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[54] Title: AGENT CONTAINING AMINOBENZOIC ACID DERIVATIVES AS AN ACTIVE INGREDIENT HAVING AN ACTIVITY TO REDUCE SIDE EFFECTS

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[57] ABSTRACT see attached sheet

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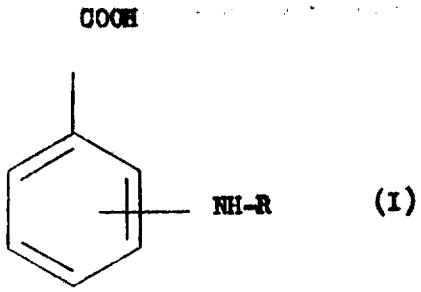
ABSTRACT OF THE DISCLOSURE

The present invention discloses a method for reducing side effects caused by an immunosuppressing agent comprising administering a pharmaceutical composition containing an effective amount of at least one derivative of aminobenzoic acid represented by the formula (I):



(I)

wherein R represents a saccharide; or a pharmaceutically acceptable salt thereof, as an active ingredient.

The characteristics of the pharmaceutical composition of the present invention are:

(1) it reduces side effects induced by an administration of an immunosuppressing agent;

(2) it does not injure an activity of immunosuppressing agents to restrain an immunorejection of an organ transplanted in a human body; and

(3) it is extremely low toxic by itself.

Accordingly, the composition of the present invention can be administered for a long period enough to exhibit its efficacy in its full capacity.

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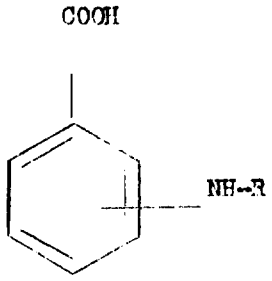
TITLE OF THE INVENTION:

AGENT CONTAINING AMINOBENZOIC ACID DERIVATIVE AS AN ACTIVE INGREDIENT HAVING AN ACTIVITY TO REDUCE SIDE EFFECTS INDUCED BY AN ADMINISTRATION OF IMMUNO-SUPPRESSANT.

BACKGROUND OF THE INVENTION

The present invention relates to a method for reducing side-effects induced by an administration of immuno-suppressant or immuno-suppressing agent comprising administering a pharmaceutical composition containing an effective amount of least once derivative of aminobenzoic acid represented by the formula (I):



(I)

wherein R represents a saccharide; or a pharmaceutically acceptable salt thereof, as an active ingredient.

Recently, as an organ transplantation becomes popular, administrations of an immunosuppressant have become essential to retrain a rejection of the organ. However, because of strong side effects of a conventional immunosuppressant, it is impossible to administer enough amount of the suppressant to restrain the rejection sufficiently. Accordingly, the reduction of these side effects has become an important issue recently. [Refer to "Clinics and Research," vol. 60, No. 7, pages 31 to 35 (1983)].

As a solution of the issue, several ideas have been proposed recently. Among them, a coadministration of various quinoline derivatives with Cyclosporin has been proposed to reduce the side effects induced by an administration of Cyclosporin. {Japanese Patent

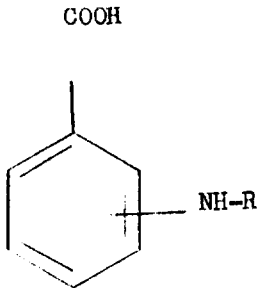
Application Laid-Open (KOKAI) No. 52-190,123 (1987)].

As an immuno-suppressant, for instance, alkylating agent, antimetabolite, folic acid antagonist, antibiotic or steroid has been used so far. These immuno-suppressants, however, have side effects on various viscera such as kidney, pancreas and liver, germ cells, stomach and/or intestines. They also reduce a resistance of a body against infectious diseases and carcinogenesis, and reduce a body weight. Scordingly, the situation was far away from satisfaction.

In order to solve the above propblems, the present inventors have extensively studied to reduce these side effects and havew found that a coadministration of these immuno-suppressants with aminobenzoic acid derivatives, which have been already proposed by the present inventors as a useful medicine, can reduce side effects induced by the suppressants. [Japanese Patent

Application Laid-Open (KOKAI) Nos. 54 135,738 (1979); 54-154,729 (1979); 55 92,319 (1980); 55-92,320 (1980) 56-34,629 (1981), 56 34,630 (1981); 56 55,369 (1981); 56 55,397 (1981) 56-86,198 (1981); 56-95,197 (1981); 57 16,898 (1982); 57 136,519 (1982); 57 136,520 (1982); 57-136,521 (1982); 57-136,522 (1982); 58-104,316 (1984) and 58 104,317 (1984)]. According to the finding, the present inventors have attained the present invention.

These derivatives of aminobenzoic acid of the present invention are represented by the formula (I):



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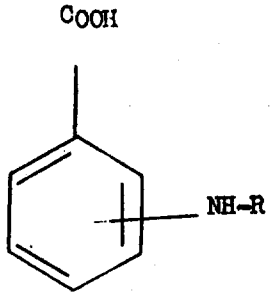
Since, in spite of its quite simple

chemical structure, the derivatives are extremely low toxic and have no antibacterial activity, a long term administration of the derivative is possible without the risk of deranging intestinal bacterial flora. Furthermore, since the derivatives do not affect mutagenesity, cell immunity and humoral immunity, they are an extremely safe medicine without having any risk to cause teratogenesis and allergic reaction.

SUMMARY OF THE INVENTION

The object of the present invention is to provide a method for reducing side effects induced by an administration of immunosuppressant comprising administering a pharmaceutical composition containing an effective amount of at least one derivative of aminobenzoic acid represented by the formula (I)



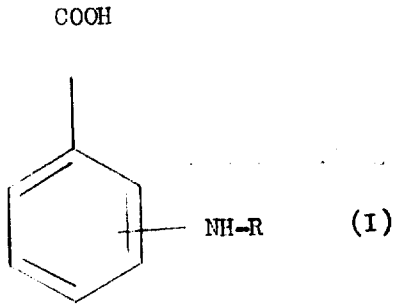
(I)

wherein R represents a saccharide; or a pharmaceutically acceptable salt thereof, as an active ingredient.

Another object of the present invention is to provde a method for reducing side effects induced by an administration of an immunosuppressant comprising administering a pharmaceutical composition containing an effective amount of at least one derivative of aminobenzoic acid represented by the above formula (I) for a long term without any risk of deranging intestinal bacterial flora and of causing tetragenesis and allergic reactions.

DETAILED DESCRIPTION OF THE INVENTION:

The present invention relates to a method for reducing side effects induced by an administration of immune suppressant comprising administering a pharmaceutical composition containing an effective amount of at least one derivative of aminobenzoic acid represented by the formula (I):



(I)

wherein R represents a saccharide; or a pharmaceutically acceptable salt thereof, as an active ingredient.

The derivative (hereinafter referred to as "the present substance") or its pharmaceutically acceptable salt (hereinafter included in the present substance) is a quite safe medicine and can administer for a long term without any risk of deranging intestinal bacterial flora and of causing teratogenesis and allergic reaction.

The present substance has three types of positional isomers, that are, para-, meta- and ortho-, depending upon a position substituted with amino group. Although there are slight differences in their activities, all of the three isomers are substantially equal in their usefulness.

Any saccharide can basically be used so long as it is bondable with an amino group of aminobenzoic acid. Even polysaccharide can be used but monosaccharide is more preferable. his saccharide can be D-form or L-form and α-type, β-type or their mixture can be

used as well.

Some of physical properties of the present substances are shown in Table 1.

Each of the present substance shown in Tables I to X is abbreviated as follows:

p-Aminobenzoic acid-N-L-arabinoside	p-L-Ara-Acid
Its Sodium Salt	p-L-Ara-Na
o-Aminobenzoic acid-N-L-arabinoside	o-L-Ara-Acid
Its Sodium Salt	o-L-Ara-Na
p-Aminobenzoic acid-N-D-xyloside	p-D-Xyl-Acid
Its Sodium Salt	p-D-Xyl-Na
o-Aminobenzoic acid-N-D-xyloside	o-D-Xyl-Acid
Its Sodium Salt	o-D-Xyl-Na
p-Aminobenzoic acid-N-D-glucoside	p-D-Glu-Acid
Its Sodium Salt	p-D-Glu-Na
o-Aminobenzoic acid-N-D-glucoside	o-D-Glu-Acid
Its Sodium Salt	o-D-Glu-Na
p-Aminobenzoic acid-N-D-galactoside	p-D-Gal-Acid
Its Sodium Salt	p-D-Gal-Na
o-Aminobenzoic acid-N-D-galactoside	o-D-Gal-Acid
Its Sodium Salt	o-D-Gal-Na
p-Aminobenzoic acid-N-L-rhamnoside	p-L-Rham-Acid
Its Sodium Salt	p-L-Rham-Na
o-Aminobenzoic acid-N-L-rhamnoside	o-L-Rham-Acid
Its Sodium Salt	o-L-Rham-Na
p-Aminobenzoic acid-N-D-mannoside	p-D-Man-Acid
Its Sodium Salt	p-D-Man-Na
m-Aminobenzoic acid-N-D-mannoside	m-D-Man-Acid
Its Sodium Salt	m-D-Man-Na

Table I-1. Physical Properties of The Present Substance

Compound No.	Present Substance	Melting point (°C)	Elementary Analysis (%)		Ultraviolet Absorption λmax (mμ)
			Theoretical Value C : H : N	Measured Value C : H : N	
1	p-L-Ara-Acid	156-158	53.5 : 5.6 : 5.2	53.3 : 5.7 : 5.2	290
2	p-L-Ara-Na	163-173 *1)	49.8 : 4.2 : 4.8	50 : 4.2 : 4.7	274
3	o-L-Ara-Acid	167	50.2 : 6.0 : 4.9	50.1 : 6.0 : 5.1	330, 250, 220
4	o-L-Ara-Na	155-162 *1)	46.6 : 5.2 : 4.5	46.6 : 5.1 : 4.6	315, 246, 212
5	p-D-Xyl-Acid	172	53.5 : 5.6 : 5.2	53.4 : 5.6 : 5.2	287
6	p-D-Xyl-Na	149-158	49.5 : 4.8 : 4.8	49.3 : 4.9 : 4.8	274
7	o-D-Xyl-Acid	168 *1)	53.5 : 5.6 : 5.2	53.4 : 5.7 : 5.0	330, 250, 220
8	o-D-Xyl-Na	160-170 *1)	49.5 : 4.8 : 4.8	49.7 : 4.8 : 4.7	316, 248, 215
9	p-D-Glu-Acid	132 *1)	49.2 : 6.0 : 4.4	49.5 : 5.8 : 4.6	288
10	p-D-Glu-Na		46.0 : 5.3 : 4.1	45.8 : 5.2 : 4.3	274
11	o-D-Glu-Acid	137-138 *1)	49.2 : 6.0 : 4.4	49.0 : 6.1 : 4.2	330, 250, 220
12	o-D-Glu-Na	145-160	46.0 : 5.3 : 4.1	46.1 : 5.2 : 4.0	318, 249, 215

*1) The substance decomposed at its melting point.

Table I-2 Physical Properties of The Present Substance

Compound No.	Present Substance	Melting point (°C)	Elementary Analysis (%)		Ultraviolet Absorption λmax (mμ)
			Theoretical Value C : H : N	Measured Value C : H : N	
13	p-D-Gal-Acid	154-156	49.2 : 6.0 : 4.4	49.0 : 6.3 : 4.5	289
14	p-D-Gal-Na	150-162	46.0 : 5.3 : 4.1	46.0 : 5.6 : 4.1	275
15	o-D-Gal-Acid	152	52.2 : 5.7 : 4.7	52.3 : 6.0 : 4.8	330, 250, 220
16	o-D-Gal-Na	157-163 *1)	48.6 : 5.0 : 4.4	48.5 : 5.2 : 4.4	317, 248, 215
17	p-L-Rham-Acid	169-170	55.1 : 6.0 : 4.9	55.0 : 6.2 : 4.8	290, 220
18	p-L-Rham-Na	173-179 *1)	51.1 : 5.2 : 4.6	51.0 : 5.1 : 4.8	273
19	o-L-Rham-Acid	165-166 *1)	55.1 : 6.0 : 4.9	54.8 : 5.9 : 4.9	330, 250, 219
20	o-L-Rham-Na	152-162	51.1 : 5.2 : 4.6	51.1 : 5.4 : 4.9	320, 249, 215
21	p-D-Man-Acid	182	52.2 : 5.7 : 4.7	52.0 : 5.7 : 4.7	290
22	p-D-Man-Na	185-196 *1)	46.0 : 5.3 : 4.1	46.1 : 5.3 : 4.0	274
23	m-D-Man-Acid	136	52.2 : 5.7 : 4.7	51.9 : 5.7 : 4.8	320, 247, 225
24	m-D-Man-Na	-	48.6 : 5.0 : 4.4	48.5 : 5.0 : 4.2	274

*1) The substance decomposed at its melting point.

Toxicological properties of the present substances are described as follows.

1) Acute Toxicity

The acute toxicity was studied with Jcl:ICR mice through intraperitoneal route and oral route. For intraperitoneal route, the present substance was dissolved in a physiological saline solution and a predetermined dose of the substance was administered with an injector to the cavvity. For oral route, the present substance was dissolved in a distilled water and administered forcibly through a stomach sonde.

After the administration, observation of toxicopathic symptoms of the mice were continued for 7 days and based on time to time death rates of the mice, LD_{50} values were calculated. Both surviving and dead mice were anatomized and observed certain organs. The LD_{50} values were calculated according to

Litchfield-Wilcoxon's drawing method and the results are shown in Table II.

Among all the value of intraperitoneal and oral routes, the minimum valu is 6.1 g/kg and the maximum is more than 15.0 kg. From these data, it is clear that the present substances are very safe medicines.

Table II. Acute Toxicity

No.	Present Substance	LD_{50} Value (g/kg)	
		Intraperitoneal	Oral
2	p-L-Ara-Na	10.22	10.80
4	o-L-Ara-Na	7.48	6.35
6	p-D-Xyl-Na	11.04	11.75
8	o-D-Xyl-Na	9.27	6.35
10	p-D-Glu-Na	> 15.00	> 15.00
12	o-D-Glu-Na	13.38	8.96
14	p-D-Gal-Na	12.00	14.55
16	o-D-Gal-Na	7.42	6.10
18	p-L-Rham-Na	15.00	12.80
20	o-L-Rham-Na	> 15.00	12.50
22	p-D-Man-Na	> 10.00	>10.00
24	m-D-Man-Na	> 10.00	> 10.00

2) Antibacterial Activity

The present substance was dissolved in distilled water according to serial doubling dilution system and these diluted solutions were mixed with ninefold amount of agar medium liquidized by heating. Each mixture was pured into a petri dish to make a plate. Heart infusion agar (for bacteria) or Sabouraoud's agar (for fungus) was used as a medium. After inoculataing preliminarily cultured bacteria or fungus to be tested by smearing on the medium, bacteria were cultured at a temperature of 37°C for 24 hours, yeast at 25°C for 3 days and mold fungi at 25°C for 7 days and observed their growth respectively.

The following bacteria, fungi or yeast were used for the tests.

Pseudononas aeruginosa	IAM 1514
Escherichia coli	IFO 12734
Staphylococcus aureus	209P
Bacillus subtilis	IAM 1069
Saccharomyces cerevisiae	IAM 4207
Candida albicans	ATCC 752
Trichophyton mentagrophytes	IFO 6124
Aspergillus niger	IAM 3001

The results indicate that the present substance show no growth inhibition on any bacteria, fungi or yeast even at a concentration of 1 mg/ml.

3) Mutagenecity

First, mutagenecity was studied with Rec-assay. A strain defectant of recombination repairing activity (Bacillus subtilis M45) and a strain keeping recombination repairing activity (Bacillus subtilis H17) were streaked

on B-II agar medium (10 g of flesh extract, 10 g of polypeptone, 5 g of NaCl and 15 g of ager were dissolved in 1,000 ml of distilled water and pH value was adjusted to 7.0) so that their own streaks do not cross at the start point. The present substance was dissolved with sterilized water, 0.05 ml of the solution was absorbed by a round filter paper having a diameter of 8 mm and immediately the filter paper eas laid on the medium (B-II agar) in a manner to cover each of the satrt point of the streak. Then, the medium was cultured for 16 hours at a temperature of 37°C and measured growth inhibited area. Kanamycin was used as a negative control and mitomycin as a positive control.

In addition, a reversion asay was performed using TA98 and TA100 of Salmonella typhimurium (both are histidine-requiring bacteria).

10% by volume of 0.5 mM bithion solution containing 0.5 mM histidine was added to a soft

agar solution (prepared with 6 g of NaCl, 6 g of agar and 1,000 ml of distilled water). Then, 0.1 ml of a solution containing 1 x 10g of the bacteria and 0.1 ml of a solution of the present substance were added to 2 ml of the soft agar solution, mixed well and obtained soft agar solution was multilayered on a minimal agar medium. The medium layered was cultured at 37°C for 2 days and number of reversion colonies was counted. Furylfuramide (AF2) was used as a positive control.

The results of Rec assay are shown in Table III and those of revversion assay in Table IV respectively.

In the REc assay of the present substance, no mutagenecity was observed until its concentration reaches high. Especially good resultswere obtained with p-aminobensoic acid sodium derivative.

In the revversion assy, a generation ratio

of mutant by the present substance show no significant difference with that of control even in a high concentration.

The results demonstrate that the safety of the present substance is very high as a medicine.

Table III-1 Rec-assay

No.	Present Substance	Concentration (μg/disk)	Growth Inhibited Area (mm)		
			M45	H17	M45 - M17
2	p-L-Ara-Na	500	0	0	0
2	p-L-Ara-Na	5,000	0	0	0
4	o-L-Ara-Na	500	0	0	0
4	o-L-Ara-Na	5,000	8	4	4
6	p-D-Xyl-Na	500	0	0	0
6	p-D-Xyl-Na	5,000	0	0	0
8	o-D-Xyl-Na	500	0	0	0
8	o-D-Xyl-Na	5,000	7	3	4
10	p-D-Glu-Na	500	0	0	0
10	p-D-Glu-Na	5,000	0	0	0
12	o-D-Glu-Na	500	0	0	0
12	o-D-Glu-Na	5,000	5	2	3
14	p-D-Gal-Na	500	0	0	0
14	p-D-Gal-Na	5,000	0	0	0
16	o-D-Gal-Na	500	0	0	0
16	o-D-Gal-Na	5,000	6	1	5
18	p-L-Rham-Na	500	0	0	0
18	p-L-Rham-Na	5,000	0	0	0
20	o-L-Rham-Na	500	0	0	0
20	o-L-Rham-Na	5,000	6	2	4

Table III-2 Rec-assay

No.	Present Substance	Concentration (μg/disk)	Growth Inhibited Area (mm)		
			M45	H17	M45 - H17
22	p-D-Man-Na	500	0	0	0
22	p-D-Man-Na	5,000	0	0	0
24	m-D-Man-Na	500	0	0	0
24	m-D-Man-Na	5,000	7	1	6
	Kanamycin (Negative Control)	10	5	4	1
	Mitomycin (Positive Control)	0.05	12	2	10

Table IV Reversion Colony Test

No.	Present Substance	Concentration (μg/disk)	No. of Reversion Colony (n/plate)	
			TA100	TA98
2	p-L-Ara-Na	5,000	51	3
4	o-L-Ara-Na	5,000	59	4
6	p-D-Xyl-Na	5,000	58	4
8	o-D-Xyl-Na	5,000	166	4
10	p-D-Glu-Na	5,000	104	11
12	o-D-Glu-Na	5,000	151	5
14	p-D-Gal-Na	5,000	51	7
16	o-D-Gal-Na	5,000	151	6
18	p-L-Rham-Na	5,000	73	4
20	o-L-Rham-Na	5,000	61	9
22	p-D-Man-Na	5,000	138	5
24	m-D-Man-Na	5,000	90	6
	Furylfuramide (AF2)	0.1	911	167
	Drug-free Control	--	149	13

4) Delayed intracutaneous reaction

Food pad reaction test was performed on Jcl:ICR mice using sheep red blood cells as an antigen to study influences of the present substance on cell immunity. 0.2 ml of 10% suppression of sheep red blood cells in a physiological saline solution was given to the mice intravenously at tails to make a primary sensitization.

After seven days, 0.005 ml of 40% suspension of sheep red blood cells was injected into the foot pad to make a secondary sensitization. 2.5% physiological

saline solutions of the present substance were administered intraperitoneally for 5 consecutive days placing the day of the primary sensitization in the middle until the total dose reaches 250 mg/kg body-weight.

The results show that no difference in the thicknees of foot pads was observed between the group administered with the present substance and the control group free from the administration.

5) Antibody producing activity

In order to study influences on humoral immunity of the present substance, 0.2 ml of 10% suspension of sheep red blood cells was given to Jcl"ICR mice intravenously at tails to make a sensitization and on the 7th day after the sensitization, blood was taken to measure its antibody producing activity with an agglutination of the blood red cells. 2.5% physiological saline solutions of the present substance were administered intraperitoneally

for 5 consecutive days placing the day of the sensitization in the middle until the total dose reaches 250 mg/kg body-weight.

The results show that no difference in agglutination of the cells was observed between the group administered with the present substance and the control group.

The pharmacological properties of the present substance are described as follows.

The present substances reduces significantly side effects induced by an administration of immuno-suppressants, for instance, significantly prevents a decrease of body-weights, increase an inulin clearance, and reduces a serum creatine as improvements of the kidney function. Additionally, the present substance remarkably reduces a saccharide level in blood and also improves insuline reactivity in a saccharide tolerance test as an improvemen of pancreases function and reduces

total amount of bilirubin in blood as an improvement of liver function. furthermore, the present substance does not reduce an activity of immuno-suppressants to restrain a rejection reaction against a transplanted organ.

As immuno-suppressants coadministrable with the present substance, alkylating agents, antimetabolites, folic acid antagonists, antibiotics, steroid, etc. can be used. As alkylating agents, cyclophosphamide and chlorambucil; as antimetabolites, azathioprine, 6-mercaptopurine and 5-fluorouracil cytosine arabinoside; as folic acid antagonists, methotrexate and as antibiotics, mitomycin, actinomycin, bredinin, cyclosporin and their derivatives can be exemplified.

Basic concepts of pharmaceutical compositions of the present substance are described below.

When the present substance is used as a

pharmaceutical composition to reduce side effects induced by an administration of immunosuppressant, compositions of any type can be used according to a kind of the side effects and its symptom as far as the type is convenient to use as the composition. The present substance can also be used by itself or as a mixture with pharmaceutically acceptable diluent and/or other pharmaceuticals.

The present substance can be administered orally or parenterally and therefore can be used in any form administerable orally or parenterally and in any dosage form.

The present substance can be used in the form of a mixture with immuno suppressants. Further, the present substance can be administered after, before or on the time of administration of immuno suppressants.

The present substance can be given to a human or an animal orally or parenterally but

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oral administration is preferable. A dosage of the present substance to be administered is different in case of either a human or an animal. In the case of a human, a dosage when orally administered is 0.1 to 1,000, preferably 1 to 500 mg/day/kg body weight and when parenterally administered is 0.01 to 300, preferably 0.1 to 100 mg/day/kg body weight and 1 to 4 times a day. However, since the dosage is different individual to individual, for instance, according to his or her age, symptom or health situation, the dosage can also be outside of the above range occasionally.

In summary, the present substance can reduce various side effects, for example, dysfunction of several viscera such as kidney, pancreas or liver, and systemic symptoms, for example, decrease of a body weight, all of which are induced by an administration of immuno-suppressants. Moreover, the present substance never injure an activity of immuno-suppressant to restrain a rejection reaction of

a transplanted organ. Further, the present substance shows almost no side effects by itself and accordingly quite a safe pharmaceuticals.

The present invertion will be described more concretely in the following Examples, however, the Examples shall not be limitative of this invention.

Example 1:

25 mg/kg body weigt/day of cyclosporin (hereinafter referred to as "CsA") were given intraperitoneally to groups each consisting of six Wistar male rats, every consecutive days for 3 weeks. 300 mg/kg body weight/day of the present substance 9as 2.5% physiological saline solution) to a testing group and same amount of distilled water to a control group were administered orally at the same time when CsA were given. After each administration of CsA, body weights of rats were measured every

day. Various clearance tests and a saccharide tolerance test were performed after completion of the administrations. Then, after sacrificing the rats, their blood was taken for serum biochemical and general blood tests.

The results of the tests show that a great decrease in body weight was observed in the group administered of CsA alone (hereinafter referred to as "control group") while an improvement on the body weight decreased was observed in the group coadministered with the present substance (hereinafter referred to as "testing group"). (Table V). For an improvement of kidney function by coadministration of the present substance, a significant increase of inulin clearance lowered and a suppression of serum creatinine increased both by a single administration of CsA were observed. (Table VI). An improvement of pancreas function was studied by a saccharide tolerance test and a blood sugar value elevated by an administration of CsA was

remarkably lowered in the testing group. (Table VII). Further, although almost no increase of insulin secretion was observed in the control group, in the testing group an amount of insulin in blood became significantly higher compared with the amount before the test. (Table VIII). Still further, the serum biochemical test demonstrates that total bilirubin, which is one of the indices of liver function and increased by an administration of CsA, was significantly declined by a coadministration of the present substance (Table IX).

Table V Body Weight of Rat at The Completion of The Test

No.	Present Substance	Body Weight (g)	No.	Present Substance	Body Weight (g)
2	p-L-Ara-Na	220	8	o-D-Xyl-Na	211
4	o-L-Ara-Na	218	10	p-D-Gul-Na	235
18	p-L-Rham-Na	238	12	o-D-Gul-Na	232
20	o-L-Rham-Na	233	22	p-D-Man-Na	245
14	p-D-Gal-Na	215	24	m-D-Man-Na	240
16	o-D-Gal-Na	210		CsA Alone	194±14
6	p-D-Xyl-Na	208		Control	248±13

Table VI Inulin Clearance and Serum Creatinine

No.	Present Substance	Kidney Function	
		Inulin Clearance (ml/min.)	Serum Creatinine (mg/dl)
2	p-L-Ara-Na	1.81	0.65
4	o-L-Ara-Na	1.78	0.67
18	p-L-Rham-Na	1.97	0.64
20	o-L-Rham-Na	1.95	0.64
14	p-D-Gal-Na	1.88	0.66
16	o-D-Gal-Na	1.81	0.65
6	p-D-Xyl-Na	1.70	0.66
8	o-D-Xyl-Na	1.72	0.65
10	p-D-Gul-Na	1.85	0.65
12	o-D-Gul-Na	1.88	0.64
22	p-D-Man-Na	2.05	0.63
24	m-D-Man-Na	2.00	0.64
	CsA Alone	1.48	0.71

Table VII Saccharide Tolerance Test

No.	Present Substance	* 1)	No.	Present Substance	* 1)
2	p-L-Ara-Na	588	6	p-D-Xyl-Na	598
4	o-L-Ara-Na	591	8	o-D-Xyl-Na	605
18	p-L-Rham-Na	573	10	p-D-Gul-Na	612
20	o-L-Rham-Na	576	12	o-D-Gul-Na	589
14	p-D-Gal-Na	584	22	p-D-Man-Na	569
16	o-D-Gal-Na	587	24	m-D-Man-Na	578
				CsA Alone	771

*1) Blood sugar value in mg/dl measured 10 minutes after the test.

Table VIII Saccharide Tolerance Test

No.	Present Substance	Insuline Value (mμ/ml)	
		Before The Test	10 Min. After The Test
2	p-L-Ara-Na	4.02	6.12
4	o-L-Ara-Na	3.89	6.22
18	p-L-Rham-Na	4.30	6.44
20	o-L-Rham-Na	4.34	6.38
14	p-D-Gal-Na	4.13	6.10
16	o-D-Gal-Na	4.22	6.16
6	p-D-Xyl-Na	4.28	6.20
8	o-D-Xyl-Na	4.21	6.18
10	p-D-Gul-Na	4.05	6.02
12	o-D-Gul-Na	4.11	6.12
22	p-D-Man-Na	4.45	6.50
24	m-D-Man-Na	4.40	6.37
	CsA Alone	1.30	1.30

Table IX Sereum Total Bilirubin Value

No.	Present Substance	TBI*1) (mg/dl)	No.	Present Substance	TBI*1) (mg/dl)
2	p-L-Ara-Na	0.35	6	p-D-Xyl-Na	0.35
4	o-L-Ara-Na	0.37	8	o-D-Xyl-Na	0.38
18	p-L-Rham-Na	0.29	10	p-D-Gul-Na	0.36
20	o-L-Rham-Na	0.31	12	o-D-Gul-Na	0.36
14	p-D-Gal-Na	0.33	22	p-D-Man-Na	0.27
16	o-D-Gal-Na	0.34	24	m-D-Man-Na	0.30
				CsA Alone	0.58

*1) TBI means seerum total bilirubin value.

Although the above Example 1 clearly shows that administration of CsA produces toxic effect that injure the function of kidney, pancreas, liver, etc., administration of the present substance significantly reduce such toxic effects induced by a dose of CsA. This effect is a novel fact found by the present inventors and based on this fact together with the fact that the present substance is extremely safe, the present novel invention has been made.

EXAMPLE 2:

A mixture of 50 µl of human lymphocyte (1.6 x 10^6/ml) with 50 µl of the lymphocytes treated with mitomycin C (MMC) (1.7 x 10^6/ml) was cultured for 6 days and an uptake of ^{3}H-thymidine, an index of proliferation of lymphocyte, was studied. The medium used for culture comprised bovine fetal serum (10% in quantity) and RPMI 1640 (90% in quantity).

The uptake value of ^{3}H-thymidine was observed both in the cases of administration of CsA alone and of coadministration with the present substance and based on the value a suppressing ratio of proliferation of lymphocytes was calculated. From the calculated ratio, the effects of the present substance on immuno function were studied.

As shown in Table X, the present substance show almost no affection on the depressing effect on a proliferation of lymphocytes induced by an administration of CsA.

Table X

No.	CsA (μg/ml)	Present Substance	Quantity (μg/ml)	Depressing Ratio (%)
	0.1	--	0	27
2	0.1	p-L-Ara-Na	100	26
4	0.1	o-L-Ara-Na	100	26
18	0.1	p-L-Rham-Na	100	27
20	0.1	o-L-Rham-Na	100	26
14	0.1	p-D-Gal-Na	100	26
16	0.1	o-D-Gal-Na	100	26
6	0.1	p-D-Xyl-Na	100	26
8	0.1	o-D-Xyl-Na	100	27
10	0.1	p-D-Gul-Na	100	26
12	0.1	o-D-Gul-Na	100	27
22	0.1	p-D-Man-Na	100	28
24	0.1	m-D-Man-Na	100	27

EXAMPLE 3: Example of Pharmaceutical Composition

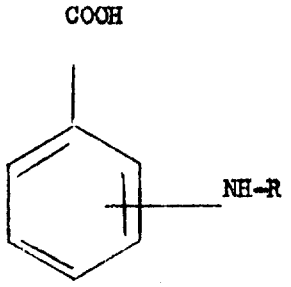
The present substance (p-aminobenzoic acid sodium-N-D-galactoside, Compound No. 14) 0.6 part

Non-ionic Surfactant	2.4 parts
Physiological saline solution	97.0.

The above were mixed under heating and sterilised to make an injectable liquid.

CLAIMS:

1. A method for reducing side effects induced by an administration of immunosuppressive antibiotic comprising administering a pharmaceutical composition containing an effective amount of at least one derivative of aminobenzoic acid represented by the formula (I):



(I)

wherein R represents a monosaccharide selected from the group consisting of arabinoside, xyloside, glucoside, galactoside, rhamnoside and mannoside; or a pharmaceutically

acceptable salt thereof.

2. The method according to claim 1, wherein said immunosuppressive antibiotic is cyclosporin.

3. The method according to claim 1, wherein said pharmaceutically acceptable salt is a sodium salt.

4. The method according to claim 1, wherein said pharmaceutical composition is administered simultaneously with said immunosuppressive antibiotic.