AUSTRALIA

PATENTS ACT 1990

NOTICE OF ENTITLEMENT

We, **Nippon Soda Co., Ltd.**, the applicant/Nominated Person in respect of Application No. 52862/93 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 inventors, be entitled to have the patent assigned to the Nominated Person.

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

DATED this TWENTY FOURTH day of MAY 1995

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

(DCC ref: 1736451)

AU9352862

(12) PATENT ABRIDGMENT (11) Document No. AU-B-52862/93
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 674550

(54) Title
PLATELET AGGREGATION INHIBITOR

International Patent Classification(s)
(51)[5] C07D 237/04 A61K 031/50 C07D 237/14

(21) Application No. : 52862/93 (22) Application Date : 22.10.93

(87) PCT Publication Number : WO94/09784

(30) Priority Data

(31) Number	(32) Date	(33) Country
4-317739	02.11.92	JP JAPAN
4-352151	10.12.92	JP JAPAN

(43) Publication Date : 24.05.94

(44) Publication Date of Accepted Application : 02.01.97

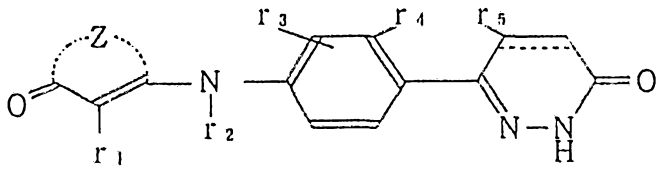
(71) Applicant(s)
NIPPON SODA CO., LTD.

(72) Inventor(s)
NOBUO MOCHIZUKI; SHUICHI SOUMA; TAKAYOSHI SASAKI; YUKIHIRO KANAGUCHI; NOBUHIRO UMEDA

(74) Attorney or Agent
DAVIES COLLISON CAVE , 1 Little Collins Street, MELBOURNE VIC 3000

(56) Prior Art Documents
AU 30466/89 C07D 237/04
AU 84602/91 C07D 237/04
AU 11535/92 C07D 237/04

(57) In Japanese Patent Laid-opened No. Hei 2-56468, compounds represented by the following general formula [II]:



[II]

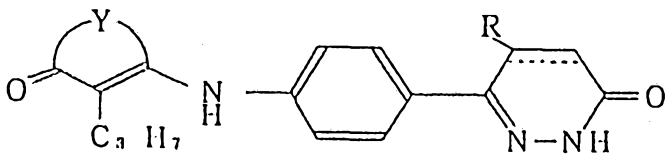
wherein Z is alkylene containing 1 to 4 carbons and optionally substituted by alkyl, lower alkoxy, lower alkylthio lower alkyl, lower alkoxycarbonyl or benzyl, or a group represented by a general formula $-C(r_6)=C(r_7)-$ wherein r_6 and r_7 are each independently hydrogen, alkyl, lower alkoxy, lower alkylthio lower alkyl, lower alkoxycarbonyl or benzyl; r_1 is lower alkyl optionally substituted by hydrogen or lower alkoxy, acetyl or lower alkenyl; r_2 is hydrogen or methyl; r_3 and r_4 are each independently hydrogen, halogen, hydroxy, lower alkyl or lower alkoxy; r_5 is lower alkyl optionally substituted by hydrogen or hydroxy; or r_4 may form in together with r_5 a bond, such as $-CH_2-$, $-CH_2CH_2-$ and $-OCH_2-$; and

.../2

represents a single bond or a double bond, and pharmaceutically-compatible complexes thereof are disclosed, and wherein it is described that these compounds and complexes have (1) an excellent cardiotonic effect and therefore can be a therapeutic drug for congestive heart failure and (2) a preventive effect on platelet aggregation.

Claim

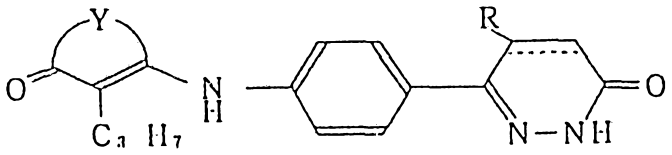
1. A preventative agent for platelet aggregation comprising an effective amount of the compound represented by the following general formula [I]:



[I]

wherein Y is $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$, R is methyl, and ⎓ represents a single bond; or a pharmaceutically acceptable complex thereof, and a pharmaceutically acceptable excipient or carrier.

5. A compound represented by the following general formula [I]:



[I]

wherein Y is $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$, R is methyl, and ⎓ represents a single bond.

OPI DATE 24/05/94 APPLN. ID 52862/93
AOJP DATE 28/07/94 PCT NUMBER PCT/JP93/01527

AU9352862

(51) 国際特許分類 5
A61K 31/50, C07D 237/04
C07D 237/14

A1

(11) 国際公開番号 WO 94/09784

(43) 国際公開日 1994年5月11日(11.05.94)

(21) 国際出願番号 PCT/JP93/01527
(22) 国際出願日 1993年10月22日(22. 10. 93)

(30) 優先権データ
特願平4/317739 1992年11月2日(02. 11. 92) JP
特願平4/352151 1992年12月10日(10. 12. 92) JP

(71) 出願人(米国を除くすべての指定国について)
日本曹達株式会社(NIPPON SODA CO., LTD.)〔JP/JP〕
〒100 東京都千代田区大手町2丁目2番1号 Tokyo, (JP)
(72) 発明者;および
(75) 発明者/出願人(米国についてのみ)
望月信夫(MOCHIZUKI, Nobuo)〔JP/JP〕
相馬秀一(SOUMA, Shuichi)〔JP/JP〕
佐々木高義(SASAKI, Takayoshi)〔JP/JP〕
金口幸裕(KANAGUCHI, Yukihiro)〔JP/JP〕
梅田信広(UMEDA, Nobuhiro)〔JP/JP〕
〒250-02 神奈川県小田原市高田字柳町345
日本曹達株式会社 小田原研究所内 Kanagawa, (JP)
(74) 代理人
弁理士 東海裕作, 外(TOKAI, Yusaku et al.)
〒100 東京都千代田区大手町2丁目2番1号
日本曹達株式会社内 Tokyo, (JP)

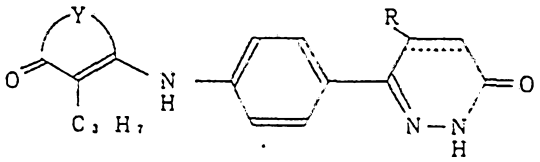
(81) 指定国 AT, AU, BB, BG, BR, CA, CH, CZ, DE, DK, ES, FI, GB, HU, KR, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, 欧州特許 (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI 特許 (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

添付公開書類 国際調査報告書

674550

(54) Title : PLATELET AGGREGATION INHIBITOR

(54) 発明の名称 血小板凝集抑制剤



(I)

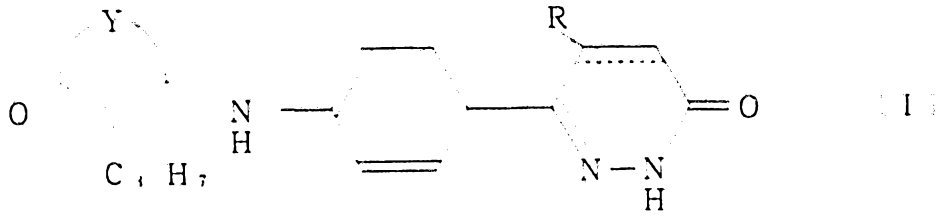
(a)

(57) Abstract

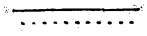
A platelet aggregation inhibitor containing a compound represented by general formula (I) or a pharmaceutically acceptable complex thereof as the active ingredient, wherein Y represents $-CH_2-CH_2-$ or $-CH_2-CH_2-CH_2-$; R represents hydrogen or methyl; and symbol (a) represents either a single or a double bond.

(57) 要約

一般式〔I〕



式中、Yは－CH_2CH_2－または－$CH_2CH_2CH_2$－を表し、Rは水素原子またはメチル基を表し、



は単結合又は二重結合を表す。〔I〕で表わされる化合物または医薬上許容される複合体を薬効成分として含有する血小板凝集抑制剤。

情報としての用途のみ
PCTに基づいて公開される国際出願のパンフレット第1頁にPCT加盟国を同定するために使用されるコード

AT オーストリア
AU オーストラリア
BB バルバードス
BE ベルギー
BF ブルキナ・ファソ
BG ブルガリア
BJ ベナン
BR ブラジル
BY ベラルーシ
CA カナダ
CF 中央アフリカ共和国
CG コンゴー
CH スイス
CI コート・ジボアール
CM カメルーン
CN 中国
CS チェッコスロヴァキア
CZ チェッコ共和国
DE ドイツ
DK デンマーク
ES スペイン
FI フィンランド
FR フランス
GA ガボン
GB イギリス
GN ギニア
GR ギリシャ
HU ハンガリー
IE アイルランド
IT イタリー
JP 日本
KP 朝鮮民主主義人民共和国
KR 大韓民国
KZ カザフスタン
LI リヒテンシュタイン
LK スリランカ
LU ルクセンブルグ
LV ラトヴィア
MC モナコ
MG マダガスカル
ML マリ
MN モンゴル
MR モーリタニア
MW マラウイ
NE ニジェール
NL オランダ
NO ノルウェー
NZ ニュージーランド
PL ポーランド
PT ポルトガル
RO ルーマニア
RU ロシア連邦
SD スーダン
SE スウェーデン
SI スロヴェニア
SK スロヴァキア共和国
SN セネガル
TD チャード
TG トーゴ
UA ウクライナ
US 米国
UZ ウズベキスタン共和国
VN ヴェトナム

S P E C I F I C A T I O N

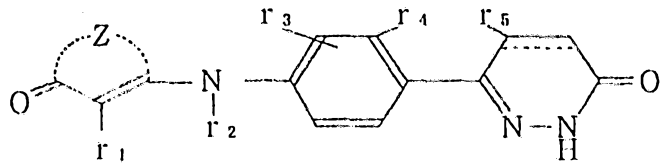
A Preventive Agent for Platelet Aggregation

Field of the Invention

The present invention relates to a preventive agent for platelet aggregation.

Background Art

In Japanese Patent Laid-opened No. Hei 2-56468, compounds represented by the following general formula [II]:



[II]

wherein Z is alkylene containing 1 to 4 carbons and optionally substituted by alkyl, lower alkoxy, lower alkylthio lower alkyl, lower alkoxycarbonyl or benzyl, or a group represented by a general formula $-C(r_6)=C(r_7)-$ wherein r_6 and r_7 are each independently hydrogen, alkyl, lower alkoxy, lower alkylthio lower alkyl, lower alkoxycarbonyl or benzyl; r_1 is lower alkyl optionally substituted by hydrogen or lower alkoxy, acetyl or lower alkenyl; r_2 is hydrogen or methyl; r_3 and r_4 are each independently hydrogen, halogen, hydroxy, lower alkyl or lower alkoxy; r_5 is lower alkyl optionally substituted by hydrogen or hydroxy; or r_4 may form in together with r_5 a bond, such as $-CH_2-$, $-CH_2CH_2-$ and $-OCH_2-$; and

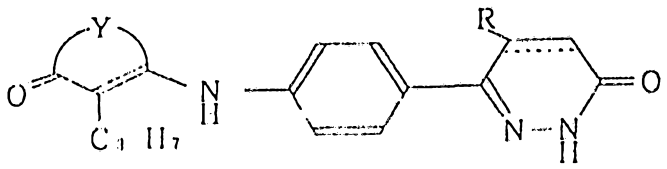
represents a single bond or a double bond, and pharmaceutically-compatible complexes thereof are disclosed, and wherein it is described that these compounds and complexes have (1) an excellent cardiotonic effect and therefore can be a therapeutic drug for congestive heart failure and (2) a preventive effect on platelet aggregation.

Disclosure of the Invention

The inventors of the present invention had investigated on compounds represented by the general formula [I] or the pharmaceutically-compatible complexes thereof for aiming at developing their novel medical use. As the result, the inventors found that compounds represented by the general formula [I], which is a compound group of the compounds represented by a general formula [II] wherein r_1 is C_3H_7, or the pharmaceutically-compatible complexes thereof have an excellent preventive effect on platelet aggregation and less cardiotonic effect, and they can be used as an preventive agent for platelet aggregation. It is an unexpected fact that the compounds represented by the general formula [I] or the pharmaceutically-compatible complexes thereof have

less cardiotonic effect, basing upon the prior knowledge in the art on the compounds represented by the general formula [I] or the pharmaceutically-compatible complexes thereof.

It is an object of the present invention to provide an excellent preventive agent for platelet aggregation, which comprises a compound represented by the following general formula [I]:



[I]

wherein Y is $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$, R is methyl and ⎓ represents a single bond provided that when R is H, ⎓ represents a double bond; or a pharmaceutically-compatible complex thereof as the active ingredient and gives less side effect.

The compounds represented by the general formula [I] and the pharmaceutically-compatible complexes thereof can be manufactured according to a method disclosed in the Japanese Patent Laid-opened No. Hei 2-56468.

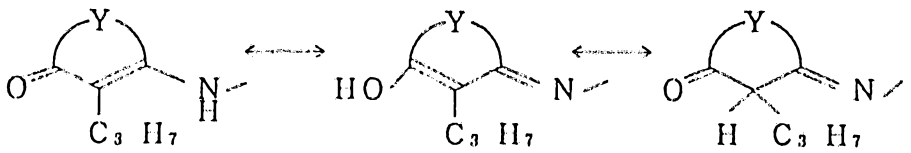
Representative compounds of formula [I] are shown in Table 1.

Table 1

Compound No.	Structural Formula			Physical Data [ ] m. p. °C
	Y	R	⎓	
1	$-CH_2\ CH_2\ CH_2-$	H	Single bond	222-225
2、2′	$-CH_2\ CH_2\ CH_2-$	CH_3	Single bond	95-100 (173-176)
3	$-CH_2\ CH_2-$	H	Single bond	165-167

Compound numbers 2 and 2′ are compounds of formula [I] according to the invention.

In addition to the representatives above, in the compounds represented by the general formula [I], pyridazinol exists in the place of pyridazine, and the tautomers, such as enol form and keto form as represented by the following formulas,



exist at the place of cycloalkenylamino group. Moreover, the optical isomers of pyridazinone also exists when R is methyl and

represents a single bond.

It should be noted that the compounds according to the present invention include all isomers as described above.

The compounds represented by the general formula [I] or the pharmaceutically-compatible complexes thereof can be administrated into humans and animals in a form as they stand or with pharmaceutically-acceptable carriers customarily used. There is no limitation in the prescription form for the compounds and the complexes, and it is possible to select any prescription forms depending upon requirements. For the examples of the prescription forms, oral drugs such as tablets, granules and oral solution, parenteral drugs such as injection can be exemplified. Also, there is no particular limitation in the dose of the active ingredient to be administrated, and the dose can be properly determined out of the wide range depending on the prescription form, compounds selected, and humans or animals having the administration, however, it is preferable to dose the compound in an amount of from 0.06 to 10 mg/Kg/Day in order to demonstrate a desired effect. Futhermore, it is preferable to incorporate the active ingredient in an amount of from 1 to 500 mg in an unit prescription form.

In the present invention, oral drugs comprising the compound of the present invention, such as tablets, capsules and oral solution, can be prepared according to methods customarily used. For the preparation of the tablets, the compound represented by the general formula [I] or the pharmaceutically-compatible complex thereof is mixed with pharmaceutically-acceptable fillers, such as starch, lactose, gelatin, magnesium stearate, talc and gum arabic to form to tablets. For the preparation of the capsules, the compound represented by the general formula [I] or the pharmaceutically-compatible complex thereof is mixed with inactive pharmaceutically-acceptable fillers or diluents and then filled into hard gelatin capsules, soft capsules, etc. For the preparation of the medicated syrups or the elixirs, the compound represented by the general formula [I] or the pharmaceutically-compatible complex thereof is mixed with sweetners such as sucrose, antiseptics such as methyl- and propyl-paraben, coloring agents and flavorings. For the preparation of the parenteral drugs

comprising the compound represented by the general formula [I] or the pharmaceutically-compatible complex thereof, a method customarily used can be employed. More specifically, the compound represented by the general formula [I] or the pharmaceutically-compatible complex thereof is dissolved into sterilized liquid carrier to prepare a drug for parenteral administration use.
For the liquid carrier, it is preferable to use water or saline solution. For the preparation of liquid-form pharmaceuticals which have a desired transparency and stability and is usable for parenteral use, the active ingredient in an amount of from 1 to 500 mg is dissolved into either water or an organic solvent, then the solution is further dissolved into polyethylene glycol of which molecular weight is in a range of from 200 to 5000. In the liquid-form pharmaceuticals, it is preferable that a lubricant, such as polyvinyl pyrrolidone, polyvinyl alcohol, carboxymethylcellulose sodium and methylcellulose, is contained therein. In addition thereto, it is possible to add antiseptics, such as benzyl alcohol, phenol and thimerosal, and fungicides.

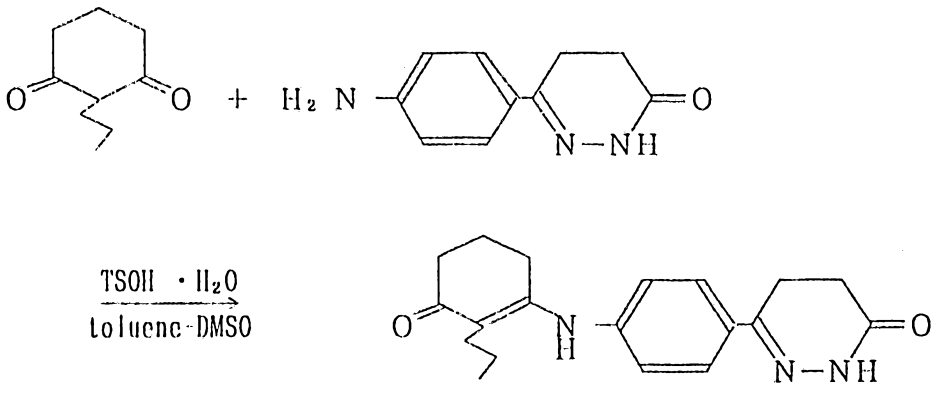
Moreover, tonicity agents, such as sucrose and sodium chloride, local anesthetics, stabilizing agents, buffer agents, etc. can be added therein, if required. For improving the stability of the pharmaceuticals for parenteral use, it is possible to freeze the pharmaceuticals after the filling and then to remove water therefrom by using lyophilization technique which has been known in the art. Using the pharmaceuticals prepared in this way, the preparation of the lyophilized-powder just prior to the use can be realized.

Best Mode for Carrying out the Invention

Now, the present invention is further explained with refferring to the following Examples.

[Reference Example 1]

Synthesis of 4,5-dihydro-6-[4- [(2-propyl-3-oxo-1-cyclohexenyl)amino] phenyl]-3(2H)-pyridazine (Compound No. 1)



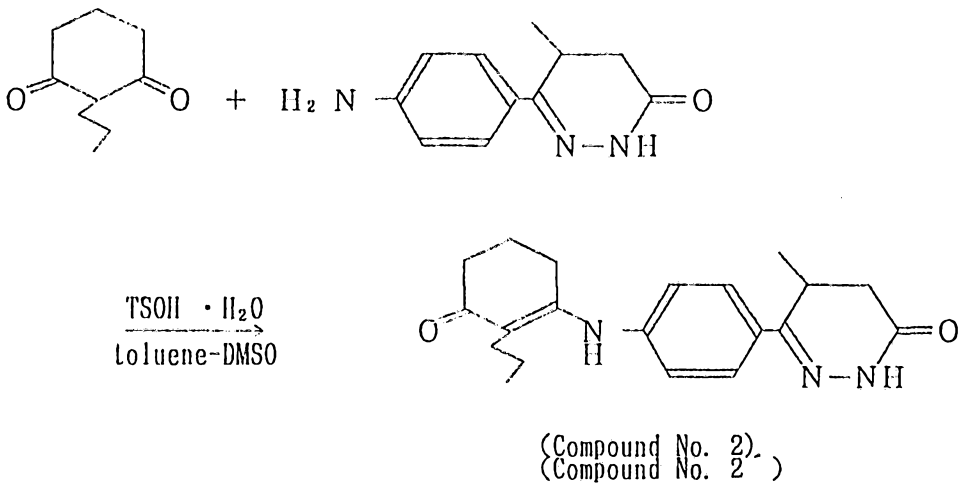
(Compound No. 1)

To a mixture of 10 ml toluene and 1 ml DMSO were dissolved 0.46g of 4,5-

dihydro-6-(4-aminophenyl)-3(2H)-pyridazinone and 0.1g of p-toluenesulfonic acid, then the solution was subjected to a reflux for 2 hours while distillating water therein by using Dean-stark. After cooling the solution subjected to reflux, the solution was added with ether for the decantation, and the residue was purified by using silica gel column chromatography (Elute used; A mixed solution of methanol:chloroform at a rate of 1:9) to obtain 0.55g of the objective product. The melting point thereof was in a range of from 222 to 225℃.

[Reference Example 2]

Synthesis of 4,5-dihydro-5-methyl-6-[4-[(2-propyl-3-oxo-1-cyclohexenyl)amino] phenyl]-3(2H)-pyridazinone (Compound No. 2 and 2´)



(Compound No. 2)
(Compound No. 2´)

According to the same procedure as described in the Reference Example 1 except replacing 4,5-dihydro-6-(4-aminophenyl)-3(2H)-pyridazinone with 4,5-dihydro-6-(4-aminophenyl)-6-methyl-3(2H)-pyridazine, a synthesis was carried out to obtain the objective compound (Compound No. 2) of which melting point is in a range of from 95 to 100 ℃. However, the melting point of the crystals of the objective product differed to a range of from 173 to 176 ℃ when the purification of the product was carried out by using silica gel column chromatography with using a different elute (A mixture of ethyl acetate and hexane at a rate of 1:1), to which Compound No. 2´ is given.

Example 1

Tablets

Component	Quantity (g)
Compound No. 1	5
Lactose (JP)	50
Corn starch (JP)	25
Crystalline cellulose (JP)	25
Methyl cellulose (JP)	1.5
Magnesium stearate (JP)	1

Compound No. 1, lactose, corn starch and crystalline cellulose were thoroughly mixed, then the mixture was prepared to granules with using 5% aqueous solution of methyl cellulose. Then the granules were sieved through 200 mesh, then dried carefully. The granules dried were then sieved again through 200 mesh, mixed with magnesium stearate, and pressed to prepare the tablets. With the granules prepared as described above, 1,000 tablets for oral use were prepared.

Example 2

Capsules

Component	Quantity(g)
Compound No. 1	10
Lactose (JP)	80
Starch (JP)	30
Talc (JP)	5
Magnesium stearate (JP)	1

Each components described above were separately pulverized to the fine powders, then all components were mixed and stirred to obtain an homogeneous mixture. The mixture was then filled into gelatin capsules in a desired size to be used for the parenteral administration. With the mixture prepared as described above, 1,000 pieces of two-piece type hard capsules for the oral use were prepared.

Example 3

Injection

Component	Quantity (g)
Compound No. 1	1
Polyethylene glycol (JP) (Molecular weight: 4000)	0.3
Sodium chloride (JP)	0.9
Polyoxyethylene sorbitan oleate (JP)	0.4
Sodium meta-bisulfite	0.1
Methyl-paraben (JP)	0.18
Propyl-paraben (JP)	0.02
Distillated water for Injection	100 (ml)

The parabens, sodium meta-bisulfite and sodium chloride described above were dissolved into approximately 50 ml of distillated water at 80 ℃ with stirring. The solution obtained was cooled to 40 ℃, then compound No. 1 and subsequently polyethylene glycol and polyoxyethylene sorbitan monooleate were dissolved into the solution. Then sterilized water for injection was added into the solution up to the final objective volume of the solution. The solution was then subjected to a filtration using filter paper for the sterilization,

then a sterilized solution adequate for the parenteral administration was prepared.

Example 4

Capsules

Component	Quantity (g)
Compound No. 1	10
Lactose (JP)	80
Starch (JP)	30
Talc (JP)	5
Magnesium stearate (JP)	1

Each components described above were separately pulverized to the fine powders, and all components were mixed and stirred to obtain an homogeneous mixture. The mixture was then filled into gelatin capsules in a desired size to be used for the parenteral administration. With the mixture prepared as described above, 1,000 pieces of two-piece type hard capsules for the oral use were prepared.

Industrial Applicability

Test Example 1

Preventive Effect on Platelet Aggregation

The preventive effect on platelet aggregation of the compounds and the complexes of the present invention was evaluated in vitro based on the preventive effect on the platelet aggregation induced by adenosine diphosphate (ADP) and collagen, which is determined by using an aggregometer, Hematracer PAT-606 produced by Nicho Bioscience Co., Ltd. Blood collected from rabbits containing 0.38% citric acid was centrifuged at 1100 rpm for 15 min. to obtain platelet rich plasm (PRP). The PRP obtained was then centrifuged at 3500 rpm for 10 min., and the supernatant obtained was provided as platelet poor plasma (PPP). PRP was diluted with PPP to adjust the concentration of platelets in PRP to a range of from 2×10^8/ml to 5×10^8 ml. 「Either ADP at the final concentration of 10 μM or collagen at the final concentration of 20 μg/ml, which was prepared with SKF buffer solution (Collagen reagent Horm, Hormon Chemie) was used for the induction of platelet aggregation. 」 Test compound was dissolved into dimethyl sulfoxide (DMSO), then 0.5 ml of PRP prepared as described above was added to 0.5 μl of the solution, then mixed for about 3 min. Then, 0.2 ml portion was taken out of the mixture, and either ADP solution or collagen solution in an amount of 22 μl was added thereto to proceed to the measurement of platelet aggregation for 10 min. by using an aggregometer. The preventive effect on platelet aggregation was determined in the prevention rate (%) in respect to the aggregation rate in the check plot. The rate of prevention onto platelet aggregation was calculated according to the following

equation.

Platelet Aggregation Prevention Rate (%) = (Maximum Aggregation Rate(%) of Platelet when only DMSO is added − Maximum Aggregation Rate(%) of Platelet when Test Compound and DMSO are added) ÷ Maximum Aggregation Rate(%) of Platelet when only DMSO is added

Based on the dose-response curve obtained according to the equation described above, EC_{50}, a dose attaining 50% prevention of platelet aggregation, was determined. The results are shown in Table 2.

Table 2

Compound No.	EC_{50} (μM) for Platelet Aggregation Prevention	
	ADP	Collagen
1	29.8	9.3
2	4.5	3.6
3	22.8	12.9
Cilostazol	10.2	4.3

Test Example 2

Preventive Effect on Thrombus-causing Death

Mice in a state without feeding for a night were orally administrated with a test compound, and then injected intravenously with collagen in an amount of 400 μg/Kg and epinephylline in an amount of 50 μg/Kg through their tail at a fixed speed in accordance with the method of DiMinno and Silver (DiMinno, G. and Silver, M. J., J. Pharmacol. Exp. Ther., 225, 57-60, 1983). After 30 min., the mice were checked to determine their survival rate and to calculate ED_{50}, a dose attaining 50% prevention of the death of the mice. The collagen and epinephylline were used in a form of a mixed solution prepared with SKF buffer solution and saline, respectively. Test compounds were administrated to mice after preparing each suspensions of the compounds in 1% aqueous solution of gum arabic.

(Note) J. Pharmacol. Exp. Ther. : The Journal of Pharmacology and Experimental Therapeutics

The results are shown in Table 3.

Table 3

Compound No.	ED_{50} (mg/Kg, p.o.) for preventing Thrombus-causing Death
1	5.0
2	1.7
3	6.8
Cilostazol	300

Test Example 3

Inhibitory Effect on Phosphodiesterase

Cyclic guanosine monophosphate inhibiting-type cyclic adenosine monophosphate phosphodiesterase (cAMP-PDE) derived from canine platelets was prepared according to the method of Thompson et. al. (Thompson, W. J., et. al., Adv. Cyclic Nucleotide Res., 10, 69-92, 1979).

More specifically, the canine platelets specimen was subjected to an elution by employing Concentration Gradient on DEAE-Cellulose column chromatography (Produced by Whatman Inc., Type DE-52, Diameter 3.2 cm, Length 13cm) using 70 to 1000 mM of sodium acetate as an elute to separate the esterase.

The phosphodiesterase activity was measured according to the method of Thompson et. al. which was partially modified by the inventors of the present invention. Namely, 1 μM [^{3}H]-cAMP was decomposed with phosphodiesterase, then 5´-AMP resulted was subjected to snake venom (Produced by Sigma, V-7000) to degrade it to adenosine. The resulting solution was added into anion-exchange resin (Produced by Bio-rad, AG1-X8), and adenosine as the reaction product and unreacted cAMP were separated by an extraction with methanol, then unadsorped adenosine to the resin was measured by using a liquid scintillation counter. Based on the concentration-inhibition curve prepared, IC_{50}, a concentration attaining 50% inhibition of enzymatic activity, was determined.

(Note) Adv. Cyclic Nucleotide Res.; Advances in Cyclic Nucleotide Research

The results are shown in Table 4.

Table 4

Compound No.	IC_{50}(μM) for cAMP-PDE
1	0.43
2	0.088
3	0.37
Cilostazol	0.60

Test Example 4

Cardiotonic Effect

Male and female Beagle dogs in a weight range of from 10 to 15 Kg were anesthetized to provide them for the test. The dogs were anesthetized by intravenous injection with sodium pentobarbital at a dose of 30 mg/Kg/hr, and the anesthetized condition was maintained by subsequent intravenous injection with sodium pentobarbital at a dose of 4 mg/Kg/hr. A cannula for drip infusion either of physiological saline solution or anesthetic injection was inserted into a femoral vein, and a cannula for measuring arterial blood pressure was inserted into a femoral artery via a pressure transducer. Heart rate was

recorded by conducting R-wave of the electrocardiogram (LCG) to a heart beat counter. Secondary induction from electrocardiogram was measured via a bioelectricity-adapted amplifier. Internal pressure of left cardiac ventricle was measured by inserting a catheter-type pressure transducer from a left carotid into left cardiac ventricle. Differential values by time of the internal pressure in left cardiac ventricle (dp/dt max) were measured by conducting the internal pressure in left cardiac ventricle to a derivative amplifier. The test compound was cummulatively administrated at a rate of from 0.001 to 0.3 mg/0.1 ml/Kg though a cannula inserted into a femoral vein. Based on a dose response curve obtained, ED_{50}, a dose attaining 50% increase of the dp/dt max in left cardiac ventricle, was determined.

The results are shown in Table 5.

Table 5

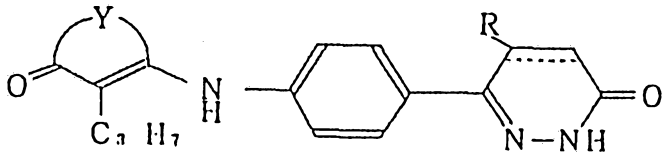
Compound No.	ED_{50} (μg/Kg, i.v.) for dp/dt max in Left Cardiac Ventricle	% Change	
		Heart Rate	Blood pressure
1	>300(32%) *	(5.2%) *	(−8.6%) *
2	52	9.8	−10.0
3	100	7.5	−10.5
Cilostazol	200	15	−2.1

* : % Change in intravenous administration at 300 mg/Kg.

The test according to Test Example 1, 2, 3 and 4 was also carried out on compound No. 2´ (m.p. 173-176 ℃), and it was found that the effects of the compound were as much as the effects given by the compound No. 2.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A preventative agent for platelet aggregation comprising an effective amount of the compound represented by the following general formula [I]:

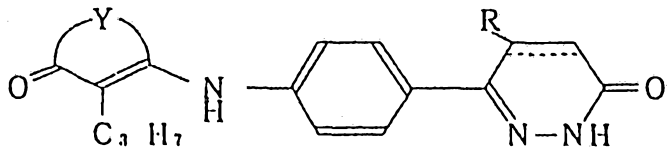


[I]

wherein Y is $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$, R is methyl, and ⎓ represents a single bond; or a pharmaceutically acceptable complex thereof, and a pharmaceutically acceptable excipient or carrier.

2. The preventive agent for platelet aggregation according to claim 1, wherein the compound is 4,5-dihydro-5-methyl-6-[4-[(2-propyl-3-oxo-1-cyclohexenyl)amino]phenyl]-3(2H)-pyridazinone.

3. A method of preventing platelet aggregation in a human or animal including the step of administering an effective amount of a compound represented by the following general formula [I]:

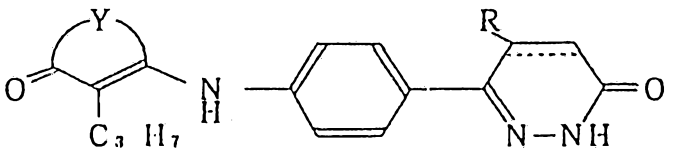


[I]

wherein Y is $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$, R is methyl, and ⎓ represents a single bond; or a pharmaceutically acceptable complex thereof.

4. A method of preventing platelet aggregation in a human or animal including the step of administering a preventative agent as claimed in claim 1 or claim 2.

5. A compound represented by the following general formula [I]:



[I]

wherein Y is $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$, R is methyl, and ⋯ represents a single bond.

DATED this 22nd day of October 1996

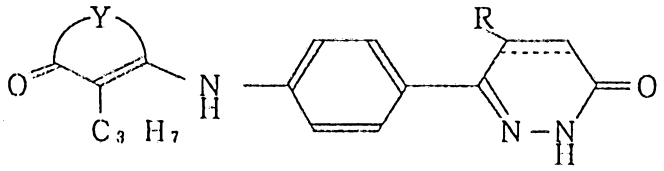
Nippon Soda Co.,Ltd

By DAVIES COLLISON CAVE

Patent Attorneys for the Applicants.

ABSTRACT FOR THE DISCLOSURE

A preventive agent for platelet aggregation comprising a compound represented by the following general formula [I]:



[I]

wherein Y is $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$, R is hydrogen or methyl, and

represents a single bond or a double bond, or a pharmaceutically-compatible complex thereof as the active ingredient, is disclosed.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP93/01527

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl^5 A61K31/50, C07D237/04, C07D237/14

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 A61K31/50, C07D237/04, C07D237/14

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, 2-56468 (Nippon Soda Co., Ltd.), February 26, 1990 (26. 02. 90), Claim & EP, A, 357788	1

☐ 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 7, 1993 (07. 01. 93)	February 1, 1994 (01. 02. 94)
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 93/01527

A. 発明の属する分野の分類（国際特許分類（IPC））

Int. Cl^5 A61K31/50, C07D237/04, C07D237/14

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. Cl^5 A61K31/50, C07D237/04, C07D237/14

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, 2-56468（日本曹達株式会社）, 26. 2月. 1990（26. 02. 90）, 特許請求の範囲&EP, A, 357788	1

☐ 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	国際調査報告の発送日
07. 01. 93	01.02.94

名称及びあて先	特許庁審査官（権限のある職員）
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	内藤伸一 4C 8615 電話番号 03-3581-1101 内線 3452

様式PCT/ISA/210（第2ページ）（1992年7月）