by one to three groups chosen from halogen, CN, NR^g_2, OR^g, SR^g, CO_2R^g, and $CON(R^g)_2$;

R^f is H, C_{1-6}alkyl or Ar-C_{0-6}alkyl;

R^e is H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, C_{3-7}cycloalkyl-C_{0-6}alkyl, or $(CH_2)_kCO_2R^g$;

R^b and R^c are independently selected from H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, or C_{3-6}cycloalkyl-C_{0-6}alkyl, halogen, CF_3, OR^f, $S(O)_kR^f$, COR^f, NO_2, $N(R^f)_2$, $CO(NR^f)_2$, $CH_2N(R^f)_2$, or R^b and R^c are joined together to form a five or six membered aromatic or non-aromatic carbocyclic or heterocyclic ring, optionally substituted by up to three substituents chosen from halogen, CF_3, C_{1-4}alkyl, OR^f, $S(O)_kR^f$, COR^f, CO_2R^f, OH, NO_2, $N(R^f)_2$, $CO(NR^f)_2$, and $CH_2N(R^f)_2$; or methylenedioxy;

Q^1, Q^2, Q^3 and Q^4 are independently N or C-R^y, provided that no more than one of Q^1, Q^2, Q^3 and Q^4 is N;

R' is H, C_{1-6}alkyl, Ar-C_{0-6}alkyl or C_{3-6}cycloalkyl-C_{0-6}alkyl;

R" is R', -C(O)R' or -C(O)OR';

R"' is H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, or C_{3-6}cycloalkyl-C_{0-6}alkyl, halogen, CF_3, OR^f, $S(O)_kR^f$, COR^f, NO_2, $N(R^f)_2$, $CO(NR^f)_2$, $CH_2N(R^f)_2$;

R^y is H, halo, $-OR^g$, $-SR^g$, -CN, $-NR^gR^k$, $-NO_2$, $-CF_3$, $CF_3S(O)_r$-, $-CO_2R^g$, $-COR^g$ or $-CONR^g_2$, or C_{1-6}alkyl optionally substituted by halo, $-OR^g$, $-SR^g$, -CN, $-NR^gR"$, $-NO_2$, $-CF_3$, $R'S(O)_r$-, $-CO_2R^g$, $-COR^g$ or $-CONR^g_2$;

a is 0, 1 or 2;

b is 0, 1 or 2;

k is 0, 1 or 2;

m is 1 or 2;

r is 0, 1 or 2;

s is 0, 1 or 2;

u is 0 or 1; and

v is 0 or 1;

or a pharmaceutically acceptable salt thereof.

Preferred formula (I) compounds used in the method of this invention are (S)-3-oxo-8-[3-(pyridin-2-ylamino)-1-propyloxy]-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid and (S)-8-[2-[6-(methylamino)pyridin-2-yl]-1-ethoxy]-3-oxo-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid, or pharmaceutically acceptable salts thereof.

Additional examples of vitronectin receptor antagonists used in the method of this invention include those antagonists described in the following: PCT Application No. PCT/US95/08306, filed June 29, 1995, published as WO 96/00730 on January 11, 1996; PCT Application No. PCT/US95/08146, filed June 29, 1995, published as WO 96/00574 on January 11, 1996; PCT Application No. PCT/US96/11108, filed June 28, 1996, published as WO 97/01540 on January 16, 1997; PCT Application No. PCT/US96/20748, filed December 20, 1996, published as WO 97/24119 on July 10, 1997; PCT Application No. PCT/US96/20744, filed December 20, 1996, published as WO 97/24122 on July 10, 1997; PCT Application No. PCT/US96/20327, filed December 20, 1996, published as WO 97/24124 on July 10, 1997; PCT Application No. PCT/US98/00490, filed January 8, 1998, published as WO 98/30542 on July 16, 1998; PCT Application No. PCT/US98/19466, filed September 18, 1998, published as WO 99/15508 on April 1, 1999; and PCT Application No. PCT/US99/28662, filed December 3, 1999, published as WO

00/33838 on June 15, 2000. The preferred compound in PCT Application WO 00/33838 is (S)-10,11-dihydro-3-[2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)-1-ethoxy]-5H-dibenzo[a,d]cycloheptene-10-acetic acid. This compound is useful in the method of this invention.

The above list of vitronectin receptor antagonists for use in the method of the present invention were taken from published patent applications. Reference should be made to each patent application for its full disclosure, including the methods of preparing the disclosed compounds, the entire disclosure of each patent application being incorporated herein by reference.

In accordance with the present invention, it has been found that the administration of a vitronectin receptor antagonist to a surgical patient inhibits or ameliorates post-operative adhesion formation.

Surgical intervention involves wounding the patient in order to effect a cure. One unwanted result from surgery is post-operative adhesion formation. The term "adhesion" as used herein refers to conglutination, the process of adhering or uniting of two surfaces or parts. It has been reported that adhesion development is a major source of post-operative morbidity and mortality.

In the therapeutic use for the inhibition of adhesion formation, the vitronectin receptor antagonist is incorporated into standard pharmaceutical compositions. It can be administered orally, parenterally, rectally, topically or transdermally.

Pharmaceutical compositions of the vitronectin receptor antagonist may be formulated as solutions or lyophilized powders for parenteral administration. Powders may be reconstituted by addition of a suitable diluent or other pharmaceutically acceptable carrier prior to use. The liquid formulation may be a buffered, isotonic, aqueous solution. Examples of suitable diluents are normal isotonic saline solution, standard 5% dextrose in water or buffered sodium or ammonium acetate solution. Such formulation is especially suitable for parenteral administration, but may also be used for oral administration or contained in a metered dose inhaler or nebulizer for insufflation. It may be desirable to add excipients such as polyvinylpyrrolidone, gelatin, hydroxy cellulose, acacia, polyethylene glycol, mannitol, sodium chloride or sodium citrate.

Alternately, the vitronectin receptor antagonist may be encapsulated, tableted or prepared in a emulsion or syrup for oral administration. Pharmaceutically acceptable solid or liquid carriers may be added to enhance or stabilize the composition, or to facilitate preparation of the composition. Solid carriers include starch, lactose, calcium sulfate dihydrate, terra alba, magnesium stearate or stearic acid, talc, pectin, acacia, agar or gelatin. Liquid carriers include syrup, peanut oil,

olive oil, saline and water. The carrier may also include a sustained release material such as glyceryl monostearate or glyceryl distearatc, alone or with a wax. The amount of solid carrier varies but, preferably, will be between about 20 mg to about 1 g per dosage unit. The pharmaceutical preparations are made following the conventional techniques of pharmacy involving milling, mixing, granulating, and compressing, when necessary, for tablet forms; or milling, mixing and filling for hard gelatin capsule forms. When a liquid carrier is used, the preparation will be in the form of a syrup, clixir, emulsion or an aqueous or non-aqueous suspension. Such a liquid formulation may be administered directly p.o. or filled into a soft gelatin capsule.

For rectal administration, the compounds of this invention may also be combined with excipients such as cocoa butter, glycerin, gelatin or polyethylene glycols and molded into a suppository.

The compound is administered either orally or parenterally to the patient, in a manner such that the concentration of drug is sufficient to be effective. The pharmaceutical composition containing the compound is administered at an oral dose of between about 0.1 to about 50 mg/kg in a manner consistent with the condition of the patient. Preferably the oral dose would be about 0.5 to about 20 mg/kg. For acute therapy, parenteral administration is preferred. An intravenous infusion of the peptide in 5% dextrose in water or normal saline, or a similar formulation with suitable excipients, is most effective, although an intramuscular bolus injection is also useful. Typically, the parenteral dose will be about 0.01 to about 100 mg/kg; preferably between 0.1 and 20 mg/kg. The compounds are administered one to four times daily at a level to achieve a total daily dose of about 0.4 to about 400 mg/kg/day. The precise level and method by which the compounds are administered is readily determined by one routinely skilled in the art by comparing the blood level of the agent to the concentration required to have a therapeutic effect.

No unacceptable toxicological effects are expected when eprosartan is administered in accordance with the present invention.

Materials and Methods

The compounds of the instant invention are tested in known models of adhesion formation. These test systems include a rabbit sidewall model of adhesion formation as described in Rogers, et al., J. Invest. Surg., 9:388-391 (1996) and Rodgers, et al., Fertility and Surgery, 69(3):403-408 (1998); a rat model for adhesion formation as described in Harris, et al., Surgery, 117:663-669 (1995); and

a rabbit animal model used to examine laparoscopic adhesion prevention. The rabbit uterine horn model may also be used to test the use of the instant vitronectin inhibiting compounds as inhibitors of adhesion formation. The experimental details and results using this model are detailed below.

PROTOCOL:

Animals: New Zealand White rabbits, 2.4-2.7 kg, were purchased and quarantined for at least 2 days prior to use. The rabbits were randomized into appropriate control and treatment groups (see experimental designs below). The rabbits were housed on a 12:12 light:dark cycle with food and water available ad libitum. Each treatment group in all studies contained 8-10 animals.

Materials: The sutures that were used to close the peritoneum and skin were 4-0 Vicryl suture (Ethicon, Somerville, NJ). COMPOUND 1 is (S)-3-oxo-8-[3-(pyridin-2-ylamino)-1-propyloxy]-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid.

Adhesion Model: The animals that received COMPOUND 1 or vehicle according to the experimental design (below). The rabbits that received placebo at surgery received two doses of vehicle orally. Rabbits were anesthetized with a mixture of 55 mg/kg ketamine hydrochloride and 5 mg/kg Rompum intramuscularly. Following preparation for sterile surgery, a midline laparotomy was performed. The uterine horns were exteriorized and traumatized by abrasion of the serosal surface with gauze until punctate bleeding developed. Ischemia of both uterine horns was induced by removal of the collateral blood supply. The remaining blood supply to the uterine horns was the ascending branches of the utero-vaginal arterial supply of the myometrium. The midline muscle and skin incision were closed.

After 7 or 14 days, the rabbits were terminated and adhesions were scored on a site and rabbit basis. Specifically, the percentage of the area of the horns adherent to various organs was determined. In addition, the tenacity of the adhesions was scored using the following system:

0 = No Adhesions
1 = mild, easily dissectable adhesions
2 = moderate adhesions; non-dissectable, does not tear the organ
3 = dense adhesions; non-dissectable, tears organ when removed

An overall score which took into account all of the above data was given to each rabbit. The following scoring system was used:

0 No adhesions

0.5+ Light, filmy pelvic adhesions involving only one organ, typically only 1 or 2 small adhesions

1.0+ Light, filmy adhesions, not extensive although slightly more extensive than 0.5

1.5+ Adhesions slightly tougher and more extensive than a 1 rating

2.0+ Tougher adhesions, a little more extensive, uterine horns usually have adhesions to both bowel and bladder

2.5+ Same as 2, except the adhesions are usually not filmy at any site and more extensive

3.0+ Tougher adhesions than 2, more extensive, both horns are attached to the bowel and bladder, some movement of the uterus possible

3.5+ Same as 3, but adhesions slightly more extensive and tougher

4.0+ Severe adhesions, both horns attached to the bowel and bladder, unable to move the uterus without tearing the adhesions

The rabbits were scored by two independent observers that were blinded to the prior treatment of the animal. If there was disagreement as to the score to be assigned to an individual animal, the higher score was given.

Statistical Analysis: The tenacity and overall scores were analyzed by rank order analysis and analysis of variance on the ranks. The percentage area of the horns involved to the various organs were compared by Student's t test.

Experimental designs:

Postoperatively received two loading doses of 60 mg/kg COMPOUND 1 orally prior to surgery. At the end of the procedure, the animals received either nothing (surgical control), or 12 ml of placebo (10% CMC) or one of two doses (1 mg/ml or 0.1 mg/ml) of COMPOUND 1 at the site of surgical injury.

Local delivery study: via osmotic minipump - initial validation study. Dose: 0.1 and 1.0 mM (10 ul/hr for 7 days). COMPOUND 1 was administered locally at the site of uterine injury by an Alzet miniosmotic pump . A polyethylene catheter (Clay Adams polyethylene tubing PE-60 ID 0.76 mm (0.030") OD 1.22 mm (0.048")) was introduced into the peritoneal cavity and sutured to the sidewall with 5-0 Ethilon immediately following uterine injury. The catheter was then attached to the pump and the midline muscle incision was be closed around the catheter. The pump was filled with 0.1 or 1 mM COMPOUND 1 (delivered at 10 µl/hour for 7 days) and placed in the subcutaneous space. The vehicle used to administer the drug was 8% cyclodextrin for the high dose and 0.8% for the low dose. Eight percent cyclodextrin was used in

minipumps implanted into the control animals. Animal were sacrificed on day 7 for adhesion assessment.

Oral administration study: Prior to surgery, the rabbits received two loading doses of COMPOUND 1 (60 mg/kg, 5 mg/ml in 0.1 N NaOH) orally 24 and 48 hours prior to surgery. Immediately before surgery, the rabbits received one additional 60 mg/kg dose. The animals then received 60 mg/kg COMPOUND 1 daily until necropsy on day 14 after uterine surgery. Controls rabbits received vehicle by the same schedule.

Oral + local study: Two loading doses of COMPOUND 1 (60 mg/kg, po) were administered orally prior to surgery. Following surgery 12 ml of a viscous solution containing SB 267268 (1 or 0.1 mg/ml in 10% CMC) was introduced at the surgical site prior to closing the wound. The rabbits that received placebo at surgery received two doses of vehicle orally followed by 12 ml of placebo (10% CMC) at the surgical site. Surgical controls received no treatments before or after the surgical procedure. Animals were sacrificed at 7 day and 14 days

RESULTS:

SAMPLE DATA SET TAKEN FROM THE ORAL + GEL COMPOUND 1 STUDY.

Table 1. Data from Control Animals, 2 Week Necropsy Time

% Horn Involved

Right Horn				Left Horn				
Bowel	Bladder	Itself	Left	Bowel	Bladder	Itself	Right	Overall
40(2)	10(1)	30(2)	30(2)	40(2)	10(1)	50(3)	30(2)	3.5
-	50(2)	40(2)	50(2)	-	50(2)	30(2)	50(2)	3.0
-	40(3)	50(2)	50(2)	-	40(3)	50(2)	50(2)	3.5
30(1)	70(1)	30(1)	30(1)	30(1)	70(1)	30(1)	30(1)	3.0
40(1)	-	50(2)	20(1)	40(1)	-	50(2)	20(1)	2.5
40(2)	-	30(1)	20(1)	40(2)	-	40(1)	20(1)	2.5
30(1)	40(1)	30(1)	30(2)	30(1)	40(1)	30(1)	30(2)	3.0
10(1)	30(1)	30(1)	40(2)	10(1)	30(1)	50(1)	40(2)	2.5
40(2)	30(1)	40(1)	50(1)	40(2)	30(1)	40(1)	50(1)	3.0
20(1)	30(1)	40(2)	50(2)	20(1)	30(1)	60(1)	50(2)	3.0
25.0±5.2	30.0±7.0	37.0±2.6	37.0±4.0	25.0±5.2	30.0±7.0	43.0 ±3.4	37.0±4.0	66.5±2.8

Table 2. Data from Placebo Control Animals, 2 Week Necropsy Time

% Horn Involved								
Right Horn				Left Horn				
Bowel	Bladder	Itself	Left	Bowel	Bladder	Itself	Right	Overall
30(2)	50(1)	40(2)	40(2)	30(2)	50(1)	40(3)	40(2)	3.5
30(1)	10(1)	40(2)	30(1)	30(1)	10(1)	20(1)	30(1)	2.0
-	30(1)	10(1)	30(1)	-	30(1)	-	30(1)	1.5
-	20(1)	-	10(1)	-	20(1)	20(1)	10(1)	1.5
40(1)	40(1)	-	40(2)	40(1)	40(1)	40(2)	40(2)	3.0
-	50(1)	10(1)	30(1)	-	50(1)	30(1)	30(1)	2.0
30(1)	20(1)	30(1)	40(2)	30(1)	20(1)	10(1)	40(2)	2.5
40(1)	10(1)	-	30(1)	40(1)	10(1)	10(1)	30(1)	2.0
-	-	30(1)	30(1)	-	-	40(1)	30(1)	1.5
-	40(1)	40(1)	40(1)	-	40(1)	-	40(1)	2.0
17.0±5.8	27.0±5.6	20.0±5.6	32.0±2.9	17.0±5.8	27.0±5.6	21.0 ±5.0	32.0±2.9	45.2±5.9

Table 3. Data from Treated Animals, 1 mg/ml COMPOUND 1, 2 Week Necropsy Time

% Horn Involved								
Right Horn				Left Horn				
Bowel	Bladder	Itself	Left	Bowel	Bladder	Itself	Right	Overall
10(1)	10(1)	-	-	-	-	-	-	0.5
30(1)	-	40(1)	-	30(1)	-	40(1)	-	2.0
-	-	30(1)	-	-	-	30(1)	-	1.0
10(1)	-	20(1)	-	-	-	20(1)	-	1.0
30(2)	-	30(2)	30(2)	30(2)	-	30(2)	30(2)	2.5
-	-	-	-	30(1)	-	10(1)	-	1.0
10(1)	10(1)	10(1)	-	10(1)	-	-	-	1.0
-	-	-	-	40(2)	20(2)	10(2)	-	1.5
10(1)	20(1)	-	-	-	20(1)	20(1)	-	1.0
30(1)	-	-	20(1)	30(1)	-	20(1)	20(1)	1.5
13.0±4.0	4.0±2.2	13.0±5.0	5.0±3.4	17.0±5.2	4.0±2.7	18.0 ±4.2	5.0±3.4	21.2±5.5

Table 4. Data from Treated Animals, 0.1 mg/ml COMPOUND 1, 2 Week Necropsy Time

% Horn Involved								
Right Horn				Left Horn				
Bowel	Bladder	Itself	Left	Bowel	Bladder	Itself	Right	Overall
20(1)	50(1)	30(2)	10(1)	20(1)	50(1)	30(2)	10(1)	2.5
-	-	-	40(1)	-	-	20(1)	40(1)	1.5
10(1)	-	30(1)	30(2)	10(1)	-	30(1)	30(2)	2.5
-	-	40(1)	30(1)	-	-	40(1)	30(1)	1.5
-	10(1)	30(2)	30(2)	10(1)	10(1)	30(2)	30(2)	2.0
10(1)	10(1)	10(1)	40(1)	-	10(1)	-	40(1)	2.0
20(1)	-	-	-	20(1)	-	20(1)	-	1.0
-	10(1)	-	-	-	-	10(1)	-	0.5
40(1)	-	-	20(1)	40(1)	-	20(1)	20(1)	1.5
-	10(1)	20(1)	10(1)	-	-	20(1)	10(1)	1.0
10.0±4.2	9.0±4.8	16.0±5.0	21.0±4.8	10.0±4.2	7.0±5.0	22.0 ±3.6	21.0±4.8	30.2±6.2

Table 5. Data from Control Animals, 1 Week Necropsy Time

% Horn Involved								
Right Horn				Left Horn				
Bowel	Bladder	Itself	Left	Bowel	Bladder	Itself	Right	Overall
50(1)	30(1)	30(1)	40(1)	50(1)	30(1)	30(1)	40(1)	3.0
50(1)	30(2)	60(1)	50(1)	50(1)	30(2)	60(1)	50(1)	3.5
40(1)	20(1)	40(1)	50(1)	40(1)	20(1)	40(1)	50(1)	3.0
50(2)	10(1)	40(1)	30(2)	50(2)	10(1)	30(2)	30(2)	3.5
20(1)	30(1)	30(1)	40(1)	20(1)	30(1)	40(2)	40(1)	3.0
30(1)	40(2)	40(1)	40(1)	30(1)	40(2)	40(1)	40(1)	3.0
30(1)	40(1)	40(1)	40(1)	30(1)	40(1)	30(1)	40(1)	2.5
50(2)	-	30(1)	40(2)	50(2)	-	50(1)	40(2)	3.0
-	40(1)	50(1)	40(2)	-	40(1)	50(1)	40(2)	3.0
30(2)	30(1)	50(2)	40(2)	30(2)	30(1)	50(2)	40(2)	3.0
35.0±5.2	27.0±4.2	41.0±3.1	41.0±1.8	35.0±5.2	27.0±4.2	42.0 ±3.3	41.0±1.8	69.1±2.1

Table 6. Data from Placebo Control Animals, 1 Week Necropsy Time

% Horn Involved

Right Horn				Left Horn				
Bowel	Bladder	Itself	Left	Bowel	Bladder	Itself	Right	Overall
-	30(1)	40(1)	20(1)	-	30(1)	40(1)	20(1)	2.0
20(1)	30(1)	40(1)	30(1)	20(1)	30(1)	40(1)	30(1)	2.5
20(1)	30(1)	30(1)	40(1)	20(1)	30(1)	20(1)	40(1)	2.0
60(1)	-	30(1)	30(1)	60(1)	-	30(1)	30(1)	3.0
-	40(2)	30(1)	10(1)	-	40(2)	50(1)	10(1)	2.5
20(1)	10(1)	10(1)	20(1)	20(1)	10(1)	30(1)	20(1)	2.0
-	-	30(1)	30(1)	-	-	30(1)	30(1)	1.5
-	20(1)	40(2)	50(1)	-	20(1)	40(2)	50(1)	2.5
40(1)	20(1)	40(2)	30(2)	40(1)	20(1)	-	30(2)	2.5
30(1)	10(1)	30(1)	20(1)	30(1)	10(1)	30(1)	20(1)	2.0
19.0±6.4	19.0±4.3	32.0±2.9	28.0±3.6	19.0±6.4	19.0±4.3	31.0 ±4.3	28.0±3.6	48.7±3.9

Table 7. Data from Treated Animals, 1 mg/ml COMPOUND 1, 1 Week Necropsy Time

% Horn Involved

Right Horn				Left Horn				
Bowel	Bladder	Itself	Left	Bowel	Bladder	Itself	Right	Overall
30(1)	-	40(1)	-	30(1)	-	40(1)	-	2.0
-	10(1)	10(1)	30(1)	20(1)	-	-	30(1)	1.5
30(1)	-	-	30(1)	30(1)	-	30(1)	30(1)	1.5
30(1)	-	-	-	30(1)	-	20(1)	-	1.0
-	-	20(1)	20(1)	-	-	20(1)	20(1)	1.0
10(1)	-	-	-	-	-	30(1)	-	0.5
20(1)	10(1)	-	10(1)	-	-	30(1)	10(1)	1.5
30(1)	-	20(1)	30(1)	30(1)	-	-	30(1)	1.5
20(1)	10(1)	-	20(2)	20(1)	-	10(1)	20(2)	1.5
20(1)	-	10(1)	10(1)	20(1)	-	-	10(1)	1.0
19.0±3.8	3.0±1.5	10.0±4.2	15.0±4.0	18.0±4.2	0.0±0.0	18.0 ±4.7	15.0±4.0	21.3±3.9

Table 8. Data from Treated Animals, 0.1 mg/ml COMPOUND 1, 2 Week Necropsy Time

% Horn Involved								
Right Horn				Left Horn				
Bowel	Bladder	Itself	Left	Bowel	Bladder	Itself	Right	Overall
-	-	10(1)	-	30(1)	-	40(1)	-	1.5
-	20(1)	-	20(1)	-	20(1)	30(1)	20(1)	1.5
10(1)	-	10(1)	30(1)	-	-	-	30(1)	1.0
40(1)	30(1)	30(1)	-	40(1)	30(1)	30(1)	-	2.0
30(1)	10(1)	-	10(1)	30(1)	10(1)	30(1)	10(1)	1.5
10(1)	10(1)	10(1)	40(1)	10(1)	10(1)	-	40(1)	1.5
30(1)	-	10(1)	30(1)	30(1)	-	50(1)	30(1)	2.0
-	-	30(1)	-	-	-	20(1)	-	1.0
-	-	10(1)	20(1)	-	-	-	20(1)	0.5
10(1)	-	-	-	10(1)	-	30(1)	-	0.5
13.0±4.7	7.0±3.4	11.0±3.5	15.0±4.8	15.0±5.0	7.0±3.4	23.0 ±5.6	15.0±4.8	22.0±4.8

Table 9. Summary of Adhesion Incidence Data

Group	# Sites Adhesion Free	% Sites Adhesion Free
Control 2 Weeks	8	10.0
Placebo 2 Weeks	17	21.25
1 mg/ml COMPOUND 1	45	56.25
0.1 mg/ml COMPOUND 1	31	38.75
Control 1 Week	4	5.0
Placebo 1 Week	13	16.25
1 mg/ml COMPOUND 1	36	45.0
0.1 mg/ml COMPOUND 1	34	42.5

It is to be understood that the invention is not limited to the embodiment illustrated hereinabove and the right is reserved to the illustrated embodiment and all modifications coming within the scope of the following claims.

2002305164 15 Jul 2005

The various references to journals, patents and other publications which are cited herein comprise the state of the art and are incorporated herein by reference as though fully set forth.

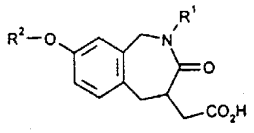
Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

The reference to any prior art in this specification is not, and should not be taken as, an acknowledgment or any form of suggestion that that prior art forms part of the common general knowledge in Australia.

2002305164 15 Jul 2005

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A method of inhibiting adhesion formation which comprises administering to a subject in need thereof an effective amount of a compound of formula (I):



(I)

wherein:

R^1 is R^7, or A-C_{0-4}alkyl, A-C_{2-4}alkenyl, A-C_{2-4}alkynyl, A-C_{3-4}oxoalkenyl, A-C_{3-4}oxoalkynyl, A-C_{1-4}aminoalkyl, A-C_{3-4}aminoalkenyl, A-C_{3-4}aminoalkynyl, optionally substituted by any accessible combination of one or more of R^{10} or R^7;

A is H, C_{3-6}cycloalkyl, Het or Ar;

R^7 is -COR^8, -$COCR'_2R^9$, -$C(S)R^8$, -$S(O)_mOR'$, -$S(O)_mNR'R''$, -$PO(OR')$, -$PO(OR')_2$, -NO_2, or tetrazolyl;

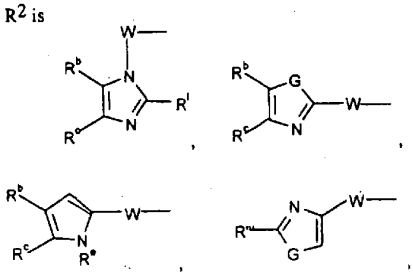
each R^8 independently is -OR', -NR'R", -NR'SO_2R', -NR'OR', or -$OCR'_2CO(O)R'$;

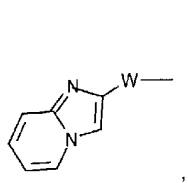
R^9 is -OR', -CN, -$S(O)_rR'$, -$S(O)_mNR'_2$, -C(O)R', C(O)NR'$_2$, or -CO_2R';

R^{10} is H, halo, -OR^{11}, -CN, -NR'R^{11}, -NO_2, -CF_3, $CF_3S(O)_r$-, -CO_2R', -CONR'$_2$, A-C_{0-6}alkyl-, A-C_{1-6}oxoalkyl-, A-C_{2-6}alkenyl-, A-C_{2-6}alkynyl-, A-C_{0-6}alkyloxy-, A-C_{0-6}alkylamino- or A-C_{0-6}alkyl-$S(O)_r$-;

R^{11} is R', -C(O)R', -C(O)NR'$_2$, -C(O)OR', -$S(O)_mR'$, or -$S(O)_mNR'_2$;

R^2 is

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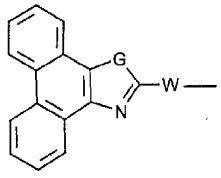
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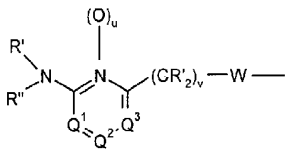
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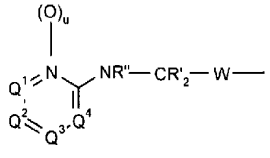
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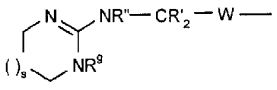

;

W is $-(CHR^g)_a-U-(CHR^g)_b-$;

U is absent or CO, CR^g_2, $C(=CR^g_2)$, $S(O)_k$, O, NR^g, CR^gOR^g, $CR^g(OR^k)CR^g_2$, $CR^g_2CR^g(OR^k)$, $C(O)CR^g_2$, $CR^g_2C(O)$, $CONR^i$, NR^iCO, OC(O), C(O)O, C(S)O, OC(S), $C(S)NR^g$, $NR^gC(S)$, $S(O)_2NR^g$, $NR^gS(O)_2$ N=N, NR^gNR^g, $NR^gCR^g_2$, $CR^g_2NR^g$, CR^g_2O, OCR^g_2, C≡C or CR^g=CR^g;

G is NR^e, S or O;

R^g is H, C_{1-6}alkyl, Het-C_{0-6}alkyl, C_{3-7}cycloalkyl-C_{0-6}alkyl or Ar-C_{0-6}alkyl;

R^k is R^g, -C(O)R^g, or -C(O)OR^f;

R^i is is H, C_{1-6}alkyl, Het-C_{0-6}alkyl, C_{3-7}cycloalkyl-C_{0-6}alkyl, Ar- C_{0-6}alkyl, or C_{1-6}alkyl substituted by one to three groups chosen from halogen, CN, NR^g_2, OR^g, SR^g, CO_2R^g, and $CON(R^g)_2$;

R^f is H, C_{1-6}alkyl or Ar-C_{0-6}alkyl;

R^e is H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, C_{3-7}cycloalkyl-C_{0-6}alkyl, or $(CH_2)_kCO_2R^g$;

R^b and R^c are independently selected from H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, or C_{3-6}cycloalkyl-C_{0-6}alkyl, halogen, CF_3, OR^f, $S(O)_kR^f$, COR^f, NO_2, $N(R^f)_2$, $CO(NR^f)_2$, $CH_2N(R^f)_2$, or R^b and R^c are joined together to form a five or six membered aromatic or non-aromatic carbocyclic or heterocyclic ring, optionally substituted by up to three substituents chosen from halogen, CF_3, C_{1-4}alkyl, OR^f,

$S(O)_kR^f$, COR^f, CO_2R^f, OH, NO_2, $N(R^f)_2$, $CO(NR^f)_2$, and $CH_2N(R^f)_2$; or methylenedioxy;

Q^1, Q^2, Q^3 and Q^4 are independently N or C-R^y, provided that no more than one of Q^1, Q^2, Q^3 and Q^4 is N;

R' is H, C_{1-6}alkyl, Ar-C_{0-6}alkyl or C_{3-6}cycloalkyl-C_{0-6}alkyl;

R" is R', -C(O)R' or -C(O)OR';

R"' is H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, or C_{3-6}cycloalkyl-C_{0-6}alkyl, halogen, CF_3, OR^f, $S(O)_kR^f$, COR^f, NO_2, $N(R^f)_2$, $CO(NR^f)_2$, $CH_2N(R^f)_2$;

R^y is H, halo, $-OR^g$, $-SR^g$, -CN, $-NR^gR^k$, $-NO_2$, $-CF_3$, $CF_3S(O)_r$-, $-CO_2R^g$, $-COR^g$ or $-CONR^g{}_2$, or C_{1-6}alkyl optionally substituted by halo, $-OR^g$, $-SR^g$, -CN, $-NR^gR$", $-NO_2$, $-CF_3$, R'S(O)$_r$-, $-CO_2R^g$, $-COR^g$ or $-CONR^g{}_2$;

a is 0, 1 or 2;

b is 0, 1 or 2;

k is 0, 1 or 2;

m is 1 or 2;

r is 0, 1 or 2;

s is 0, 1 or 2;

u is 0 or 1; and

v is 0 or 1;

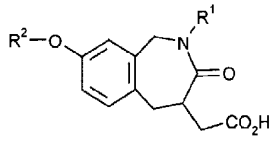
or a pharmaceutically acceptable salt thereof.

2. The method of claim 1 wherein the compound is (S)-3-oxo-8-[3-(pyridin-2-ylamino)-1-propyloxy]-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid or a pharmaceutically acceptable salt thereof.

3. The method of claim 1 wherein the compound is (S)-8-[2-[6-(methylamino)pyridin-2-yl]-1-ethoxy]-3-oxo-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid or a pharmaceutically acceptable salt thereof.

4. A method of inhibiting adhesion formation which comprises administering to a subject in need thereof an effective amount of (S)-10,11-dihydro-3-[2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)-1-ethoxy]-5H-dibenzo[a,d]cycloheptene-10-acetic acid or a pharmaceutically acceptable salt thereof.

5. The use of a compound of the formula (I):



(I)

wherein:

R^1 is R^7, or A-C_{0-4}alkyl, A-C_{2-4}alkenyl, A-C_{2-4}alkynyl, A-C_{3-4}oxoalkenyl, A-C_{3-4}oxoalkynyl, A-C_{1-4}aminoalkyl, A-C_{3-4}aminoalkenyl, A-C_{3-4}aminoalkynyl, optionally substituted by any accessible combination of one or more of R^{10} or R^7;

A is H, C_{3-6}cycloalkyl, Het or Ar;

R^7 is -COR^8, -$COCR'_2R^9$, -$C(S)R^8$, -$S(O)_mOR'$, -$S(O)_mNR'R''$, -PO(OR'), -$PO(OR')_2$, -NO_2, or tetrazolyl;

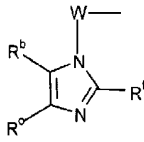
each R^8 independently is -OR', -NR'R'', -$NR'SO_2R'$, -NR'OR', or -$OCR'_2CO(O)R'$;

R^9 is -OR', -CN, -$S(O)_rR'$, -$S(O)_mNR'_2$, -C(O)R', C(O)NR'_2, or -CO_2R';

R^{10} is H, halo, -OR^{11}, -CN, -$NR'R^{11}$, -NO_2, -CF_3, $CF_3S(O)_r$-, -CO_2R', -$CONR'_2$, A-C_{0-6}alkyl-, A-C_{1-6}oxoalkyl-, A-C_{2-6}alkenyl-, A-C_{2-6}alkynyl-, A-C_{0-6}alkyloxy-, A-C_{0-6}alkylamino- or A-C_{0-6}alkyl-$S(O)_r$-;

R^{11} is R', -C(O)R', -C(O)NR'_2, -C(O)OR', -$S(O)_mR'$, or -$S(O)_mNR'_2$;

R^2 is



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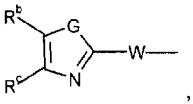

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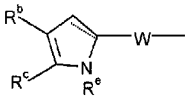

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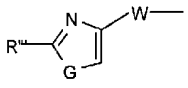

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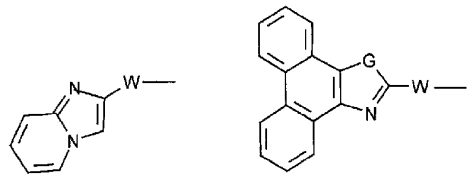
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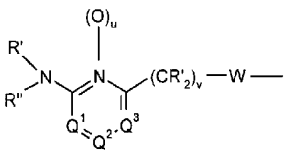
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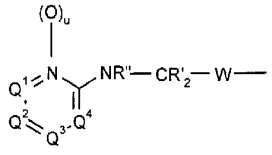
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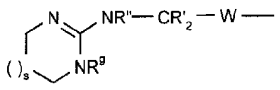
;

W is -$(CHR^g)_a$-U- $(CHR^g)_b$-;

U is absent or CO, CR^g_2, $C(=CR^g_2)$, $S(O)_k$, O, NR^g, CR^gOR^g, $CR^g(OR^k)CR^g_2$, $CR^g_2CR^g(OR^k)$, $C(O)CR^g_2$, $CR^g_2C(O)$, $CONR^i$, NR^iCO, OC(O), C(O)O, C(S)O, OC(S), C(S)NR^g, $NR^gC(S)$, $S(O)_2NR^g$, $NR^gS(O)_2$ N=N, NR^gNR^g, $NR^gCR^g_2$, $CR^g_2NR^g$, CR^g_2O, OCR^g_2, C≡C or CR^g=CR^g;

G is NR^e, S or O;

R^g is H, C_{1-6}alkyl, Het-C_{0-6}alkyl, C_{3-7}cycloalkyl-C_{0-6}alkyl or Ar-C_{0-6}alkyl;

R^k is R^g, -C(O)R^g, or -C(O)OR^f;

R^i is H, C_{1-6}alkyl, Het-C_{0-6}alkyl, C_{3-7}cycloalkyl-C_{0-6}alkyl, Ar- C_{0-6}alkyl, or C_{1-6}alkyl substituted by one to three groups chosen from halogen, CN, NR^g_2, OR^g, SR^g, CO_2R^g, and $CON(R^g)_2$;

R^f is H, C_{1-6}alkyl or Ar-C_{0-6}alkyl;

R^e is H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, C_{3-7}cycloalkyl-C_{0-6}alkyl, or $(CH_2)_kCO_2R^g$;

R^b and R^c are independently selected from H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, or C_{3-6}cycloalkyl-C_{0-6}alkyl, halogen, CF_3, OR^f, $S(O)_kR^f$, COR^f, NO_2, $N(R^f)_2$, $CO(NR^f)_2$, $CH_2N(R^f)_2$, or R^b and R^c are joined together to form a five or six membered aromatic or non-aromatic carbocyclic or heterocyclic ring, optionally substituted by up to three substituents chosen from halogen, CF_3, C_{1-4}alkyl, OR^f, $S(O)_kR^f$, COR^f, CO_2R^f, OH, NO_2, $N(R^f)_2$, $CO(NR^f)_2$, and $CH_2N(R^f)_2$; or methylenedioxy;

Q^1, Q^2, Q^3 and Q^4 are independently N or C-R^y, provided that no more than one of Q^1, Q^2, Q^3 and Q^4 is N;

R' is H, C_{1-6}alkyl, Ar-C_{0-6}alkyl or C_{3-6}cycloalkyl-C_{0-6}alkyl;

R" is R', -C(O)R' or -C(O)OR';

R"' is H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, or C_{3-6}cycloalkyl-C_{0-6}alkyl, halogen, CF_3, OR^f, $S(O)_kR^f$, COR^f, NO_2, $N(R^f)_2$, $CO(NR^f)_2$, $CH_2N(R^f)_2$;

R^y is H, halo, $-OR^g$, $-SR^g$, -CN, $-NR^gR^k$, $-NO_2$, $-CF_3$, $CF_3S(O)_r$-, $-CO_2R^g$, $-COR^g$ or $-CONR^g_2$, or C_{1-6}alkyl optionally substituted by halo, $-OR^g$, $-SR^g$, -CN, $-NR^gR''$, $-NO_2$, $-CF_3$, $R'S(O)_r$-, $-CO_2R^g$, $-COR^g$ or $-CONR^g_2$;

a is 0, 1 or 2;

b is 0, 1 or 2;

k is 0, 1 or 2;

m is 1 or 2;

r is 0, 1 or 2;

s is 0, 1 or 2;

u is 0 or 1; and

v is 0 or 1;

or a pharmaceutically acceptable salt thereof,

in the manufacture of a medicament for the inhibition of adhesion formation.

6. The use according to claim 5 wherein the compound is (S)-3-oxo-8-[3-(pyridin-2-ylamino)-1-propyloxy]-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid or a pharmaceutically acceptable salt thereof.

7. The use according to claim 5 wherein the compound is (S)-8-[2-[6-(methylamino)pyridin-2-yl]-1-ethoxy]-3-oxo-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid or a pharmaceutically acceptable salt thereof.

8. The use of (S)-10,11-dihydro-3-[2-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)-1-ethoxy]-5H-dibenzo[a,d]cycloheptene-10-acetic acid, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the inhibition of adhesion formation.

9. The method of claim 1, substantially as hereinbefore described.

10. The use of claim 5 substantially as hereinbefore described.

DATED this 15th day of July, 2005

SmithKline Beecham Corporation

By DAVIES COLLISON CAVE

Patent Attorneys for the Applicant