THERAPEUTIC AGENT FOR INFLAMMATORY BOWEL DISEASE COMPRISING 2-AMINO-1,3-PROPANEDIOL DERIVATIVE AS ACTIVE INGREDIENT, AND METHOD FOR TREATMENT OF INFLAMMATORY BOWEL DISEASE

TECHNICAL FIELD

[0001]

The present invention relates to a therapeutic agent for inflammatory bowel diseases that contains, as an active ingredient, 2-amino-1,3-propanediol derivative, a sphingosine-1-phosphate receptor agonist, or a pharmaceutically acceptable salt or hydrate thereof. The present invention also relates to a method for treating inflammatory bowel diseases.

BACKGROUND ART

[0002]

Inflammatory bowel diseases, represented by Crohn's disease and ulcerative colitis, are intractable diseases that often develop at relatively young ages and cause abdominal pain, fever, diarrhea, hematochezia and other symptoms. Crohn's disease is a granulomatous inflammatory disease of unknown cause that affects any part of the gastrointestinal tract from mouth to anus in a discontinuous manner. The disease progresses from ulcer to fibrosis and stricture, involving all layers of the bowel wall from mucosa to serosa. It is associated with systemic symptoms such as abdominal pain, chronic diarrhea, fever and malnutrition. On the other hand, ulcerative colitis is characterized by diffuse nonspecific inflammation of

the large intestine of unknown cause. The disease primarily affects mucosa and often forms erosions and ulcers. It is also associated with various systemic symptoms including bloody diarrhea. Inflammatory bowl disease also refers to other inflammatory disorders in small and large intestines, including intestinal Behcet's disease, ulcerative colitis, bleeding rectal ulcer and pouchitis. Although it is believed that the etiology of inflammatory bowel diseases involves abnormal immune function, the exact cause of the diseases still remains unknown (Non-Patent Documents 1 and 2).

[0003]

Medications for inflammatory bowel diseases include immunosuppressors, steroids, salazosulfapyridine and mesalazine. While immunosuppressors, in particular antimetabolites such as azathiopurine and 6-mercaptopurine, are considered effective against Crohn's disease, the drugs exhibit low efficacy at an early stage of administration and often cause allergies, pancreatitis, leukopenia and other side effects. High doses of cyclosporine are effective against inflammatory and fistulous diseases, but the drug cannot be used for a prolonged period due to its toxicity. Infliximab, a monoclonal antibody that inhibits a tumor necrosis factor, is administered by intravenous infusion to treat moderate or serious Crohn's disease (especially those accompanied by fistula) resistant to other treatments. However, long-term effects and side effects of the treatment are unknown. Other potential immunosuppressors

include interleukin-1 blockers, anti-interleukin-12 antibodies, anti-CD4 antibodies, adhesive molecule inhibitors, and monoclonal antibodies against down-regulatory cytokines and tumor necrosis factors. Each of the current therapeutic approaches for the treatment of inflammatory bowel diseases has its own disadvantages. Thus, there is a need for more effective and safe medications (Non-Patent Documents 3, 4 and 5).

[0004]

2-amino-1,3-propanediol derivatives described in the present application are known as effective immunosuppressors used to prevent rejection in organ transplantation (Patent Literatures No. 1 and 2). While 2-amino-1,3-propanediol derivatives have been known to act as sphingosine-1-phosphate receptor agonists, their usefulness in the treatment of inflammatory bowel diseases has never been described.

[Non-Patent Document 1] 1997 Annual Report by the Research Committee of Intractable Inflammatory Bowel Disorders: The Ministry of Health and Welfare of Japan.

[Non-Patent Document 2] New Engl J Med, 2002, 347: 417-429

[Non-Patent Document 3] Am J Gastroenterol, 2001, 96: 1977-1997

[Non-Patent Document 4] Nucl Med Commun, 2005, 26:649-655

[Non-Patent Document 5] Saishin Igaku 2004、59:1070-1075

[Patent Document 1] WO2003/029184 Pamphlet

[Patent Document 2] WO2003/029205 Pamphlet

DISCLOSURE OF THE INVENTION

PROBLEMS TO BE SOLVED BY THE INVENTION

[0005]

It is an objective of the present invention to provide a therapeutic agent for the treatment of inflammatory bowel diseases that contains, as an active ingredient, a 2-amino-1,3-propanediol derivative, or a pharmaceutically acceptable salt or hydrate thereof. It is another objective to provide a method for treating inflammatory bowel diseases.

MEANS FOR SOLVING THE PROBLEMS

[0006]

The present inventors discovered that a 2-amino-1,3-propanediol derivative, a sphingosine-1-phosphate receptor agonist, or a pharmaceutically acceptable salt or hydrate thereof is useful in the treatment or prevention of inflammatory bowel diseases (Crohn's disease, Crohn's disease in large intestine, intestinal Behcet's disease, ulcerative colitis, bleeding rectal ulcer and pouchitis) and thus devised the present invention.

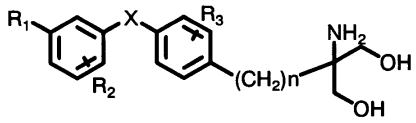
[0007]

Specifically, the present invention concerns the following:

1) A therapeutic or prophylactic agent for an inflammatory bowel disease containing, as an active ingredient, a 2-amino-1,3-propanediol derivative represented by the chemical formula (1):

[0008]

(Chemical formula 1)



(1)

[0009]

[wherein R_1 is a halogen atom, a trihalomethyl group, a hydroxy group, a lower alkyl group having 1 to 7 carbon atoms, a substituted or unsubstituted phenyl group, an aralkyl group, a lower alkoxy group having 1 to 4 carbon atoms, a trifluoromethyloxy group, a phenoxy group, a cyclohexylmethyloxy group, a substituted or unsubstituted aralkyloxy group, a pyridylmethyloxy group, a cinnamyloxy group, a naphthylmethyloxy group, a phenoxymethyl group, a hydroxymethyl group, a hydroxyethyl group, a lower alkylthio group having 1 to 4 carbon atoms, a lower alkylsulfinyl group having 1 to 4 carbon atoms, a lower alkylsulfonyl group having 1 to 4 carbon atoms, a benzylthio group, an acetyl group, a nitro group or a cyano group; R_2 is a hydrogen atom, a halogen atom, a trihalomethyl group, a lower alkoxy group having 1 to 4 carbon atoms, a lower alkyl group having 1 to 7 carbon atoms, a phenethyl group or a benzyloxy group; R_3 is a hydrogen atom, a halogen atom, a trifluoromethyl group, a lower alkoxy group having 1 to 4 carbon atoms, a hydroxy group, a benzyloxy group, a lower alkyl group having 1 to 7 carbon atoms, a phenyl group, a lower alkoxymethyl group having 1 to 4 carbon atoms or a lower alkylthio group having 1 to 4 carbon atoms; X is O, S, SO or SO_2; and n is an integer from 2 to 4], or a pharmaceutically acceptable salt or hydrate thereof.

[0010]

2) The therapeutic or prophylactic agent for an inflammatory bowel disease according to 1), wherein the compound represented by the chemical formula (1) is 2-amino-2-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]ethyl-1,3-propanediol.

[0011]

3) The therapeutic or prophylactic agent for an inflammatory bowel disease according to 1), wherein the compound represented by the chemical formula (1) is a hydrochloride of 2-amino-2-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]ethyl-1,3-propanediol.

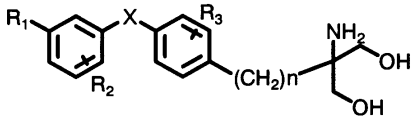
4) The therapeutic or prophylactic agent for an inflammatory bowel disease according to 1) to 3), wherein the inflammatory bowel disease is Crohn's disease, Crohn's disease in large intestine, intestinal Behcet's disease, ulcerative colitis, bleeding rectal ulcer, or pouchitis.

[0012]

5) A method for treating an inflammatory bowel disease, using as an active ingredient a 2-amino-1,3-propanediol derivative represented by the chemical formula (1):

[0013]

(Chemical formula 2)



(1)

[0014]

[wherein R_1 is a halogen atom, a trihalomethyl group, a hydroxy group, a lower alkyl group having 1 to 7 carbon atoms, a substituted or unsubstituted phenyl group, an aralkyl group, a lower alkoxy group having 1 to 4 carbon atoms, a trifluoromethyloxy group, a phenoxy group, a cyclohexylmethyloxy group, a substituted or unsubstituted aralkyloxy group, a pyridylmethyloxy group, a cinnamyloxy group, a naphthylmethyloxy group, a phenoxymethyl group, a hydroxymethyl group, a hydroxyethyl group, a lower alkylthio group having 1 to 4 carbon atoms, a lower alkylsulfinyl group having 1 to 4 carbon atoms, a lower alkylsulfonyl group having 1 to 4 carbon atoms, a benzylthio group, an acetyl group, a nitro group or a cyano group; R_2 is a hydrogen atom, a halogen atom, a trihalomethyl group, a lower alkoxy group having 1 to 4 carbon atoms, a lower alkyl group having 1 to 7 carbon atoms, a phenethyl group or a benzyloxy group; R_3 is a hydrogen atom, a halogen atom, a trifluoromethyl group, a lower alkoxy group having 1 to 4 carbon atoms, a hydroxy group, a benzyloxy group, a lower alkyl group having 1 to 7 carbon atoms, a phenyl group, a lower alkoxymethyl group having 1 to 4 carbon atoms or a lower alkylthio group having 1 to 4 carbon atoms; X is O, S, SO or SO_2; and n is an integer from 1 to 4], or a pharmaceutically acceptable salt or hydrate thereof.

[0015]

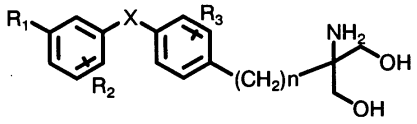
6) The method for treating an inflammatory bowel disease according to 5), wherein the inflammatory bowel disease is Crohn's disease, Crohn's disease in large intestine, intestinal Behcet's disease, ulcerative colitis, bleeding rectal ulcer, or pouchitis.

[0016]

7) A therapeutic or prophylactic agent for an inflammatory bowel disease, comprising a 2-amino-1,3-propanediol derivative represented by the general formula (1):

[0017]

(Chemical formula 3)



(1)

[0018]

[wherein R_1 is a halogen atom, a trihalomethyl group, a hydroxy group, a lower alkyl group having 1 to 7 carbon atoms, a substituted or unsubstituted phenyl group, an aralkyl group, a lower alkoxy group having 1 to 4 carbon atoms, a trifluoromethyloxy group, a phenoxy group, a cyclohexylmethyloxy group, a substituted or unsubstituted aralkyloxy group, a pyridylmethyloxy group, a cinnamyloxy group, a naphthylmethyloxy group, a phenoxymethyl group, a hydroxymethyl group, a hydroxyethyl group, a lower alkylthio group having 1 to 4 carbon atoms, a lower alkylsulfinyl group having 1 to 4 carbon atoms, a lower alkylsulfonyl group having 1 to 4 carbon atoms, a

benzylthio group, an acetyl group, a nitro group or a cyano group; R_2 is a hydrogen atom, a halogen atom, a trihalomethyl group, a lower alkoxy group having 1 to 4 carbon atoms, a lower alkyl group having 1 to 7 carbon atoms, a phenethyl group or a benzyloxy group; R_3 is a hydrogen atom, a halogen atom, a trifluoromethyl group, a lower alkoxy group having 1 to 4 carbon atoms, a hydroxy group, a benzyloxy group, a lower alkyl group having 1 to 7 carbon atoms, a phenyl group, a lower alkoxymethyl group having 1 to 4 carbon atoms or a lower alkylthio group having 1 to 4 carbon atoms; X is O, S, SO or SO_2; and n is an integer from 1 to 4] or a pharmaceutically acceptable salt or hydrate thereof, in combination of at least one therapeutic agent for an inflammatory bowel disease.

[0019]

8) The therapeutic or prophylactic agent for an inflammatory bowel disease according to 7), wherein the at least one therapeutic agent for an inflammatory bowel disease comprises a sulfasalazine, a steroid, or an immunosuppressor.

ADVANTAGES OF THE INVENTION

[0020]

According to the present invention, there is provided a therapeutic or prophylactic agent for inflammatory bowel diseases that contains, as an active ingredient, a diarylsulfide or diarylether derivative having a 2-amino-1,3-propanediol structure, or a pharmaceutically acceptable salt or hydrate thereof. The diarylsulfide or diarylether derivative acts as a

sphingosine-1-phosphate receptor agonist. There is also provided a method for treating or preventing inflammatory bowel diseases, including Crohn's disease, Crohn's disease in large intestine, intestinal Behcet's disease, ulcerative colitis, bleeding rectal ulcer, or pouchitis.

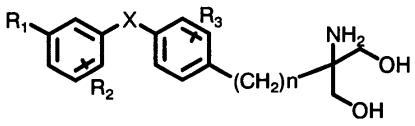
BEST MODE FOR CARRYING OUT THE INVENTION

[0021]

The 2-amino-1,3-propanediol derivatives of the present invention are sphingosine-1-phosphate receptor agonists and comprise a group of compounds represented by the chemical formula (1) and pharmaceutically acceptable salts and hydrates thereof:

[0022]

(Chemical formula 4)



(1)

[0023]

[wherein R_1 is a halogen atom, a trihalomethyl group, a hydroxy group, a lower alkyl group having 1 to 7 carbon atoms, a substituted or unsubstituted phenyl group, an aralkyl group, a lower alkoxy group having 1 to 4 carbon atoms, a trifluoromethyloxy group, a phenoxy group, a cyclohexylmethyloxy group, a substituted or unsubstituted aralkyloxy group, a pyridylmethyloxy group, a cinnamyloxy group, a naphthylmethyloxy group, a phenoxymethyl group, a hydroxymethyl group, a hydroxyethyl group, a lower alkylthio group having 1 to

4 carbon atoms, a lower alkylsulfinyl group having 1 to 4 carbon atoms, a lower alkylsulfonyl group having 1 to 4 carbon atoms, a benzylthio group, an acetyl group, a nitro group or a cyano group; R_2 is a hydrogen atom, a halogen atom, a trihalomethyl group, a lower alkoxy group having 1 to 4 carbon atoms, a lower alkyl group having 1 to 7 carbon atoms, a phenethyl group or a benzyloxy group; R_3 is a hydrogen atom, a halogen atom, a trifluoromethyl group, a lower alkoxy group having 1 to 4 carbon atoms, a hydroxy group, a benzyloxy group, a lower alkyl group having 1 to 7 carbon atoms, a phenyl group, a lower alkoxymethyl group having 1 to 4 carbon atoms or a lower alkylthio group having 1 to 4 carbon atoms; X is O, S, SO or SO_2; and n is an integer from 1 to 4].

[0024]

The term "halogen atom" in the chemical formula (1) of the present invention includes a fluorine atom, a chlorine atom, a bromine atom and an iodine atom. The term "trihalomethyl group" includes a trifluoromethyl group and a trichloromethyl group. The term "lower alkyl group having 1 to 7 carbon atoms" includes straight-chained or branched hydrocarbons having 1 to 7 carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl, hexyl and heptyl.

[0025]

The term "substituted or unsubstituted phenoxy group" includes those in which the benzene ring has at any position a halogen atom, such as a fluorine atom, a chlorine atom, a bromine atom and an iodine atom, a trifluoromethyl group, a lower alkyl group having

1 to 4 carbon atoms or a lower alkoxy group having 1 to 4 carbon atoms. The term "aralkyl group" as in "aralkyl group" and "aralkyloxy group" includes a benzyl group, a diphenylmethyl group, a phenethyl group and phenylpropyl group. The term "lower alkyl group" in "lower alkoxy group having 1 to 4 carbon atoms," "lower alkylthio group having 1 to 4 carbon atoms," "lower alkylsufinyl group having 1 to 4 carbon atoms," and "lower alkylsulfonyl group having 1 to 4 carbon atoms" includes straight-chained or branched hydrocarbons having 1 to 4 carbon atoms, such as methyl, ethyl, propyl, isopropyl and butyl. The term "substituted or unsubstituted aralkyl group" includes those in which the benzene ring has at any position a halogen atom, such as a fluorine atom, a chlorine atom, a bromine atom and an iodine atom, a trifluoromethyl group, a lower alkyl group having 1 to 4 carbon atoms or a lower alkoxy group having 1 to 4 carbon atoms.

[0026]

Examples of pharmaceutically acceptable salts of the compound of the chemical formula (1) of the present invention include acid-addition salts such as hydrochlorides, hydrobromides, acetates, trifluoroacetates, methanesulfonates, citrates and tartrates.

[0027]

More specific examples of the compound of the general formula (1) are

2-amino-2-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]ethyl-1,3-propanediol and hydrochlorides thereof.

[0028]

The compounds of the general formula (1) of the present invention are described in, for example, WO03/029184 pamphlet and WO03/029205 pamphlet and can be produced by techniques described in these publications.

[0029]

The thus-obtained compounds of the present invention or pharmaceutically acceptable salts and hydrates thereof are useful in the treatment of inflammatory bowel diseases. The therapeutic agents of the present invention are administered systemically or topically and orally or parenterally. The compounds may be formulated as oral or parenteral preparations depending on their properties. Specifically, the active ingredients may be mixed with pharmaceutically acceptable carriers, excipients, binders, diluents or other auxiliary agents and formulated as granules, powders, tablets, capsules, syrups, suppositories, suspensions, solutions and other dosage forms. While the compounds may be administered in different doses depending on their use, the weight, age and conditions of the patients, they are typically administered in a single dose of 0.01 to 100mg/patient, preferably at a single dose of 0.1 to 5mg/patient, once to three times a day.

[0030]

These preparations may be used in combination with at least one drug used to treat inflammatory bowel diseases. Examples of such drugs include sulfasalazines, steroids and immunosuppressors.

Examples of sulfasalazines include mesalazine, olsalazine, sulfasalazine and balsalazide. Examples of steroids include hydrocortisone, methylprednisolone, budesonide and betamethasone phosphate. Examples of immunosuppressors include azathioprine, 6-mercaptopurine, cyclosporine, tacrolimus, anti-TNF-α antibody and anti-α4 integrin antibody.

[0031]

Examples

The present invention will now be described with reference to examples. While these examples primarily concern 2-amino-2-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]ethyl-1,3-propanediol hydrochloride (which may be referred to as "KRP-203," hereinafter), one of the compounds represented by the chemical formula (1), other compounds are also encompassed by the present invention and the scope of the invention is by no means limited by these examples.

Example 1

[0032]

Therapeutic effects on dextran sodium sulfate-induced colitis in mice

Colitis was induced in BALB/C male mice by allowing animals to drink a 5% aqueous solution of dextran sodium sulfate (DSS) (average molecular weight = 5000) for 7 days [Kitajima, S. *et. al.*, Exp Anim, Vol.49, No.1: 9-15 (2000)]. KRP-203 dissolved in distilled water (at 0.01, 0.03 and 0.1 mg/kg) was orally administered once a day

for 8 days, starting the day before the administration of DSS solution. One group was administered distilled water as a placebo.

[0033]

8 days after the start of the DSS period, mice were anesthetized with diethyl ether and sacrificed by cervical dislocation. The large intestine (the segment from colon to anus) was removed from each animal. Because it is known that the ingestion of DSS solution causes colitis in mice that causes a decrease in the length of large intestine [Okayasu, I. *et. al.*, Gastroenterology, Vol.98: 694-702 (1990)], the length of the large intestine from the colon to anus was measured with a caliper. The large intestine was then cut open longitudinally to expose the lumen and the content was washed off with physiological saline. The specimens were assayed and compared for the activity of myeloperoxidase, a marker of inflammation in colitis [Grisham, MB. *et. al.*, Methods Enzymol, Vol.186: 729-742 (1990)].

[0034]

The comparison of the length of large intestine is shown in Table 1. The results indicate that KRP-203 significantly reduced the colitis-induced decrease in the length of large intestine.

[0035]

Table 1: Reduction of the decrease in the length of large intestine by KRP-203

Groups tested	Number of Samples	Length of large intestine (mm)
Placebo group	8	64.7 ± 1.7##
0.01mg/kg KRP-203 group	10	67.4 ± 1.4
0.03mg/kg KRP-203 group	10	72.7 ± 1.5**
0.1mg/kg KRP-203 group	9	71.4 ± 1.4*
Normal group	4	84.7 ± 2.2

Data are given in average ± standard error.

: $p<0.01$ (Student's t-test on normal group)

* : $p<0.05$ (Dunnett's test on placebo group)

** : $p<0.01$ (Dunnett's test on placebo group)

[0036]

The results of the assay for myeloperoxidase activity in large intestine are shown in Table 2. The results indicate that KRP-203 significantly reduced the colitis-induced increase in the myeloperoxidase activity in large intestine.

[0037]

Table 2: Suppression of the increase in myeloperoxidase activity in large intestine by KRP-203

Groups tested	Number of Samples	myeloperoxidase activity (U/g protein)
Placebo group	8	108.2 ± 20.7##
0.01mg/kg KRP-203 group	10	55.8 ± 16.2*
0.03mg/kg KRP-203 group	10	36.8 ± 5.9**
0.1mg/kg KRP-203 group	9	44.4 ± 6.4**
Normal group	4	5.0 ± 0.1

Data are given in average ± standard error.

: $p<0.01$ (Aspin-Welch's t-test on normal group)

* : $p<0.05$ (Dunnett's test on placebo group)

** : $p<0.01$ (Dunnett's test on placebo group)

[0038]

DDS-induced colitis in mice is frequently used as a disease model of inflammatory bowel diseases in humans [Elson, CO. *et. al.*, Gastroenterology, Vol.109: 1344-1367 (1995); Hibi, T. *et. al.*, J Gastroenterol, Vol.37: 409-417 (2002)]. Thus, these results demonstrate the usefulness of KRP-203 in the treatment of inflammatory bowel diseases.

Example 2

[0039]

Comparative Example

Several drugs are used in the treatment of inflammatory bowel diseases. Immunosuppressors, drugs used to prevent rejection in organ transplantation, are one such option. As with KRP-203, two representative immunosuppressors cyclosporine and tacrolimus were examined for their effects.

[0040]

Cyclosporine was dissolved in soybean oil (at 10 and 30 mg/kg) and was orally administered once a day for 8 days, starting the day before the start of the DSS period. One group was administered soybean oil as a placebo. The increase in the myeloperoxidase activity in large intestine was suppressed by 54% in the 10mg/kg group and by 73% in the 30mg/kg group as compared to the placebo group.

[0041]

Tacrolimus was suspended in a 0.5% aqueous solution of

carboxymethylcellulose sodium (CMC-Na)(at 3 mg/kg) and was administered once a day for 8 days, starting the day before the start of the DSS period. One group was administered 0.5% aqueous CMC-Na solution as a placebo. The increase in the myeloperoxidase activity in large intestine was suppressed by 37% in the 3mg/kg group as compared to the placebo group.

[0042]

The effect on DDS-induced colitis in mice was then compared between cyclosporine and tacrolimus, two representative immunosuppressors, and KRP-203: The increase in the myeloperoxidase activity in large intestine was suppressed by administration of KRP-203 by 51% in the 0.01mg/kg group, by 69% in the 0.03mg/kg group, and by 62% in the 0.1mg/kg group as compared to the placebo group (Table 2). These results suggest that lesser doses of KRP-203 have a comparable or greater therapeutic effect on inflammatory bowel diseases than cyclosporine and tacrolimus.

Example 3

[0043]

Effect of KRP-203 on IL-10 knockout mice

B6.129P2-IL10$^{<tm1Cgn>}$/J (IL-10 knockout) mice (male, 5-6 week old) were obtained for the test. KRP-203 dissolved in distilled water was orally administered at a dose of 0.1mg/kg once a day for 4 weeks, starting 8 weeks after the animals were obtained. One group was administered distilled water alone as a placebo. Following the administration period, the animals were dissected to remove large

intestine, which was then fixed in formalin. Subsequently, tissue slices were prepared from the formalin-fixed large intestine and were stained with hematoxylin and eosin. The proximal, middle, and distal segments of the large intestine were then histologically scored according to the standard procedure (BergDJ, *et al.*, Gastroenterology, 123: 1527-1542 (2002)). The scores for the three segments were added together to determine the histological scores for individual animals. The results are given in average ± standard error.

[0044]

As shown in Table 3, the histological score was significantly lower in the group administered KRP-203 than in the placebo group, a demonstration that KRP-203 reduces colitis in IL-10 knockout mice. These results suggest that the test compound KRP-203 is effective in the treatment of inflammatory bowel diseases.

[0045]

Table 3: Histological Score

Groups tested	Number of Samples	Histological Score
Placebo group	8	4.1±1.3
KRP-203 group	8	0.3±0.2*

*; $p<0.05$ vs placebo group (Mann-Whitney's test)

Example 4

[0046]

Preparation Example : Capsule preparation (in one capsule)

Composition

Compound (KRP-203)	0.1 mg
D-mannitol	247.5 mg
Magnesium stearate	2.5 mg

Specifically, the compound of the present invention was mixed with D-mannitol. Magnesium stearate was then blended in the mixture to form a powdery mixture. This mixture was packaged in a capsule to make a capsule preparation.

INDUSTRIAL APPLICABILITY

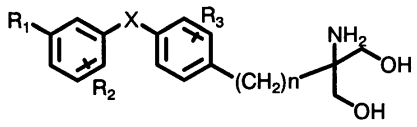
[0047]

As set forth, the compound of the present invention proved highly effective in a disease model of inflammatory bowel diseases in humans and caused a significant reduction in the tissue lesion in knockout mice. Thus, the 2-amino-1,3-propanediol derivatives of the present invention and pharmaceutically acceptable salts and hydrates thereof are useful in the treatment or prevention of inflammatory bowel diseases. Accordingly, the present invention provides a therapeutic and prophylactic agent for inflammatory bowel diseases including Crohn's disease, Crohn's disease in large intestine, intestinal Behcet's disease, ulcerative colitis, bleeding rectal ulcer and pouchitis, as well as a method for treating or preventing these diseases.

CLAIMS

1. A therapeutic or prophylactic agent for an inflammatory bowel disease containing, as an active ingredient, a 2-amino-1,3-propanediol derivative represented by the chemical formula (1):

(Chemical formula 1)



(1)

[wherein R_1 is a halogen atom, a trihalomethyl group, a hydroxy group, a lower alkyl group having 1 to 7 carbon atoms, a substituted or unsubstituted phenyl group, an aralkyl group, a lower alkoxy group having 1 to 4 carbon atoms, a trifluoromethyloxy group, a phenoxy group, a cyclohexylmethyloxy group, a substituted or unsubstituted aralkyloxy group, a pyridylmethyloxy group, a cinnamyloxy group, a naphthylmethyloxy group, a phenoxymethyl group, a hydroxymethyl group, a hydroxyethyl group, a lower alkylthio group having 1 to 4 carbon atoms, a lower alkylsulfinyl group having 1 to 4 carbon atoms, a lower alkylsulfonyl group having 1 to 4 carbon atoms, a benzylthio group, an acetyl group, a nitro group or a cyano group; R_2 is a hydrogen atom, a halogen atom, a trihalomethyl group, a lower alkoxy group having 1 to 4 carbon atoms, a lower alkyl group having 1 to 7 carbon atoms, a phenethyl group or a benzyloxy group; R_3 is a hydrogen atom, a halogen atom, a trifluoromethyl group, a lower

alkoxy group having 1 to 4 carbon atoms, a hydroxy group, a benzyloxy group, a lower alkyl group having 1 to 7 carbon atoms, a phenyl group, a lower alkoxymethyl group having 1 to 4 carbon atoms or a lower alkylthio group having 1 to 4 carbon atoms; X is O, S, SO or SO_2; and n is an integer from 2 to 4], or a pharmaceutically acceptable salt or hydrate thereof.

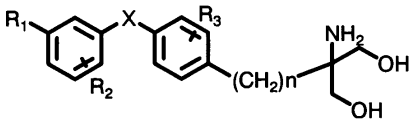
2. The therapeutic or prophylactic agent for an inflammatory bowel disease according to claim 1, wherein the compound represented by the chemical formula (1) is 2-amino-2-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]ethyl-1,3-propanediol.

3. The therapeutic or prophylactic agent for an inflammatory bowel disease according to claim 1, wherein the compound represented by the chemical formula (1) is a hydrochloride of 2-amino-2-[4-(3-benzyloxyphenylthio)-2-chlorophenyl]ethyl-1,3-propanediol.

4. The therapeutic or prophylactic agent for an inflammatory bowel disease according to any one of claims 1 to 3, wherein the inflammatory bowel disease is Crohn's disease, Crohn's disease in large intestine, intestinal Behcet's disease, ulcerative colitis, bleeding rectal ulcer, or pouchitis.

5. A method for treating an inflammatory bowel disease, using, as an active ingredient, a 2-amino-1,3-propanediol derivative represented by the chemical formula (1):

(Chemical formula 2)



(1)

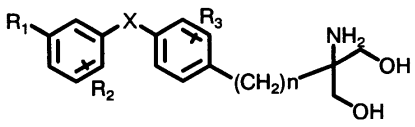
[wherein R_1 is a halogen atom, a trihalomethyl group, a hydroxy group, a lower alkyl group having 1 to 7 carbon atoms, a substituted or unsubstituted phenyl group, an aralkyl group, a lower alkoxy group having 1 to 4 carbon atoms, a trifluoromethyloxy group, a phenoxy group, a cyclohexylmethyloxy group, a substituted or unsubstituted aralkyloxy group, a pyridylmethyloxy group, a cinnamyloxy group, a naphthylmethyloxy group, a phenoxymethyl group, a hydroxymethyl group, a hydroxyethyl group, a lower alkylthio group having 1 to 4 carbon atoms, a lower alkylsulfinyl group having 1 to 4 carbon atoms, a lower alkylsulfonyl group having 1 to 4 carbon atoms, a benzylthio group, an acetyl group, a nitro group or a cyano group; R_2 is a hydrogen atom, a halogen atom, a trihalomethyl group, a lower alkoxy group having 1 to 4 carbon atoms, a lower alkyl group having 1 to 7 carbon atoms, a phenethyl group or a benzyloxy group; R_3 is a hydrogen atom, a halogen atom, a trifluoromethyl group, a lower alkoxy group having 1 to 4 carbon atoms, a hydroxy group, a benzyloxy group, a lower alkyl group having 1 to 7 carbon atoms, a phenyl group, a lower alkoxymethyl group having 1 to 4 carbon atoms or

a lower alkylthio group having 1 to 4 carbon atoms; X is O, S, SO or SO_2; and n is an integer from 1 to 4], or a pharmaceutically acceptable salt or hydrate thereof.

6. The method for treating an inflammatory bowel disease according to claim 5, wherein the inflammatory bowel disease is Crohn's disease, Crohn's disease in large intestine, intestinal Behcet's disease, ulcerative colitis, bleeding rectal ulcer, or pouchitis.

7. A therapeutic or prophylactic agent for an inflammatory bowel disease, comprising a 2-amino-1,3-propanediol derivative represented by the general formula (1):

(Chemical formula 3)



(1)

[wherein R_1 is a halogen atom, a trihalomethyl group, a hydroxy group, a lower alkyl group having 1 to 7 carbon atoms, a substituted or unsubstituted phenyl group, an aralkyl group, a lower alkoxy group having 1 to 4 carbon atoms, a trifluoromethyloxy group, a phenoxy group, a cyclohexylmethyloxy group, a substituted or unsubstituted aralkyloxy group, a pyridylmethyloxy group, a cinnamyloxy group, a naphthylmethyloxy group, a phenoxymethyl group, a hydroxymethyl group, a hydroxyethyl group, a lower alkylthio group having 1 to 4 carbon atoms, a lower alkylsulfinyl group having 1 to 4 carbon

atoms, a lower alkylsulfonyl group having 1 to 4 carbon atoms, a benzylthio group, an acetyl group, a nitro group or a cyano group; R_2 is a hydrogen atom, a halogen atom, a trihalomethyl group, a lower alkoxy group having 1 to 4 carbon atoms, a lower alkyl group having 1 to 7 carbon atoms, a phenethyl group or a benzyloxy group; R_3 is a hydrogen atom, a halogen atom, a trifluoromethyl group, a lower alkoxy group having 1 to 4 carbon atoms, a hydroxy group, a benzyloxy group, a lower alkyl group having 1 to 7 carbon atoms, a phenyl group, a lower alkoxymethyl group having 1 to 4 carbon atoms or a lower alkylthio group having 1 to 4 carbon atoms; X is O, S, SO or SO_2; and n is an integer from 1 to 4] or a pharmaceutically acceptable salt or hydrate thereof, in combination of at least one therapeutic agent for an inflammatory bowel disease.

8. The therapeutic or prophylactic agent for an inflammatory bowel disease according to claim 7, wherein the at least one therapeutic agent for an inflammatory bowel disease comprises a sulfasalazine, a steroid, or an immunosuppressor.