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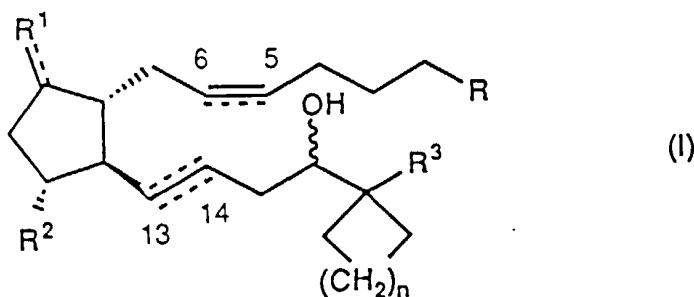
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(54) **Omega-cycloalkyl-prostaglandin E2 derivatives**

(57) ω -Cycloalkyl-prostaglandin E₂ derivatives of formula (I)



wherein R is carboxy or hydroxymethyl; R¹ is oxo, methylene or halogen atom; R² is H, OH or C1-4 alkoxy; R³ is H, C1-8 alkyl, C2-8 alkenyl, C2-8 alkynyl, C1-8 alkyl, C2-8 alkenyl or C2-8 alkynyl substituted by 1-3 substituents selected from halogen atom, C1-4 alkoxy, C3-7 cycloalkyl, phenyl, and phenyl substituted by 1-3 substituents selected from halogen atom, C1-4 alkyl, C1-4 alkoxy, nitro and trifluoromethyl; n is 0-4;

and non-toxic salts thereof, prodrugs thereof and cyclodextrin clathrates thereof strongly bind on the EP₂ subtype receptor. Therefore, they are useful for prevention and/or treatment of immunological diseases (autoimmune diseases, organ transplantation, etc.), asthma, abnormal bone formation, neuronal cell death, liver damage, abortion, premature birth or retina neuropathy of glaucoma etc.

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DescriptionField of Invention

5 This invention relates to ω -cycloalkyl-prostaglandin E₂ derivatives, processes for their preparation and pharmaceutical compositions containing them.

Background

10 Prostaglandin E₂ (abbreviated as PGE₂ hereafter) has been known as metabolite in the arachidonate cascade. It has been known that PGE₂ has cyto-protective activity, uterine contractile activity, a pain-inducing effect, a promoting effect of digestive peristalsis, an awaking effect, a suppressive effect of gastric acid secretion, hypotensive activity and diuretic activity etc.

In recent study, it was found that PGE₂ receptor was divided into some subtype which possess different physiological role each other. At present, four receptor subtype are known and they are called as EP₁, EP₂, EP₃ and EP₄ (Negishi M. et al, J. Lipid Mediators Cell Signaling, 12, 379-391 (1995)).

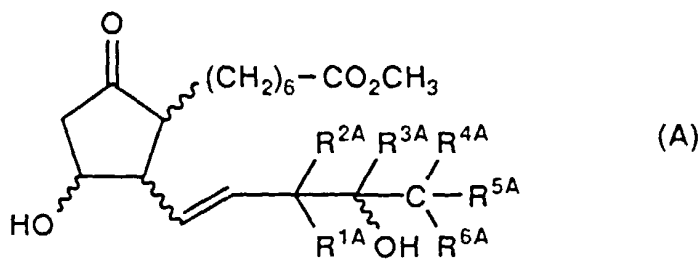
The present inventors investigated to find new compounds which bind on each receptors specifically, we found that the compounds of present invention could bind strongly on EP₂ subtype receptor and achieved the present invention.

20 The compounds of formula (I) of the present invention, as hereinafter defined, possess a binding activity for EP₂ subtype receptor strongly. Therefore, they are useful for prevention and/or treatment of immunological diseases (autoimmune diseases, organ transplantation, etc.), asthma, osteodystrophy, neuronal cell death, hepatopathy, abortion, premature birth or retina neuropathy of glaucoma etc.

Among the compounds of the present invention of the formula (I), compounds which bind weakly on receptor subtypes except for EP₂ and other arachidonic acid metabolism receptors (thromboxane receptor, PGI₂ receptor, etc.) do not express other effects and therefore, it is thought that such compounds will be a medical agent which have less side-effects.

On the other hand, many patent applications of PG derivatives were known. The following application is mentioned for example.

In the specification of United State Patent No. 4132738, a compound of the formula (A)

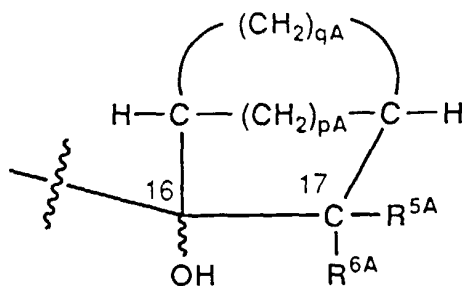


wherein R^{1A} and R^{2A} is hydrogen atom;

45 R^{3A} is hydrogen atom, or together with R^{4A} is a methylene chain of 4 carbon atoms such that a cycloalkyl of 6 carbon atoms inclusive is formed, or together with R^{4A} is a bicycloalkenyl or bicycloalkyl moiety having the formula

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15 (in which p_A is an integer having a value of from 0 to 1 and q_A is an integer having a value of from 2 to 3 and wherein the double bond of such bicycloalkenyl is in the q_A bridge);

R^{4A} is together with R^{3A} forms a cycloalkyl or bicycloalkyl or bicycloalkenyl as defined above, or together with R^{5A} is a methylene chain of 3 carbon atoms such that a cycloalkyl of 4 carbon atoms inclusive is formed;

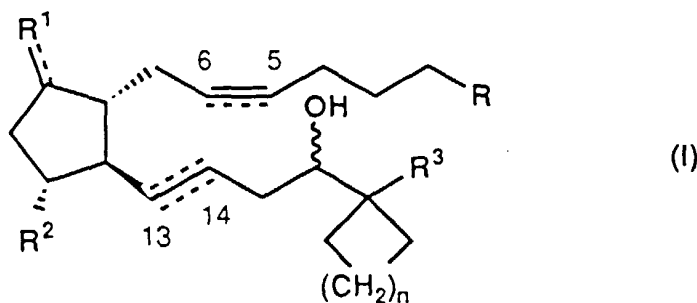
R^{5A} is hydrogen atom, or together with R^{4A} forms a cycloalkyl as defined above; and

20 R^{6A} is hydrogen atom or straight-chain alkyl having from 1 to 8 carbon atoms; are disclosed as having an inhibitory activity on prostaglandin like.

Disclosure of the Invention

25 The present invention accordingly provides

(1) an ω -cycloalkyl-prostaglandin E_2 derivative of formula (I)



wherein R is carboxy or hydroxymethyl;

R^1 is oxo, methylene or halogen atom;

R^2 is hydrogen atom, hydroxy or C1-4 alkoxy;

R^3 is hydrogen atom, C1-8 alkyl, C2-8 alkenyl, C2-8 alkynyl or C1-8 alkyl, C2-8 alkenyl or C2-8 alkynyl substituted by 1-3 substituents selected from (1)-(5):

50 (1) halogen atom,

(2) C1-4 alkoxy,

(3) C3-7 cycloalkyl,

(4) phenyl, and

(5) phenyl substituted by 1-3 substituents selected from halogen atom, C1-4 alkyl, C1-4 alkoxy, nitro and trifluoromethyl;

55 n is 0-4;

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is single bond or double bond;

10



is double bond or triple bond; and

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is a single bond, double bond or triple bond;

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and wherein the double bond at the 13-14 position, when present, is in the E, Z or EZ mixture form; with the proviso that when the 5-6 position is a triple bond, the 13-14 position is not a triple bond; or a non-toxic salt thereof, prodrug thereof or cyclodextrin clathrate thereof,

(2) processes for the preparation thereof, and

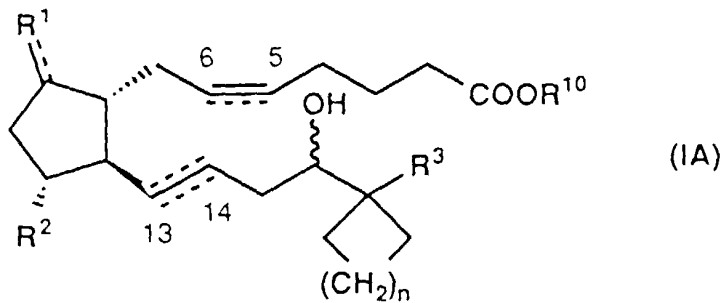
(3) pharmaceutical agents containing such a derivative as an active ingredient.

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In the present invention, prodrug means

1) for compounds of formula (I) of the present invention, those in which R represents COOR¹⁰ (in which R¹⁰ is C1-6 alkyl), i.e. the compounds of formula (IA)

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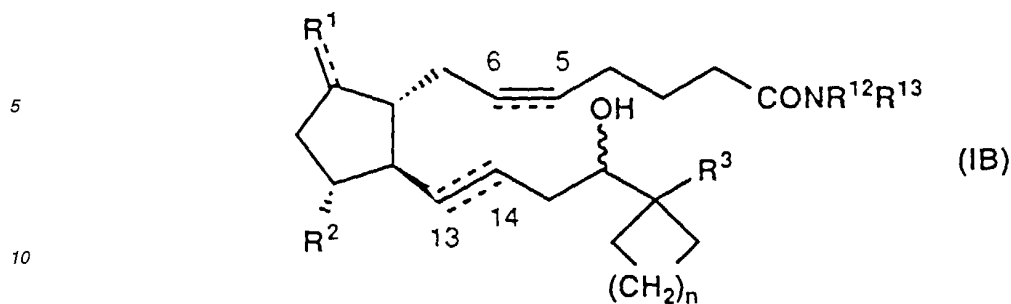
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wherein all symbols are as hereinbefore defined,

2) for compounds of formula (I) of the present invention, those in which R represents CONR¹²R¹³ (in which R¹² and R¹³ each, independently, is hydrogen atom or C1-6 alkyl), i.e., the compounds of formula (IB)

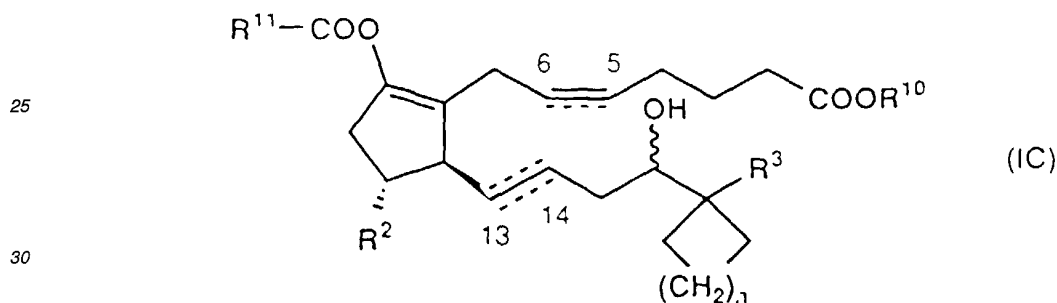
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15 wherein all symbols are as hereinbefore defined, or

3) for compounds of formula (I) of the present invention, those in which R represents COOR¹⁰ (in which R¹⁰ is as hereinbefore defined), R¹ represents R¹¹-COO (in which R¹¹ is C1-4 alkyl, C1-4 alkoxy, phenyl, phenyl-C1-4 alkyl, R¹⁴-OOC-C1-4 alkyl or R¹⁴-OOC-C2-4 alkenyl (in which R¹⁴ is hydrogen atom or C1-4 alkyl) and 8-9 position is double bond, i.e. the compounds of formula (IC)



35 wherein all symbols are as hereinbefore defined.

In formula (I) or (IC), C1-4 alkyl in the definitions of R³, R¹¹ and R¹⁴ means methyl, ethyl, propyl, butyl and isomers thereof.

In formula (I), (IA) or (IB), C1-6 alkyl represented by R¹⁰, R¹² and R¹³ means methyl, ethyl, propyl, butyl, pentyl, hexyl and isomers thereof.

In formula (I), C1-8 alkyl represented by R³ means methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl and isomers thereof.

In formula (I), C2-4 alkenyl in the definition of R¹¹ means vinyl, propenyl, butenyl and isomers thereof.

In formula (I), C2-8 alkenyl represented by R³ means vinyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl and isomers thereof.

In formula (I), C2-8 alkynyl represented by R³ means ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl and isomers thereof.

In formula (I), or (IC), C1-4 alkoxy in the definitions of R², R¹¹ and R³ means methoxy, ethoxy, propoxy, butoxy and isomers thereof.

In formula (I), C3-7 cycloalkyl in the definition of R³ means cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl.

In formula (I), a halogen atom in the definition of R¹ and R³ means fluorine, chlorine, bromine and iodine.

In the present invention, it may be easily understood by those skilled in the art, unless otherwise specified, the symbol:



5 indicates that the substituent attached thereto is in front of the sheet, unless otherwise specified, the symbol:



10 indicates that the substituent attached thereto is behind the sheet, unless otherwise specified, the symbol:



20 indicates that the substituent attached thereto is a mixture of in front of and behind the sheet or may be in front of or behind the sheet.

Unless otherwise specified, all isomers are included in the present invention. For example, the alkyl, alkenyl and alkynyl groups include straight-chain and also branched-chain ones. The double bond in alkenyl group includes E, Z and EZ mixtures. Isomers generated by the existence of asymmetric carbon atom(s) e.g. in branched-chain alkyl are included in the present invention.

25 Preferred compounds of the present invention include compounds of the formula (I) listed in the examples or in Tables 1-14 or prodrugs thereof.

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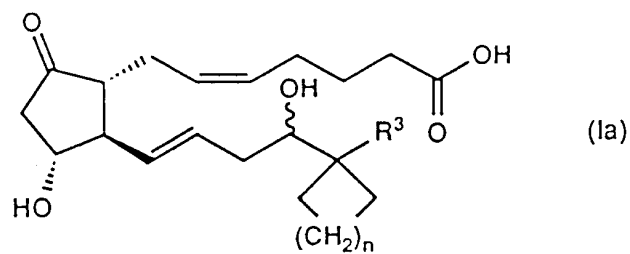
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[Table 1]



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No.	n	R ³	No.	n	R ³
1	0		11	1	
2	0		12	1	
3	0		13	1	
4	0		14	1	
5	0		15	1	
6	0		16	1	
7	0		17	1	
8	0		18	1	
9	0		19	1	
10	0		20	1	

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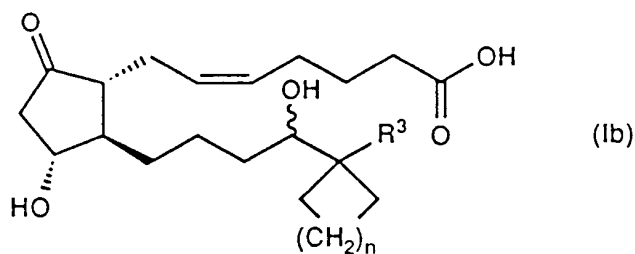
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[Table 2]



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No.	n	R ³	No.	n	R ³
1	0		11	1	
2	0		12	1	
3	0		13	1	
4	0		14	1	
5	0		15	1	
6	0		16	1	
7	0		17	1	
8	0		18	1	
9	0		19	1	
10	0		20	1	

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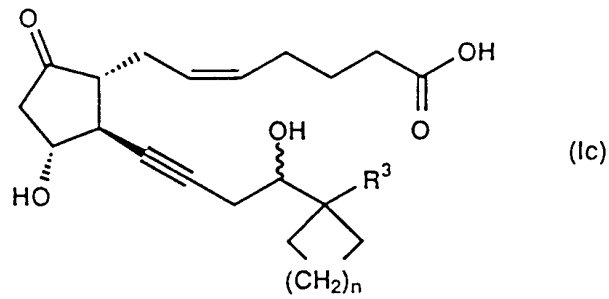
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[Table 3]



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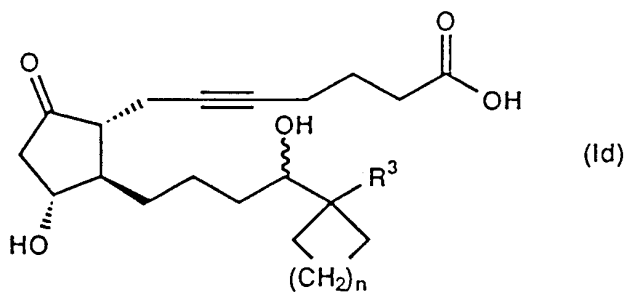
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No.	n	R ³	No.	n	R ³
1	0		11	1	
2	0		12	1	
3	0		13	1	
4	0		14	1	
5	0		15	1	
6	0		16	1	
7	0		17	1	
8	0		18	1	
9	0		19	1	
10	0		20	1	

[Table 4]

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No.	n	R ³	No.	n	R ³
1	0		11	1	
2	0		12	1	
3	0		13	1	
4	0		14	1	
5	0		15	1	
6	0		16	1	
7	0		17	1	
8	0		18	1	
9	0		19	1	
10	0		20	1	

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