683112

AUSTRALIA
PATENTS ACT 1990
NOTICE OF ENTITLEMENT

We, **Sankyo Company Limited**, the applicant/Nominated Person in respect of Application No. 10346/95 state the following:-

The Nominated Person is entitled to the grant of the patent because the Nominated Person would, on the grant of a patent for the invention to the inventor, be entitled to have the patent assigned to the Nominated Person.

The Nominated Person is entitled to claim priority from the application listed in the declaration under Article 8 of the PCT because the Nominated Person made the application listed in the declaration under Article 8 of the PCT.

DATED this TWENTY FOURTH day of JUNE 1996

.....

a member of the firm of
DAVIES COLLISON CAVE
for and on behalf of the
applicant(s)

(DCC ref: 1826575)

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INFLAMMATORY CYTOKINE PRODUCTION INHIBITOR CONTAINING POLYPRENYL DERIVATIVE AS ACTIVE INGREDIENT

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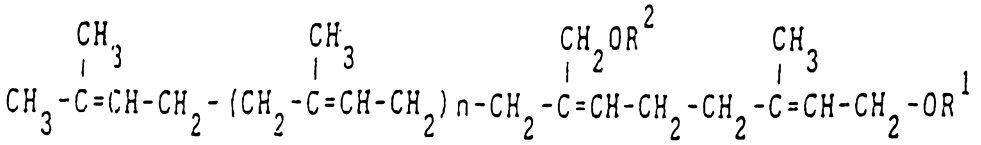
(57) Claim

1. A method for the prophylaxis and therapy of diseases, which method is based on the inhibition of inflammatory cytokine formation, using polyprenyl derivatives having the general formula as the active ingredient:



(I)

where R^1 and R^2 are the same or different, and each represents a hydrogen atom, a C_1-C_4 alkyl group, a C_2-C_{12} aliphatic acyl group, a C_7-C_{11} aromatic acyl group or a C_8-C_{12} aryl-substituted aliphatic acyl group; and n represents an integer from 0 to 2.

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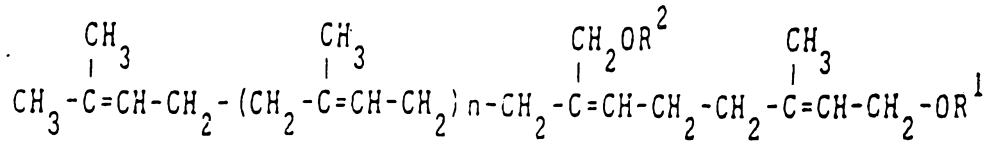
9. A method for the prophylaxis and therapy of ulcerative colitis, using polyprenyl derivatives having the general formula as the active ingredient:



(I)

where R^1 and R^2 are the same or different, and each represents a hydrogen atom, a C_1-C_4 alkyl group, a C_2-C_{12} aliphatic acyl group, a C_7-C_{11} aromatic acyl group or a C_8-C_{12} aryl-substituted aliphatic acyl group; and n represents an integer from 0 to 2.

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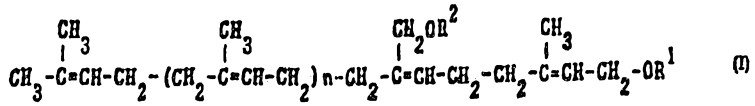
683112

(54) Title : INFLAMMATORY CYTOKINE PRODUCTION INHIBITOR CONTAINING POLYPRENYL DERIVATIVE AS ACTIVE INGREDIENT

(54) 発明の名称 ポリプレニル誘導体を有効成分とする炎症性サイトカイン産生抑制剤



(I)

(57) Abstract

An inflammatory cytokine production inhibitor containing a polyprenyl derivative represented by general formula (I) as the active ingredient, wherein R^1 and R^2 may be the same or different from each other and each represents hydrogen, C_1-C_4 alkyl, C_2-C_{12} aliphatic acyl, C_7-C_{11} aromatic acyl or C_8-C_{12} arylaliphatic acyl; and n represents 0 to 2. The derivative has an excellent effect of inhibiting inflammatory cytokine production and an excellent effect of curing inflammatory intestinal diseases, such as ulcerous colitis and Crohn's disease, and Behcet's disease, so that it is useful as an inflammatory cytokine production inhibitor and a curative or preventive for inflammatory intestinal diseases and Behcet's disease.

SPECIFICATION

An inhibitor of inflammatory cytokine formation comprising polyprenyl derivatives as the active ingredient

[Technical field]

The present invention concerns an inhibitor of inflammatory cytokine formation comprising polyprenyl derivatives as the active ingredient, and a method for the prophylaxis and/or treatment of diseases, which method is based on the inhibition of inflammatory cytokine formation by use of polyprenyl derivatives as the active ingredient.

[Technical background]

Inflammatory bowel diseases include ulcerative colitis and Crohn's disease. In both of these diseases, intractable ulceration or inflammation occurs in the intestinal tract of a young adult, and each is designated as one of the intractable diseases in this country.

Inflammatory bowel diseases occur frequently in the developed countries in Europe and America, and their sudden increase has also been observed in this country. A therapeutic method for these diseases has not yet been established, with the lone exception of a finding that sulfasalazine or a steroid derivative such as prednisolone is partly effective.

On the other hand, Behcet syndrome is a disease showing four main symptoms, stomatitis, skin symptoms, pudendal ulcer and eye symptoms. A disease showing the above four symptoms and having additional intestinal symptoms is known as intestinal type Behcet syndrome. These four main symptoms are convenient for diagnosis. However, these do not directly cause direct death, the main cause of death from Behcet syndrome being peritonitis caused by intestinal perforation.

Accompanied by the recent progress of immunology and gene manipulation, it is becoming clear that inflammatory cytokines including tumor necrotizing factor-α (hereinafter, abbreviated to TNFα) interleukine-6 (hereinafter, abbreviated to IL-6) and interleukine-8 (hereinafter, abbreviated to IL-8) participate in the cause and aggravation of these inflammatory bowel diseases and Behcet syndrome: in more detail, it is found that formation of these inflammatory cytokines is increased at the injured sites. Therefore, it is considered that inhibition of the formation of these inflammatory cytokines may be useful for the therapy and prevention of inflammatory bowel diseases and Behcet syndrome.

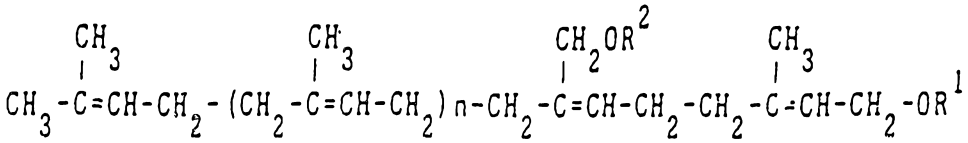
As mentioned above, the development of a drug having an excellent activity in inhibiting the formation of inflammatory cytokines and which is useful for the therapy and prevention of inflammatory bowel diseases and Behcet syndrome has been desired.

[Disclosure of the present invention]

The present inventors studied the pharmacological activities of various polyprenyl derivatives for many years. Their study resulted in the discovery that certain polyprenyl derivatives have an excellent activity in inhibiting the formation of inflammatory cytokines and they exhibit an excellent therapeutic effect on inflammatory bowel diseases including ulcerative colitis and Crohn's disease and on Behcet syndrome, and they have low toxicity; and that these derivatives are useful as an agent for inhibiting inflammatory cytokine formation and as a therapeutic and preventive agent for inflammatory bowel diseases and Behcet syndrome; and this resulted in completion of the present invention. Although the polyprenyl derivatives of the present invention are known to have antiulcer activity (for example, Japanese Patent Application Kokai No. Sho 52-62213 etc.,), their activity in inhibiting the formation of inflammatory cytokines, their therapeutic effect on inflammatory bowel diseases etc., are not known.

[Constitution of Invention]

The polyprenyl derivatives, the active ingredient of the present invention, have the general formula:



(I)

In the formula above:

R^1 and R^2 are the same or different, and each represents a hydrogen atom, a C_1-C_4 alkyl group, a C_2-C_{12} aliphatic acyl group, a C_7-C_{11} aromatic acyl group or a C_8-C_{12} aryl-substituted aliphatic acyl group; and n represents an integer from 0 to 2.

The C_1-C_4 alkyl group may be, for example, a methyl, ethyl, propyl, isopropyl, butyl, sec-butyl or isobutyl group; preferably a C_1-C_2 alkyl group; and particularly preferably a methyl group.

The C_2-C_{12} aliphatic acyl group may have double bond(s) and may be an acetyl, propionyl, butyryl, valeryl, isovaleryl, caproyl, heptanoyl, octanoyl, nonanoyl, decanoyl, lauroyl, acryloyl, metacryloyl, crotonoyl or 3-butenoyl group; preferably a C_2-C_6 aliphatic acyl group and particularly preferably an acetyl group.

The C_7-C_{11} aromatic acyl group may be,for example, a benzoyl or naphtoyl group; preferably a benzoyl group. The aromatic acyl group may have substituent(s) on the ring; and the substituent may be the aforementioned C_1-C_4 alkyl group; a C_1-C_4 alkoxy group such as a methoxy, ethoxy, propoxy, isopropoxy or butoxy group; or a halogen atom such as a fluorine, chlorine, bromine or iodine atom; preferably a methyl, methoxy, fluorine or chlorine atom.

The C_8-C_{12} aryl-substituted aliphatic acyl group may have double bond, and may be a phenylacetyl, phenylpropionyl, phenylbutyryl, phenylvaleryl, naphthylacetyl or cinnamoyl group; preferably a

phenylacetyl or cinnamoyl group; and particularly preferably a cinnamoyl group. The aryl-substituted aliphatic acyl group may have substituent(s) on the ring; and the substituents may be the same substituents as mentioned already for the aromatic acyl group.

In compound (I), there are geometric isomers due to the double bond in the molecule. The scope of the active ingredient of the present invention covers all these isomers, and preferable isomers are those in which all the double bonds have a trans configuration.

Of the compounds having the general formula (I) mentioned above, the following may be mentioned as preferable ones, in which:

(1) R^1 and R^2 are the same, and each represents a hydrogen atom, a methyl group, a C_2-C_{12} aliphatic acyl group, a benzoyl group or a cinnamoyl group;

(2) R^1 and R^2 are the same, and each represents a hydrogen atom or a C_2-C_6 aliphatic acyl group;

(3) R^1 and R^2 are the same, and each represents a hydrogen atom or an acetyl group;

(4) R^1 and R^2 are the same, and each represents a hydrogen atom; and

(5) n is 1.

In addition, a compound in which the groups are combined with ones selected optionally from the groups (1) to (5) may be also preferable.

Preferred compounds represented by the general formula (I) may be exemplified concretely in the following Table 1.

[Table 1]

Compound No.	R^1	R^2	n
1	H	H	0
2	Me	Me	0
3	MeCO	MeCO	0
4	EtCO	EtCO	0
5	PrCO	PrCO	0
6	$C_5H_{11}CO$	$C_5H_{11}CO$	0
7	$C_{11}H_{23}CO$	$C_{11}H_{23}CO$	0
8	CH_2=CHCO	CH_2=CHCO	0
9	CH(Me)=CHCO	CH(Me)=CHCO	0
10	PhCO	PhCO	0
11	PhCH=CHCO	PhCH=CHCO	0
12	H	H	1
13	Me	Me	1
14	Et	Et	1
15	MeCO	MeCO	1
16	H	MeCO	1
17	EtCO	EtCO	1
18	PrCO	PrCO	1
19	i-PrCO	i-PrCO	1
20	BuCO	BuCO	1
21	$C_5H_{11}CO$	$C_5H_{11}CO$	1
22	$C_{11}H_{23}CO$	$C_{11}H_{23}CO$	1
23	CH_2=CHCO	CH_2=CHCO	1

24	CH_2=C(Me)CO	CH_2=C(Me)CO	1
25	CH(Me)=CHCO	CH(Me)=CHCO	1
26	PhCO	PhCO	1
27	4-Me-PhCO	4-Me-PhCO	1
28	PhCH=CHCO	PhCH=CHCO	1
29	H	H	2
30	Me	Me	2
31	MeCO	MeCO	2
32	EtCO	EtCO	2
33	PrCO	PrCO	2
34	C_5H_{11}CO	C_5H_{11}CO	2
35	$C_{11}H_{23}$CO	$C_{11}H_{23}$CO	2
36	CH_2=CHCO	CH_2=CHCO	2
37	CH(Me)=CHCO	CH(Me)=CHCO	2
38	PhCO	PhCO	2
39	PhCH=CHCO	PhCH=CHCO	2

In the above table, the following abbreviations are used:

Bu = butyl

Et = ethyl

Me = methyl

Ph = phenyl

Pr = propyl

i-Pr = isopropyl

In the table above:

Preferred compounds are Compound Nos. 1, 3, 6, 7, 9, 10, 11, 12, 13, 15, 17, 21, 22, 23, 25, 26, 28, 29, 31, 34, 35, 37, 38 and 39;

More preferred compounds are Compound Nos. 1, 3, 12, 13, 15, 21, 22, 25, 26, 28, 29 and 31;

Much more preferred compounds are Compound Nos. 12, 13, 15, 21, 22, 25, 26 and 28;

Yet more preferred compounds are Compound Nos. 12 and 15; and

The particularly preferred compound is No. 12.

The polyprenyl derivatives having the general formula (I), which are the active ingredient of the present invention, are known compounds, or can be prepared easily according to the known methods (for example, Japanese Patent Application Kokai No. Sho 52-62213 etc.).

[Effect of Invention]

The polyprenyl derivatives of the present invention have an excellent activity in inhibiting the formation of inflammatory cytokines, they exhibit an excellent therapeutic effect on inflammatory bowel diseases and Behcet syndrome, and they show low toxicity. Therefore these derivatives are useful as a therapeutic and preventive agent for various kinds of diseases mentioned below, based on their inhibiting effect on the formation of inflammatory cytokines etc.

(1) Inflammatory bowel diseases including ulcerative colitis and Crohn's disease;

(2) Behcet syndrome;

(3) Autoimmune diseases including articular rheumatism, systemic lupus erythematosus (SLE) and diabetes mellitus;

(4) Stomatitis;

(5) Diseases with fistulation;

(6) Organ injuries associated with such diseases as cerebral infarction, pulmonary infarction, myocardial infarction etc., and resultant ischemia;

(7) Organ injuries and tissue injuries accompanied with reperfusion;

and

(8) Rejection reactions in organ transplantation etc.

Among these diseases, polyprenyl derivatives having the general formula (I), which are the active ingredient of the present invention, are preferably useful as a therapeutic and prophylatic agent for inflammatory bowel diseases or for Behcet syndrome, more preferably as a therapeutic and preventive agent for inflammatory bowel diseases, and particularly preferably as a therapeutic and preventive agent for ulcerative colitis and Crohn's disease.

[Possible usage in industry]

As mentioned above, polyprenyl derivatives having the

general formula (I), which are the active ingredient of the present invention, have an excellent activity in inhibiting the formation of inflammatory cytokines, they exhibit an excellent therapeutic effect on inflammatory bowel diseases and Behcet syndrome, and they are useful as a therapeutic and prophylactic agent for inflammatory bowel diseases.

When the polyprenyl derivatives having the general formula (I), which are the active ingredient of the present invention, are used as an agent for inhibiting inflammatory cytokine formation, the derivatives by themselves or a mixture of the derivatives and any pharmaceutically acceptable carriers, vehicles, diluents etc., may be administered orally or parenterally (including intrarectal administration) as pharmaceutical compositions such as powders, granules, tablets, capsules, injections, suppositories etc., and preferably orally. Though the dosage may be varied depending on the disease in question, the condition and age of the patient in question, the mode of administration etc., a dose of from 1 mg to 1000 mg (preferably from 10 mg to 500 mg) in a case of oral administration, and a dose of from 0.1 mg to 500 mg (preferably from 1 mg to 300 mg) in the case of intravenous administration, may be given one to three times a day according to the symptoms.

[The best mode for working the present invention]

Test Examples and Preparation Examples shown below

will explain the present invention in more detail. However, these examples do not limit the scope of the present invention.

(Test Example 1)

Cytokine formation inhibiting effect

About 30 ml of a peripheral blood sample (to which heparin was added) was taken from each of 3 patients with ulcerative colitis during active stage and 3 patients with Crohn's disease. The samples were separated by their specific gravity using Ficoll-Lonray Percoll to give monocyte (Mo) and macrophage (MΦ) fractions. 10% fetal cow serum (FCS) was added to these fractions and the mixture was prepared to be 1 x 10^4 cells/ml, by use of Rosewell Park Memorial Institute medium (RPMI-1640).

100 μl/ml of a known concentration of a test compound [Compound No. 12 (plaunotol): 10^{-5}M, 10^{-6}M and 10^{-7}M; sulfasalazine: 10^{-3}M, 10^{-4}M and 10^{-5}M; prednisolone: 2 x 10^{-5}M] was added to the diluted preparation. At that time, 0.01 mg/ml of lipopolysaccharide was added as a stimulant. After incubation for 3 hours under carbon dioxide, the serum cytokine levels were determined by solid phase enzyme-linked immunosorbent assay. The results are shown in Table 2 and Table 3.

[Table 2]

Cytokine formation inhibiting effect in a Mo-MΦ cell system derived from the peripheral blood samples of patients with ulcerative colitis

Test compounds (Concentration)	Formation rates of cytokines (%) TNFα	IL-6	IL-8
Compound No. 12 (10^{-6}M)	54.1±21.2*)	32.9±3.5**)	62.8±22.7
Sulfasalazine (10^{-4}M)	55.8±47.0*)	38.8±8.3**)	58.5±34.3
Prednisolone (2×10^{-5}M)	32.1±22.3*)	24.2±6.8**)	57.0±31.6
Control	100	100	100

*) $P < 0.05$
**) $P < 0.01$.

[Table 3]

Cytokine formation inhibiting effect in Mo-MΦ cell system derived from the peripheral blood samples of patients with Crohn's disease

Test compounds (Concentration)	Formation rates of cytokines (%) TNFα	IL-6	IL-8
Compound No. 12 (10^{-6}M)	19.9±12.4*)	29.9±3.9*)	46.9±5.1*)
Sulfasalazine (10^{-4}M)	10.9±18.6*)	21.6±6.7*)	44.2±6.6*)
Prednisolone (2×10^{-5}M)	9.4±16.2*)	13.8±7.2*)	33.0±2.7*)
Control	100	100	100

*) $P < 0.01$

As shown in these tables above, Compound No. 12 has a significant inhibitory effect, at a concentration of 10^{-6}M, on the formation of three kinds of cytokines, TNFα, IL-6 and IL-8, in the Mo-MΦ cell systems derived from peripheral blood samples of patients with ulcerative colitis and Crohn's disease (a decreased effect was observed on the levels of IL-8 in the peripheral blood Mo-MΦ cell system derived from patients with ulcerative colitis); and it shows equivalent or greater utility compared to sulfasalazine or prednisolone.

(Test Example 2)

Clinical effect in patients with ulcerative colitis

Compound No. 12 was administered to 5 patients with ulcerative colitis (active stage) at a daily dosage of from 3 tablets (240 mg) to 6 tablets (480 mg) divided into 3 doses. The patients were 3 females and 2 males from 21 to 46 years old. Among these patients, 4 cases had not shown improvement even after administration of 6 tablets (3.0 g) a day of sulfasalazine for 3 months, and the other case was incipient. The results are shown in Table 4.

[Table 4]

Clinical effect of Compound No. 12 in patients with ulcerative colitis

Case (Age)	Dosage & Adm. period	Clinical symptom Before Adm.	Clinical symptom After Adm.	Clinical judgement	Effect of combined drug 3 months before Adm.
1. Female (29)	3 tablets /day 3 months	Diarrhoea 5-6 times Bloody stool (+++) Stomach pain (+)	Diarrhoea 2-3 times Bloody stool (-) Stomach pain (-)	Remarkable	None*)
2. Male (28)	3 tablets /day 3 months	Diarrhoea 2 times Bloody stool (+)	Soft to normal stool 1-2 times Bloody stool (-)	Effective	None*)
3. Female (46)	3 tablets /day 3 months	Bloody stool (+) Mucous stool (+)	Bloody stool (-) Mucous stool (-)	Effective	None*)
4. Male (21)	6 tablets /day 2 months	Soft stool 4-5 times Bloody stool (++) Muscous stool (+)	Normal stool once Bloody stool (-) Mucous stool (-)	Remarkable	Not combined (initial admin.)
5. Female (24)	6 tablets /day 1.5 months	Diarrhea 4-5 times Bloody stool (++)	Soft stool 1-2 times Bloody stool (+)	Remarkable	None*)

*) Six tablets (3.0g) a day of sulfasalazine were administered.

As shown in the table above, the effect of Compound No. 12 was noted to be remarkable in 3 cases and effective in 2 cases. Neither unchanged nor aggravated cases were observed and no cases with adverse reaction were observed.

In the four cases where no improvement had been observed even after administration of sulfasalazine at a daily dosage of 6 tablets (3.0 g) for 3 months, administration of Compound No. 12 at a daily dosage of from 3 to 6 tablets for from 1.5 to 3 months brought about 2 remarkable cases and 2 effective cases. Compound No. 12 was proved to show a more excellent therapeutic effect than sulfasalazine.

(Test Example 3)

Clinical effect in patients with Crohn's disease

Compound No. 12 was administered to 3 patients with Crohn's disease (active stage) at a daily dosage of 6 tablets (480 mg) divided into 3 doses. The patients were 1 female and 2 males from 28 to 44 years old. Among these patients, 2 cases had not been improved even after administration of 6 tablets (3.0 g) a day of sulfasalazine for 3 months, and 1 case had not been improved even after combined administration of 6 tablets (3.0 g) a day of sulfasalazine, 6 tablets (3.0 g) a day of camostat mesilate and 6 tablets (3.0 g) a day of cepharanthine for 3 months. The results are shown in Table 5.

[Table 5]

Clinical effect of Compound No. 12 in patients with Crohn's disease

Case (Age)	Dosage & Adm. period	Clinical symptom Before Adm.	Clinical symptom After Adm.	Clinical judgement	Effect of combined drug 3 months before Adm.
1. Male (44)	6 tablets /day 1.5 months	Diarrhoea 2 times	Soft stool 2 times	Effective	None*)
		Bloody stool(-) Stomach pain(++)	Bloody stool(-) Stomach pain(-)		
2. Male (28)	6 tablets /day 6 months	Diarrhoea 2-3 times	Normal stool 1-2 times	Remarkable	None**)
		Stomach pain 2-3 times /day	Stomach pain 0-1 times /day		
3. Female (44)	6 tablets /day 3 months	Recto-vaginal fistula	Perfect recovery	Remarkable	None*)
		CRP(++)***)	CRP(-)***)		
		Eryth. sed. rate 35/h	Eryth. sed. rate 12/h		

*) Six tablets (3.0 g) a day of sulfasalazine were administered for 3 months.

**) Six tablets (3.0 g) a day of sulfasalazine, 6 tablets a day of camostat mesilate and 6 mg a day of cepharanthine were administered in combination for 3 months.

***) C reactive protein.

As shown in Table 5, the effect of Compound No. 12 was observed to be remarkable in 2 cases and effective in 1 case.

In the two cases where no improvement had been observed even after administration of sulfasalazine at a daily dosage of 6 tablets (3.0 g) for 3 months, administration of Compound No. 12 at a daily dosage of 6 tablets for from 1.5 to 3 months brought about 1 remarkable case and 1 effective case. In addition, in the case where no improvement had been observed even after combined administration of sulfasalazine at a daily dosage of 6 tablets (3.0 g), 6 tablets (3.0 g) a day of camostat mesilate and 6 mg a day of cepharanthine, administration of Compound No. 12 at a daily dosage of 6 tablets for 6 months brought about remarkable improvement. Compound No. 12 was proved to show a more excellent therapeutic effect than sulfasalazine.

From the fact that rectrovaginal fistula was closed by administration of Compound No. 12, this compound may be effective for the therapy of fistula such as internal fistula or outer fistula.

(Test Example 4)

Clinical effect in a patient with Behcet syndrome

Compound No. 12 was administered to a patient with Behcet syndrome (active stage) at a daily dosage of 6

tablets (480 mg) divided into 3 doses. The patient was a 51 years old female with the main three symptoms of Behcet syndrome, pudendal ulceration, recurrent stomatitis and erythema nodosum of the legs, accompanied by multiple apthous ulceration throughout the intestinal tract. Even after combined administration of sulfasalazine at a daily dosage of 6 tablets (3.0 g) and cepharanthine at a daily dosage of 6 mg for 3 months, diarrhoea, stomach pain and stomatitis had been observed.

The results are shown in Table 6.

[Table 6]

Clinical effect of Compound No. 12 in patients with Behcet disease

Case (Age)	Dosage & Adm. period	Clinical symptom Before Adm.	Clinical symptom After Adm.	Clinical judgement	Effect of combined drug 3 months before Adm.
1. Female (51)	6 tablets /day 3 months	Stomatitis (+) Diarrhoea (+) Stomach pain(+) Bloody stool(-)	Stomatitis (-) Diarrhoea (-) Stomach pain(-) Bloody stool(-)	Remarkable	None*)

*) Six tablets (3.0 g) a day of sulfasalazine together with 6 mg a day of cepharanthine were administered for 3 months.

As shown in Table 6, the effect of Compound No. 12 was found to be remarkable. Additionally, this compound was effective on stomatitis.

(Preparation Example 1)

Capsule preparation

Compound No. 12	20.0 mg
Lactose	108.0 mg
Corn starch	70.0 mg
Magnesium metasilicate aluminate	50.0 mg
Magnesium stearate	2.0 mg
	250 mg

A powder containing the above components is mixed, filtered through a sieve of 60 mesh and then incorporated in a No. 2 gelatine capsule for 250 mg to obtain the desired capsule preparation.

(Preparation Example 2)

Tablet prepation

Compound No. 12	20.0 mg
Lactose	103.0 mg
Low-substituted hydroxypropylcellulose	50.0 mg
Corn starch	25.0 mg
Magnesium metasilicate aluminate	50.0 mg
Magnesium stearate	2.0 mg
	250 mg

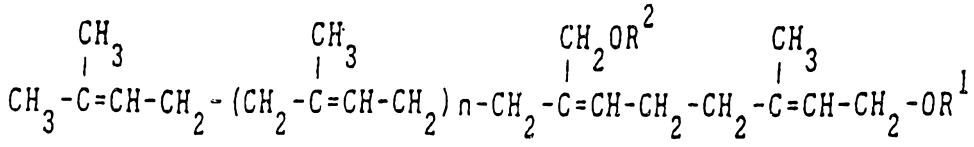
A powder containing the above components is mixed and tableted by use of a tableting machine to obtain the aimed 250 mg tablet preparation.

If necessary, this tablet can be covered with a sugar coating.

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

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A method for the prophylaxis and therapy of diseases, which method is based on the inhibition of inflammatory cytokine formation using polyprenyl derivatives having the general formula as the active ingredient:



(I)

where R^1 and R^2 are the same or different, and each represents a hydrogen atom, a C_1-C_4 alkyl group, a C_2-C_{12} aliphatic acyl group, a C_7-C_{11} aromatic acyl group or a C_8-C_{12} aryl-substituted aliphatic acyl group; and n represents an integer from 0 to 2.

2. The method for the prophylaxis and therapy of diseases, which method is based on the inhibition of inflammatory cytokine formation, according to Claim 1, in which the active ingredient is a polyprenyl derivative wherein R^1 and R^2 are the same, and each represents a hydrogen atom, a methyl group, a C_2-C_{12} aliphatic acyl group, a benzoyl group or a cinnamoyl group.

3. The method for the prophylaxis and therapy of diseases, which method is based on the inhibition of inflammatory cytokine formation, according to Claim 1, in which the active ingredient is a polyprenyl derivative wherein R^1 and R^2 are the same, and each represents a hydrogen atom or a C_2-C_6 aliphatic acyl group.

4. The method for the prophylaxis and therapy of diseases, which method is based on the inhibition of inflammatory cytokine formation, according to Claim 1, in which the active ingredient is a polyprenyl derivative wherein R^1 and R^2 are the same, and each represents a hydrogen atom or an acetyl group.

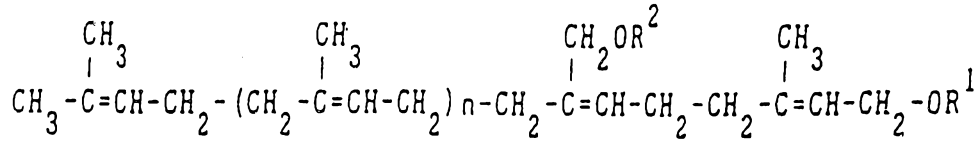
5. The method for the prophylaxis and therapy of diseases, which method is based on the inhibition of inflammatory cytokine formation, according to Claim 1, in which the active ingredient is a polyprenyl derivative wherein each of R^1 and R^2 is a hydrogen atom.

6. The method for the prophylaxis and therapy of diseases, which method is based on the inhibition of inflammatory cytokine formation, according to Claim 1, in which the active ingredient is a polyprenyl derivative wherein n is 1.

7. The method for the prophylaxis and therapy of diseases, which method is based on the inhibition of inflammatory cytokine formation, according to Claim 1, in which the active ingredient is a polyprenyl derivative wherein R^1 and R^2 are the same, and each represents a hydrogen atom or an acetyl group; and n is 1.

8. The method for the prophylaxis and therapy of diseases, which method is based on inhibition of inflammatory cytokine formation, according to Claim 1, in which the active ingredient is a polyprenyl derivative wherein each of R^1 and R^2 is a hydrogen atom and n is 1.

9. A method for the prophylaxis and therapy of ulcerative colitis, using polyprenyl derivatives having the general formula as the active ingredient:



(I)

where R^1 and R^2 are the same or different, and each represents a hydrogen atom, a C_1-C_4 alkyl group, a C_2-C_{12} aliphatic acyl group, a C_7-C_{11} aromatic acyl group or a C_8-C_{12} aryl-substituted aliphatic acyl group; and n represents an integer from 0 to 2.

10. The method for the prophylaxis and therapy of ulcerative colitis according to Claim 9, in which the active ingredient is a polyprenyl derivative wherein R^1 and R^2 are the same, and each represents a hydrogen atom,

a methyl group, a C_2-C_{12} aliphatic acyl group, a bezoyl group or a cinnamoyl group.

11. The method for the prophylaxis and therapy of ulcerative colitis according to Claim 9, in which the active ingredient is a polyprenyl derivative wherein R^1 and R^2 are the same, and each represents a hydrogen atom or a C_2-C_6 aliphatic acyl group.

12. The method for the prophylaxis and therapy of ulcerative colitis according to Claim 9, in which the active ingredient is a polyprenyl derivative wherein R^1 and R^2 are the same, and each represents a hydrogen atom or an acetyl group.

13. The method for the prophylaxis and therapy of ulcerative colitis according to Claim 9, in which the active ingredient is a polyprenyl derivative wherein each of R^1 and R^2 is a hydrogen atom.

14. The method for the prophylaxis and therapy of ulcerative colitis according to Claim 9, in which the active ingredient is a polyprenyl derivative wherein n is 1.

15. The method for the prophylaxis and therapy of ulcerative colitis according to Claim 9, in which the active ingredient is a polyprenyl derivative wherein R^1 and R^2 are the same, and each represents a hydrogen atom or an acetyl group; and n is 1.

16. The method for the prophylaxis and therapy of ulcerative colitis according to Claim 9, in which the active ingredient is a polyprenyl derivative wherein each of R^1 and R^2 is a hydrogen atom and n is 1.

17. The method for the prophylaxis and therapy of ulcerative colitis according to Claim 9, in which the active ingredient is a polyprenyl derivative wherein each of R^1 and R^2 is a hydrogen atom and n is 1.

18. A method according to any one of claims 1 to 17 substantially as hereinbefore described with reference to the Examples.

DATED this 15th day of July 1997

Sankyo Company Limited

By DAVIES COLLISON CAVE

Patent Attorneys for the Applicants

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP94/01971

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl^{6} A61K31/045, 31/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Int. Cl^{5} A61K31/045, 31/12

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS Online

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JP, A, 57-154123 (Sankyo Co., Ltd.), September 22, 1982 (22. 09. 82) & GB, A, 2095996 & DE, A, 3209722 & US, A, 4434179	1-26
A	JP, A, 52-62213 (Sankyo Co., Ltd.), May 23, 1977 (23. 05. 77) & GB, A, 1533377 & DE, A, 2652256 & US, A, 4192953	1-26

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
January 10, 1995 (10. 01. 95)	February 7, 1995 (07. 02. 96)
Name and mailing address of the ISA/ Japanese Patent Office	Authorized officer
Facsimile No.	Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)

国際調査報告

国際出願番号 PCT/JP 94/01971

A. 発明の属する分野の分類（国際特許分類（IPC））

Int. Cℓ⁶ A61K31/045, 31/12

B. 調査を行った分野

調査を行った最小限資料（国際特許分類（IPC））

Int. Cℓ⁵ A61K31/045, 31/12

最小限資料以外の資料で調査を行った分野に含まれるもの

国際調査で使用した電子データベース（データベースの名称、調査に使用した用語）

CAS Online

C. 関連すると認められる文献

引用文献のカテゴリー＊	引用文献名 及び一部の箇所が関連するときは、その関連する箇所の表示	関連する請求の範囲の番号
A	JP, A, 57-154123（三共株式会社）, 22. 9月. 1982（22. 09. 82） &GB, A, 2095996&DE, A, 3209722 &US, A, 4434179	1-26
A	JP, A, 52-62213（三共株式会社）, 23. 5月. 1977（23. 05. 77） &GB, A, 1533377&DE, A, 2652256 &US, A, 4192953	1-26

☐ C欄の続きにも文献が列挙されている。

☐ パテントファミリーに関する別紙を参照。

＊ 引用文献のカテゴリー
「A」特に関連のある文献ではなく、一般的技術水準を示すもの
「E」先行文献ではあるが、国際出願日以後に公表されたもの
「L」優先権主張に疑義を提起する文献又は他の文献の発行日若しくは他の特別な理由を確立するために引用する文献（理由を付す）
「O」口頭による開示、使用、展示等に言及する文献
「P」国際出願日前で、かつ優先権の主張の基礎となる出願の日の後に公表された文献
「T」国際出願日又は優先日後に公表された文献であって出願と矛盾するものではなく、発明の原理又は理論の理解のために引用するもの
「X」特に関連のある文献であって、当該文献のみで発明の新規性又は進歩性がないと考えられるもの
「Y」特に関連のある文献であって、当該文献と他の1以上の文献との、当業者にとって自明である組合せによって進歩性がないと考えられるもの
「&」同一パテントファミリー文献

国際調査を完了した日
10. 01. 95

国際調査報告の発送日 07.02.95

名称及びあて先
日本国特許庁（ISA/JP）
郵便番号100
東京都千代田区霞が関三丁目4番3号

特許庁審査官（権限のある職員） 4C 9283
星野紹英

電話番号 03-3581-1101 内線 3453

様式PCT/ISA/210（第2ページ）（1992年7月）