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(54) Title: PYRIMIDINONE COMPOUNDS, PHARMACEUTICAL COMPOSITIONS CONTAINING THE COMPOUNDS AND THE PROCESS FOR PREPARING THE SAME

(57) Abstract

The present invention relates to a novel pyrimidinone compounds and the pharmaceutical acceptable salts thereof having remarkable antagonistic action against angiotensin II receptor, thereby, being useful in treating cardiovascular disease caused by binding angiotensin II to its receptor.


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BACKGROUND OF THE INVENTION

Technical Field

The present invention relates to a novel pyrimidinone compounds and the pharmaceutically acceptable salts thereof. This invention also relates to a process for preparing the novel pyrimidinone compounds and a pharmaceutical composition containing the pyrimidinone compounds.

Background Art

Pyrimidinone derivatives according to this invention and the pharmaceutically acceptable salts thereof are useful as antagonists against angiotensin II, especially, in treatment of cardiovascular diseases caused by binding angiotensin II to its receptor.

Renin-angiotensin system plays a central role in the regulation of blood pressure in human body. Angiotensin II, consisting of eight amino acids, is produced through the cleavage of angiotensin I by angiotensin converting enzyme (ACE) localized on the arterial blood vessels of lung. Angiotensin II interacts with specific receptors present in blood vessels, smooth muscle, kidney, and adrenal gland, to induce the blood pressure and the electrolyte concentration to increase.

Thus, several antagonistic compounds have been developed to inhibit the effect of angiotensin II by selectively blocking its receptors.

Conventionally, peptide antagonists analogous to angiotensin II have been proposed, but their clinical
applications have been limited because of their short half-life, oral inertia as well as local increase of blood pressure.

Recently, lots of researches have been reported in connection with non-peptide angiotensin II antagonists (U. S. Pat. No. 4,207,324, 4,340,598, 4,576,958, 4,582,847, and 4,880,804; European Patent Laying-Open Publication Nos. 028,834, 245,637, 253,310, 291,969, 323,841 and 324,377). European Patent Laying-Open Publication Nos. 028,834 and 253,310 disclose Imidazole derivatives substituted by biphenyl (for example, Losartan) and European Patent Laying-Open Publication No. 245,637, imidazopyridine derivatives (for example, L158,809) as potent angiotensin II antagonists.

In European Patent Laying-Open Publication Nos. 407,342, 419,048 and 445,811, pyrimidinone compounds similar to the compounds of this invention in their 6 membered heterocyclic ring structure are disclosed, including nitrogen which is very different from the 5 membered imidazole derivatives. But, the pyrimidinone compounds have lower activities than the imidazole derivatives described in the above mentioned application.

In the meantime, the inventors of this invention have filed a PCT application (WO 96-08476) for a novel compounds having noticeably high activities (in vitro (rabbit aorta), 60~70% inhibition for $10^{-8}$ to $10^{-9}$ mole in vitro blood vessel dilation study) which is 50 times higher than or equal to imidazole derivatives known in the above mentioned application.

Disclosure of Invention

In search of novel pyrimidinone compounds, the inventors of this invention have developed novel pyrimidinone derivatives of thioamid and amidine, which are superior to pyrimidinone derivatives disclosed in the prior art or the said imidazole derivatives in the activities and active time periods.

An object of the invention, therefore, is to provide with
novel pyrimidinone derivatives and the pharmaceutically
acceptable salts thereof which inhibit the action of angiotensin
II effectively with high activities.

In order to achieve the aforementioned objects, the
present invention provides with pyrimidinone derivatives and
the pharmaceutically acceptable salts thereof having the
general formula (I):

(I)

\[
\begin{array}{c}
R^1 \quad \text{(CH}_2)_n \quad N \quad R^3 \quad R^4 \\
R^2 \quad \text{NR}^3 \quad R^4 \\
\end{array}
\]

wherein:

R\(^1\) is C\(_1\)~C\(_4\) normal or side chain alkyl, cycloalkyl, C\(_1\)~C\(_4\) alkylalkoxy or C\(_1\)~C\(_4\) alkylmercapto;

R\(^2\) is H, halogen, C\(_1\)~C\(_4\) alkyl, aryl or arylalkyl;

R\(^3\), R\(^4\) is same or different H, C\(_1\)~C\(_4\) normal or side chain alkyl, cycloalkyl, aryl, arylalkyl, C\(_1\)~C\(_4\) alkyl or arylcarbonyl, C\(_1\)~C\(_4\) alkoxyalkyl, or substituted aminocarbonyl, being optionally substituted by H, halogen, hydroxy, C\(_1\)~C\(_4\) alkoxy, amino, alkylamino or dialkylamino (each alkyl having C\(_1\)~C\(_4\)), C\(_1\)~C\(_4\) alkoxyalkyl, carboxy, or substituted aminocarbonyl,

R\(^3\) and R\(^4\) are together with N atom forming 4 to 8 membered heterocyclic ring, which can be further substituted with one or two substituents selected from the group consisting of
cycloalkyl, aryl or arylalkyl, halogen, hydroxy, and C\(_1\)~C\(_4\).
alkoxy, amino, alkylamino or dialkylamino (each alkyl residue having C₁-C₅), C₁-C₄ alkoxycarbonyl, carboxy or substituted aminocarbonyl, and C₁-C₄ normal or side chain alkyl being optionally substituted by H; and the heterocyclic ring can further include -O-, -S-, -SO-, -SO₂-, >N-R⁶;

R⁵ is H, C₁-C₄ alkyl, aryl, arylalkyl, substituted alkenyl, pyridyl, pyrimidyl, C₁-C₄ alkyl or arylcarbonyl, C₁-C₄ alkoxy carbonyl, substituted aminocarbonyl, CN or SO₂NR³R⁴;

X is S or >N-R⁶; and

Z is CN, COOR³, SO₂NR³R⁴ or tetrazol-5-yl radical having below general formula,

![General formula](image)

wherein R⁶ is H, t-butyl or triphenylmethyl;
m is 1 or 2; and
n is 1, 2, 3, 4, 5 and 6.

The pyrimidinone compounds according to the present invention and pharmaceutically acceptable salts thereof exhibit remarkable activities.

Preferable are such compounds wherein R¹ is ethyl, n-propyl, n-butyl, cyclopropyl, ethoxy or propoxy; R⁵ is H, halogen or C₁-C₄ normal or side chain alkyl; R³ and R⁴ are same or different H, methyl, ethyl, propyl or butyl, or R³ and R⁴ are together with N atom forming 4 to 8 membered cyclic ring, which can be further substituted with one or two substituents selected from the group consisting of cycloalkyl, aryl or arylalkyl, halogen, hydroxy, C₁-C₄ alkoxy, amino, alkylamino, or dialkylamino (each alkyl residue having C₁-C₅), C₁-C₄ alkoxycarbonyl, carboxy and substituted aminocarbonyl, and C₁-C₄ normal or side chain alkyl.
being optionally substituted by H; and the heterocyclic ring
5 can further include -O-, -S-, -SO-, -SO₂-, >N-R³; R³ is H, C₁₋₅ alkyl, aryl, arylalkyl, substituted alkenyl, pyridyl, pyrimidyl,
aliphatic C₁₋₅ alkyl or arylcarbonyl, C₁₋₅ alkoxy carbonyl, substituted
aminocarbonyl, CN or SO₂NR³R⁴, more preferably H, C₁₋₅ alkyl,
C₁₋₅ alkoxy carbonyl, substituted aminocarbonyl, CN or SO₂NR³R⁴;
X is S or >N-R³; Z is tetrazol-5-yl radical; and m is 1.

Best Mode for Carrying Out the Invention

The pharmaceutically acceptable salts of the invention include inorganic salts obtainable by reacting corresponding
pyrimidinone compounds (I) with hydroxides of alkali metal or
alkaline earth metals such as sodium hydroxide, potassium
hydroxide, calcium hydroxide or magnesium hydroxide, potassium
hydroxide, calcium hydroxide or magnesium hydroxide, carbonate
of alkali metal or alkaline earth metals such as sodium carbonate,
potassium carbonate, calcium carbonate or magnesium carbonate,
or alcoholate of alkali metal or alkaline earth metals such as
sodium, potassium, calcium or magnesium, and organic salts
obtainable by reacting with organic amine in H₂O, alcohols such
as methanol, ethanol, isopropyl alcohol, t-butyl alcohol, etc.,
tetrahydrofuran, or the mixture thereof.

The compound (I) can be prepared by reacting formula (I)
of below-mentioned compound (II).
[Reacting Formula I]

\[
\begin{align*}
\text{Compound formula II} & \quad \text{Compound formula I} \\
\text{wherein } R^1, R^2, R^3, R^4, X, Z, m, \text{ and } n \text{ have the meaning defined as above.}
\end{align*}
\]

Starting materials of the compound of formula II may be prepared by the process which has been disclosed in the PCT application Laying-Open Publication No. WO96-08476 by the present inventors. The compound of formula I, in which \( X \) is \( S \), may be easily prepared by reacting compound (II) with \( P_4S_{10} \), bis(tricyclohexyltartar)sulfide or Lawesson's reagent in a solvent selected among benzen, dichloromethan or tetrahydrofuran. On the other hand, the compound of formula I, in which \( X \) is \( NR^5 \); may be easily prepared from the compound (II) by adding substituted amine after preparation of iminium intermediate by using a reagent such as oxalylchloride, phosphorous oxychloride or ethyl chloroformate in a solvent selected among benzene, ether or tetrahydrofuran.

Representative compounds of the invention are as follows, wherein name in the parentheses respectively after the compounds represent tentative name used through the specification.

2-n-butyl-5-aminothiocarbonylmethyl-6-methyl-3-[2'-
(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-pyrimidine-4(3H)-
one (Compound 1),

2-n-butyl-5-dimethylaminothiocarbonylmethyl-6-methyl-
3-[[2'-((1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-pyrimidine-4(3H)-one (Compound 2),
2-n-butyl-5-diethylaminothiocarbonylmethyl-6-methyl-3-[[2'-((1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-pyrimidine-4(3H)-one (Compound 3),
2-n-butyl-5-heptamethyleniminothiocarbonylmethyl-6-methyl-3-[[2'-((1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-pyrimidine-4(3H)-one (Compound 4),
2-n-butyl-5-thiomorpholinothiocarbonylmethyl-6-methyl-3-[[2'-((1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-pyrimidine-4(3H)-one (Compound 5),
2-n-butyl-5-morpholinothiocarbonylmethyl-6-methyl-3-[[2'-((1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-pyrimidine-4(3H)-one (Compound 6),
2-n-butyl-5-piperidinothiocarbonylmethyl-6-methyl-3-[[2'-((1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-pyrimidine-4(3H)-one (Compound 7),
2-n-butyl-5-pyrrolidinothiocarbonylmethyl-6-methyl-3-[[2'-((1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-pyrimidine-4(3H)-one (Compound 8),
2-n-butyl-5-azetidinothiocarbonylmethyl-6-methyl-3-[[2'-((1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-pyrimidine-4(3H)-one (Compound 9),
2-n-butyl-5-(2'-aminothiocarbonyl)ethyl)-6-methyl-3-[[2'-((1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-pyrimidine-4(3H)-one (Compound 10),
2-n-butyl-5-(2'-dimethylaminothiocarbonyl)ethyl)-6-methyl-3-[[2'-((1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-pyrimidine-4(3H)-one (Compound 11),
2-n-butyl-5-(2'-diethylaminothiocarbonyl)ethyl)-6-methyl-3-[[2'-((1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-pyrimidine-4(3H)-one (Compound 12),
2-n-butyl-5-(2'-thiomorpholinothiocarbonyl)ethyl)-6-methyl-3-[[2'-((1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-
pyrimidine-4(3H)-one (Compound 13), and
2-n-buty1-5-(2'-morp~olnothiocarbonyl ethyl)-6-methyl-3-\[2'-\(1H\text{-}tetricol-5-yl\)-biphenyl-4-yl]methyl\]-pyrimidine-4(3H)-one (Compound 14).

A compound of formula I and the pharmaceutically acceptable salts thereof may be administered orally or parenterally in a conventional dosage form from such as tablet, capsule, powder, troches, dry mixes, ointment, suspension or solution prepared according to conventional pharmaceutical practices.

The compounds of formula I, etc. can be administered at a dosage of from about 40mg/kg to about 100mg/kg preferably of body weight per day.

The compounds of the present invention have extremely low toxicity. The LD50 in mice is in excess of 5000mg/kg of body weight, as shown in the experimental test 2.

The present invention will be described in more detail with reference to preferred embodiments hereinafter and as such are not to be considered as limiting the scope of the present invention.

EXAMPLE 1

2-n-buty1-5-aminthiocarbonylmethyl-6-methyl-3-\[2'-\(1H\text{-}tetricol-5-yl\)biphenyl-4-yl]methyl\]-pyrimidine-4(3H)-one (Compound 1),

PROCESS 1

1.2g of 2-n-buty1-5-aminocarbonylmethyl-6-methyl-3-\[2'-\(N\text{-}\text{triphenylmethyl}tetricol-5-yl\)biphenyl-4-yl]methyl\]-pyrimidine-4(3H)-one (WO 96-08476) were dissolved in 20mL of benzene at room temperature, and 600mg of Lawesson's reagent was added thereto. After heating the mixture and stirring it
for 5 hours, the mixture was cooled at room temperature, unnecessary solid material was filtrated therefrom, and concentrated under the reduced pressure. The residue was separated and purified on a chromatography using acetate/hexane (1:2) to obtain 700mg (57%) of intermediate product.

After dissolving the intermediate product in 100mL of tetrahydrofuran, the solution was cooled at 0-5°C and 5ml of 4M hydrochloric acid solution was slowly added thereto. The solution was refluxed for 4 hour and then neutralized by adding 4M sodium hydroxide solution. H₂O layer was saturated with solid sodium chloride and extracted three times by using chloroform. The organic solution thus obtained was washed with saturated brine, and then dried and concentrated with anhydride magnesium sulfate. The residue was eluted on a chromatography using chloroform and chloroform/methanol (9:1) to yield 310mg (65%) of the compound 1.

**PROCESS 2**

500mg of 2-n-butyl-5-aminocarbonylmethyl-6-methyl-3-[[1H-tetrazol-5-yl]biphenyl-4-yl]methyl]-pyrimidine-4(3H)-one (WO 96-08476) were dissolved in 20mL of tetrahydofuran at room temperature, and 400mg of Lawesson's reagent was added thereto. After heating the mixture and stirring it for 5 hours, the mixture was cooled at room temperature, unnecessary solid material was filtrated therefrom, and concentrated under the reduced pressure. The residue was separated and purified on a chromatography using chloroform and chloroform/methanol (9:1) to yield 200mg (45%) of the compound 1.

M.P. : 94.6 ~102.3°C

TLCRₐ: 0.33(5% MeOH in CHCl₃)

1H NMR(DMSO-d₆) :  δ 0.83(t,3H),  1.19~1.40(m,2H),
1.48~1.65(m,2H),  2.21(s,3H),  2.60(s,2H),  3.35(s,2H),
5.27(s,2H),  7.01~7.09(m,4H),  7.39~7.61(m,4H),  6.83(s,1H),
7.07 (s, 4H), 7.30 (s, 1H), 7.40 ~ 7.68 (m, 4H)

Through the same process, the following compounds were prepared.

EXAMPLE 2

2-n-butyl-5-dimethylaminothiocarbonylmethyl-6-methyl-3-[[2'- (1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-pyrimidine-4(3H)-one (Compound 2),

M.P. : 96.8 ~ 101.8°C

TLCRf : 0.28 (5% MeOH in CHCl3)

1H NMR (CDCl3): δ 0.89 (t, 3H), 1.28 ~ 1.45 (m, 2H), 1.58 ~ 1.74 (m, 2H), 2.26 (s, 3H), 2.63 (t, 2H), 3.44 (s, 3H), 3.46 (s, 3H), 3.77 (s, 2H), 5.22 (s, 2H), 7.07 (s, 5H), 7.33 ~ 7.60 (m, 3H), 7.94 (dd, 1H)

EXAMPLE 3

2-n-butyl-5-diethylaminothiocarbonylmethyl-6-methyl-3-[[2'- (1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-pyrimidine-4(3H)-one (Compound 3),

M.P. : 96.8 ~ 98.6°C

TLCRf : 0.31 (5% MeOH in CHCl3)

1H NMR (CDCl3): δ 0.91 (t, 3H), 1.26 (t, 3H), 1.31 ~ 1.45 (m, 2H), 1.61 ~ 1.80 (m, 2H), 2.31 (s, 3H), 2.67 (t, 2H), 3.76 (q, 2H), 3.81 (s, 2H), 3.99 (q, 2H), 5.26 (s, 2H), 7.01 ~ 7.18 (m, 3H), 7.20 ~ 7.28 (m, 1H), 7.33 ~ 7.41 (m, 1H), 7.45 ~ 7.62 (m, 2H), 8.06 (dd, 1H)

EXAMPLE 4

2-n-butyl-5-heptamethyleniminothiocarbonylmethyl-6-methyl-3-[[2'- (1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-pyrimidine-4(3H)-one (Compound 4),
M.P. : 104.2 ~107.3°C

TLCRf : 0.47(7% MeOH in CHCl3)

1H NMR(CDCl3):  δ 0.83(t, 3H), 1.21~1.30(m, 2H), 1.40~1.70(m, 8H), 1.71~1.95(m, 4H), 2.21(s, 3H), 2.53(t, 2H), 3.60~3.88(m, 4H), 4.02(s, 2H), 5.15(s, 2H), 6.98~7.09(m, 5H), 7.22~7.58(m, 3H), 7.77(dd, 1H)

EXAMPLE 5

2-n-butyl-5-thiomorpholinothiocarbonylmethyl-6-methyl-3-[[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl]methyl]-pyrimidine-4(3H)-one (Compound 5)

M.P. : 115.5 ~119.1°C

TLCRf : 0.33(7% MeOH in CHCl3)

1H NMR(CDCl3):  δ 0.91(t, 3H), 1.31~1.48(m, 2H), 1.61~1.74(m, 2H), 2.30(s, 3H), 2.65(t, 2H), 2.72~2.84(m, 4H), 3.81(s, 2H), 4.22(t, 2H), 4.59(t, 2H), 5.25(s, 2H), 7.03~7.15(m, 5H), 7.35~7.61(m, 3H), 8.00(dd, 1H)

EXAMPLE 6

2-n-butyl-5-morpholinothiocarbonylmethyl-6-methyl-3-[[2'- (1H-tetrazol-5-yl)-biphenyl-4-yl]methyl]-pyrimidine-4(3H)-one (Compound 6)

M.P. : 91.8~94.3°C

TLCRf : 0.30(7% MeOH in CHCl3)

1H NMR(CDCl3):  δ 0.92(t, 3H), 1.31~1.48(m, 2H), 1.63~1.81(m, 2H), 2.34(s, 3H), 2.69(t, 2H), 2.68~2.82(m, 4H), 3.85(s, 2H), 3.97(t, 2H), 4.34(t, 2H), 5.27(s, 2H), 7.05~7.20(m, 5H), 7.35~7.65(m, 3H), 8.05(dd, 1H)

EXAMPLE 7

2-n-butyl-5-piperidinothiocarbonylmethyl-6-methyl-3-[[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl]methyl]-pyrimidine-
4(3H)-one (Compound 7)

M. P.: 94.2~97.6°C

TLCRf: 0.37 (5% MeOH in CHCl3)

1H NMR (CDCl3):  δ 0.91 (t, 3H), 1.31~1.48 (m, 2H), 1.61~1.80 (m, 8H), 2.30 (s, 3H), 2.67 (t, 2H), 3.72~3.90 (m, 4H), 4.26 (s, 2H), 5.25 (s, 2H), 7.03~7.15 (m, 5H), 7.35~7.61 (m, 3H), 8.01 (dd, 1H)

EXAMPLE 8

2-n-butyl-5-pyrroldinothiocarbonylmethyl-6-methyl-3-[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl]methyl]-pyrimidine-4(3H)-one (Compound 8)

M. P.: 94.4~97.3°C

TLCRf: 0.26 (5% MeOH in CHCl3)

1H NMR (CDCl3):  δ 0.91 (t, 3H), 1.31~1.48 (m, 2H), 1.61~1.80 (m, 2H), 1.91~2.18 (m, 4H), 2.32 (s, 3H), 2.67 (t, 2H), 3.60~3.90 (m, 6H), 5.24 (s, 2H), 7.03~7.15 (m, 5H), 7.35~7.61 (m, 3H), 8.02 (dd, 1H)

EXAMPLE 9

2-n-butyl-5-azetidinothiocarbonylmethyl-6-methyl-3-[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl]methyl]-pyrimidine-4(3H)-one (Compound 9)

M. P.: 92.4~93.8°C

TLCRf: 0.24 (5% MeOH in CHCl3)

1H NMR (CDCl3):  δ 0.91 (t, 3H), 1.31~1.45 (m, 2H), 1.61~1.75 (m, 2H), 2.20~2.35 (m, 2H), 2.39 (s, 3H), 2.67 (t, 2H), 3.59 (s, 2H), 4.21 (t, 2H), 4.47 (t, 2H), 5.24 (s, 2H), 7.03~7.15 (m, 4H), 7.18~7.25 (m, 1H), 7.35~7.61 (m, 3H), 8.04 (dd, 1H)

EXAMPLE 10
2-n-butyl-5-(2'-aminothiocarbonylthyl)-6-methyl-3-[[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl]methyl]-pyrimidine-4(3H)-one (Compound 10)

M.P. : 97.8~99.0°C

TLCR<sub>r</sub> : 0.43(5% MeOH in CHCl<sub>3</sub>)

1H NMR(CDC<sub>3</sub>): δ 0.93(t,3H), 1.32~1.48(m,2H), 1.62~1.80(m,2H), 2.40(s,3H), 2.60~2.80(m,4H), 2.87(t,2H), 5.27(s,2H), 7.10~7.25(m,4H), 7.35~7.65(m,4H), 8.10(dd,1H)

EXAMPLE 11
2-n-butyl-5-(2'-dimethylaminothiocarbonylthyl)-6-methyl-3-[[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl]methyl]-pyrimidine-4(3H)-one (Compound 11)

M.P. : 76.2~81.2°C

TLCR<sub>r</sub> : 0.21(5% MeOH in CHCl<sub>3</sub>)

1H NMR(CDC<sub>3</sub>): δ 0.90(t,3H), 1.28~1.45(m,2H), 1.58~1.74(m,2H), 2.37(s,3H), 2.63(t,2H), 2.85~3.05(m,4H), 3.42(s,3H), 3.47(s,3H), 5.23(s,2H), 6.95~7.13(m,4H), 7.27~7.65(m,4H), 7.87(dd,1H)

EXAMPLE 12
2-n-butyl-5-(2'-diethylaminothiocarbonylthyl)-6-methyl-3-[[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl]methyl]-pyrimidine-4(3H)-one (Compound 12)

M.P. : 77.8~81.1°C

TLCR<sub>r</sub> : 0.37(5% MeOH in CHCl<sub>3</sub>)

1H NMR(CDC<sub>3</sub>): δ 0.88(t,3H), 1.12~1.45(m,8H), 1.55~1.74(m,2H), 2.37(s,3H), 2.59(t,2H), 2.85~3.15(m,4H), 3.70(q,2H), 3.37(q,2H), 5.20(s,2H), 6.90~7.05(m,4H), 7.20~7.55(m,4H), 7.78(dd,1H)

EXAMPLE 13
2-n-butyl-5-(2'-thiomorpholinothiocarbonylethyl)
)-6-methyl-3-[[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl]
methyl]-pyrimidine-4(3H)-one (Compound 13)
M.P. : 80.1~83.3°C
TLCRf : 0.28(5% MeOH in CHCl3)

1H NMR(CDC13): δ 0.91(t,3H), 1.30~1.45(m,2H),
1.60~1.70(m,2H), 2.39(s,3H), 2.55~2.90(m,8H), 2.97(t,2H),
4.22(t,2H), 4.58(t,2H), 7.04~7.25(m,5H), 7.35~7.42(m,1H),
7.45~7.65(m,2H), 8.08(dd,1H)

EXAMPLE 14
2-n-butyl-5-(2'-morpholinothiocarbonylethyl)-6-methyl-
3-[[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl]
methyl]-pyrimidine-4(3H)-one (Compound 14)
M.P. : 92.2~94.7°C
TLCRf : 0.39(7% MeOH in CHCl3)

1H NMR(CDC13): δ 0.91(t,3H), 1.30~1.45(m,2H),
1.60~1.75(m,2H), 2.39(s,3H), 2.67(t,2H), 2.88(t,2H),
3.05(t,2H), 3.65~3.80(m,4H), 3.94(t,2H), 4.31(t,2H),
5.27(s,2H), 7.04~7.30(m,5H), 7.38~7.42(m,1H),
7.50~7.68(m,2H), 8.08(dd,1H)

The antagonistic activity of the compound (I) against the
angiotensin II, which is prepared by the process according to
a preferred embodiment of the invention, was evaluated with
relation to rats. The results are shown in Table 1.

Experimental test 1

In vivo Angiotensin II antagonism in conscious
normotensive rats.

Male SD rats (Charles River Japan, 9 weeks, 300-350g) were
anesthetized with pentobarbital at 50mg/kg i.p. Both the left
femoral artery and the right femoral vein were cannulated. A heparin-filled catheter (50U/ml) was tunneled subcutaneously (s.c.) to the dorsal side of the neck and exteriorized.

Rats were permitted to recover overnight from anesthesia and allowed free access to water, but food was withheld.

The next day, the femoral artery catheter was connected to a pressure transducer (COBE 041-500-508, USA) coupled to a polygraph (GRASS Model 7, USA) to monitor arterial blood pressure. After an appropriate equilibration period, Angiotensin II (0.1µg/kg) was injected in the femoral vein three times during the control period.

Test compounds were then administered orally (p.o.) at a constant volume of 2ml/kg.

Angiotensin II challenges were repeated at set times thereafter.

ID$_{50}$ values, the dose of test compound necessary to produce 50% inhibition of Angiotensin II-induced pressor response, were calculated from peak inhibition percentage with several doses of test compound.

[Table I]
<table>
<thead>
<tr>
<th>COMPOUND NO.</th>
<th>ID₅₀ (mg/kg, P.O.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound 1</td>
<td>&gt;3.0</td>
</tr>
<tr>
<td>Compound 2</td>
<td>1.10</td>
</tr>
<tr>
<td>Compound 3</td>
<td>&lt;3.0</td>
</tr>
<tr>
<td>Compound 4</td>
<td>3.10</td>
</tr>
<tr>
<td>Compound 5</td>
<td>&lt;3.0</td>
</tr>
<tr>
<td>Compound 6</td>
<td>&lt;3.0</td>
</tr>
<tr>
<td>Compound 7</td>
<td>&lt;3.0</td>
</tr>
<tr>
<td>Compound 8</td>
<td>0.93</td>
</tr>
<tr>
<td>Compound 9</td>
<td>1.19</td>
</tr>
</tbody>
</table>

**Experimental test II**

**Acute toxicity test**

Respective 5 mice of ICR system, which was distributed from Korean Laboratory Animal Center, were bred in a polycarbonate breeding box at a breeding environment of 23±1°C of temperature, 55±5% of humidity, 10-15 times/hr of evacuation, 12hr cycle of fluorescent light luminance, and 150-300 Lux of illumination.

After observing the mice for one week of acclimation breeding period, only normal mice were selected for laboratory work. The mice were fed with sterilized feed for laboratory animals, which was made by Cheil Jedang Co., Ltd, and supplied with purified water to drink.

During the acclimation period, mice, who were evaluated to be healthy, were weighed and divided into groups randomly. Individual identification of laboratory animals was performed by indumentum pigment display and tag display per breeding box.

Establishment of dose was carried out according to a result
of preliminary test in such a manner that a maximum dose group for both male and female was set to 5000mg/kg and azeotropy was set to 1.71. Medium-high, medium and medium-low dose groups were respectively set as follows and a control group was administrated with physiological saline for injection.

[Table II]

<table>
<thead>
<tr>
<th>TESTING GROUP</th>
<th>DOSE (MG/KG)</th>
<th>ADMINISTRATION DOSE (ML/KG)</th>
<th>TOTAL TESTING ANIMALS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MALE</td>
<td>FEMALE</td>
<td></td>
</tr>
<tr>
<td>Control Group</td>
<td>0</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Maximum Dose Group</td>
<td>5000</td>
<td>5000</td>
<td>10</td>
</tr>
<tr>
<td>Medium-high dose Group</td>
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<td>10</td>
</tr>
<tr>
<td>Medium dose Group</td>
<td>1710</td>
<td>1710</td>
<td>10</td>
</tr>
<tr>
<td>Medium-low dose group</td>
<td>1000</td>
<td>1000</td>
<td>10</td>
</tr>
</tbody>
</table>

Before administration of testing substances, body weight of the laboratory animals was in the range of 24-28g in case of male and in the range of 19-28g in case of female, respectively. The laboratory animals were aged 6 weeks.

Preparation of the testing substances was dissolved in physiological saline before administration. Dose was calculated according to the body weight which was measured before administration and dispensed by oral administration to a mouse who was in abrosia for 18 hours before testing.

Observation of clinical symptom such as general change, toxic symptom and mortality was performed for all laboratory animals once an hour during 6 hours after administration on the very administration day, and once a day from the next day to 14th day of administration.

Administration group, who was administered with testing
substances, and the control group were weighed on the administration day, first, third, seventh, tenth and fourteenth days from the administration at a predetermined time for all animals who were alive.

After finish of the test, all animals were slightly anesthetized with ether and bleeding-killed. Appearance and internal organs of the animals were examined with naked eye carefully. Animals, who died during the test, were examined in the same manner.

[Table III]
Mortality and LD$_{50}$ value in mouse administered orally with compounds
<table>
<thead>
<tr>
<th>Test substance</th>
<th>Sex</th>
<th>Dose (mg/kg)</th>
<th>Days after treatment&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Final mortality&lt;sup&gt;b&lt;/sup&gt;</th>
<th>LD&lt;sub&gt;50&lt;/sub&gt; (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>0  1  2  3  7  14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compound 2</td>
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<td>0/5</td>
<td>5000†</td>
</tr>
<tr>
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<td>0/5</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
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<td>0/5 0/5 0/5 0/5 0/5 0/5 0/5</td>
<td>0/5</td>
<td></td>
</tr>
<tr>
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<td></td>
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<td></td>
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<td>0/5</td>
<td>5000†</td>
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<td>0/5</td>
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<td>0/5</td>
<td></td>
</tr>
<tr>
<td>Compound 8</td>
<td>Male</td>
<td>5000</td>
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<td>4/5</td>
<td>3167</td>
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<td>3/5</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1710</td>
<td>2/5 0/3 0/3 0/3 0/3 0/3 0/3</td>
<td>2/5</td>
<td></td>
</tr>
<tr>
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<td></td>
</tr>
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<td>0/5</td>
<td></td>
</tr>
<tr>
<td></td>
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<td>0/5</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Values are expressed as death number/survival number of animal
<sup>b</sup> Values are expressed as death number/total number of animal
EXEMPLARY 15 TO 28

Preparation of Tablet

The below ingredients (1) to (4) were mixed and granulated. To the granules magnesium stearate 5) was added, mixed and compressed to give a unit tablet (200mg) (Example 15).

Similarly, tablets containing other compounds (2) to (14) of the invention were prepared (Examples 16 to 28).

[Table IV]

<table>
<thead>
<tr>
<th>COMPOSITION</th>
<th>WEIGHT (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Compound 1</td>
<td>40</td>
</tr>
<tr>
<td>2) Lactose</td>
<td>30</td>
</tr>
<tr>
<td>3) Corn Starch</td>
<td>100</td>
</tr>
<tr>
<td>4) Microcrystalline Cellulose</td>
<td>25</td>
</tr>
<tr>
<td>5) Magnesium Stearate</td>
<td>5</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>200</strong></td>
</tr>
</tbody>
</table>

EXEMPLARY 29 TO 42

Preparation of Capsule

In a conventional way the ingredients of Table 2 were mixed, granulated and dispensed to give a unit capsule (200mg) (Example 29).

Similarly, capsules containing other compounds (2) to (14) of the invention were prepared (Examples 30 to 42).
Industrial Applicability

According to the present invention, it is possible to obtain a novel compound of general formula (I) which is useful as antagonists against angiotensin II.

Although the preferred embodiments of the present invention have been disclosed for illustrative purposes, those skilled in the art will appreciate that various modifications, additions and substitutions are possible, without departing from the scope and spirit of the invention as recited in the accompanying claims.
1. A pyrimidinone compound of formula (I) or pharmaceutically acceptable salts thereof:

\[ \text{(I)} \]

wherein:

- \( R^1 \) is \( C_1 \sim C_4 \) normal or side chain alkyl, cycloalkyl, \( C_1 \sim C_4 \) alkylalkoxy or \( C_1 \sim C_4 \) alkylmercapto;

- \( R^2 \) is H, halogen, \( C_1 \sim C_4 \) alkyl, aryl or arylalkyl;

- \( R^3, R^4 \) is same or different H, \( C_1 \sim C_4 \) normal or side chain alkyl, cycloalkyl, aryl, arylalkyl, \( C_1 \sim C_4 \) alkyl or arylcarbonyl, \( C_1 \sim C_4 \) alkoxy carbonyl, or substituted aminocarbonyl, being optionally substituted by H, halogen, hydroxy, \( C_1 \sim C_4 \) alkoxy, amino, alkylamino or dialkylamino (each alkyl having \( C_1 \sim C_3 \)), \( C_1 \sim C_4 \) alkoxy carbonyl, carboxy, or substituted aminocarbonyl,

- \( R^3 \) and \( R^4 \) are together with N atom forming 4 to 8 membered heterocyclic ring, which can be further substituted with one or two substituents selected from the group consisting of cycloalkyl, aryl or arylalkyl, halogen, hydroxy, \( C_1 \sim C_4 \) alkoxy, amino, alkylamino or dialkylamino (each alkyl residue having \( C_1 \sim C_3 \)), \( C_1 \sim C_4 \) alkoxy carbonyl, carboxy or substituted aminocarbonyl, and \( C_1 \sim C_4 \) normal or side chain alkyl being optionally substituted by H; and the heterocyclic ring can
further include -O-, -S-, -SO-, -SO₂-, >N-R⁶;

R⁶ is H, C₁～C₄ alkyl, aryl, arylalkyl, substituted alkenyl,
pyridyl, pyrimidyl, C₁～C₄ alkyl or arylcarbonyl, C₁～C₄ alkoxy
 carbonyl, substituted aminocarbonyl, CN or SO₂NR³R⁴;

X is S or >N-R⁶; and

Z is CN, COOR³, SO₂NR³R⁴ or tetrazol-5-yl radical having
below general formula,

\[
\begin{array}{c}
\text{N} \\
\text{N} \\
\text{N} \\
\text{R}^6
\end{array}
\] \hspace{1cm} \begin{array}{c}
\text{N} \\
\text{N} \\
\text{N} \\
\text{N} \\
\text{R}^6
\end{array}
\]

wherein R⁶ is H, t-butyl or triphenylmethyl;

m is 1 or 2; and

n is 1, 2, 3, 4, 5 and 6.

2. The compound or pharmaceutically acceptable salts
thereof, according to claim 1, wherein :

R¹ is ethyl, n-propyl, n-butyl, cyclopropyl, etoxy or
propany; and

R² is H, halogen or C₁～C₄ normal or side chain alkyl.

3. The compound or pharmaceutically acceptable salts
thereof, according to claim 2, wherein :

R³ and R⁴ are same or different H, methyl, ethyl, propyl
or butyl , or R³ and R⁴ are together with N atom forming 4 to
8 membered cyclic ring, which can be further substituted with
one or two substiuents selected from the group consisting of
cycloalkyl, aryl or arylalkyl, halogen, hydroxy, C₁～C₄ alkoxy,
amino, alkylamino or dialkylamino (each alkyl residue having
C₁～C₄), C₁～C₄ alkoxy carbonyl, carboxy and substituted
aminocarbonyl, and C₁～C₄ normal or side chain alkyl being
optionally substituted by H; and the heterocyclic ring can further include \(-O-, -S-, -SO-, -SO_2-, >N-R^5\), wherein \(R^5\) is H, \(C_1\sim C_4\) alkyl, aryl, arylalkyl, substituted alkenyl, pyridyl, pyrimidyl, \(C_1\sim C_4\) alkyl or arylcarbonyl, \(C_1\sim C_4\) alkoxy carbonyl, substituted aminocarbonyl, CN or \(SO_2NR_3R^4\).

4. The compound or pharmaceutically acceptable salts thereof, according to claim 3, wherein:

\(R^5\) is H, \(C_1\sim C_4\) alkyl, \(C_1\sim C_4\) alkoxy carbonyl, substituted aminocarbonyl, CN or \(SO_2NR_3R^4\).

5. The compound or pharmaceutically acceptable salts thereof, according to claim 4, wherein:

\(Z\) is tetrazol-5-yl radical; and

\(m\) is 1.

6. The compound or pharmaceutically acceptable salts thereof, according to claim 1, wherein said compound of formula (I) is the one selected from the group consisting of:

\[2'-(1H-tetrazol-5-yl)biphenyl-4-yl\]methyl]-pyrimidine-4(3H)-one (Compound 1),

\[2'-(1H-tetrazol-5-yl)biphenyl-4-yl\]methyl]-pyrimidine-4(3H)-one (Compound 2),

\[2'-(1H-tetrazol-5-yl)biphenyl-4-yl\]methyl]-pyrimidine-4(3H)-one (Compound 3),

\[2'-(1H-tetrazol-5-yl)biphenyl-4-yl\]methyl]-pyrimidine-4(3H)-one (Compound 4),

\[2'-(1H-tetrazol-5-yl)biphenyl-4-yl\]methyl]-pyrimidine-4(3H)-one (Compound 5),

\[2'-(1H-tetrazol-5-yl)biphenyl-4-yl\]methyl]-pyrimidine-4(3H)-one (Compound 6),

\[2'-(1H-tetrazol-5-yl)biphenyl-4-yl\]methyl]-pyrimidine-4(3H)-one (Compound 7).
methyl]-pyrimidine-4(3H)-one (Compound 5),
2-n-butyl-5-morpholinothiocarbonylmethyl-6-methyl-3-[[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl]
methyl]-pyrimidine-4(3H)-one (Compound 6),
2-n-butyl-5-piperidinothiocarbonylmethyl-6-methyl-3-[[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl]
methyl]-pyrimidine-4(3H)-one (Compound 7),
2-n-butyl-5-pyrrolidinothiocarbonylmethyl-6-methyl-3-[[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl]
methyl]-pyrimidine-4(3H)-one (Compound 8),
2-n-butyl-5-azetidinothiocarbonylmethyl-6-methyl-3-[[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl]
methyl]-pyrimidine-4(3H)-one (Compound 9),
2-n-butyl-5-(2'-aminothiocarbonylethyl)-6-methyl-3-[[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl]
methyl]-pyrimidine-4(3H)-one (Compound 10),
2-n-butyl-5-(2'-dimethylaminothiocarbonylethyl)
-6-methyl-3-[[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl]
methyl]-pyrimidine-4(3H)-one (Compound 11),
2-n-butyl-5-(2'-diethylaminothiocarbonylethyl)-6-
methyl-3-[[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl]
methyl]-pyrimidine-4(3H)-one (Compound 12),
2-n-butyl-5-(2'-thiomorpholinothiocarbonylethyl)
-6-methyl-3-[[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl]
methyl]-pyrimidine-4(3H)-one (Compound 13), and
2-n-butyl-5-(2'-morpholinothiocarbonylethyl)-6-methyl-
3-[[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl]
methyl]-pyrimidine-4(3H)-one (Compound 14).

7. The compound or pharmaceutically acceptable salts thereof, according to any one of claim 1 to claim 6, wherein said salts are inorganic salts obtainable by reacting corresponding pyrimidinone compounds (I) with hydroxides, carbonate or alcoholate of alkali metal or alkaline earth metals
in H₂O, alcohols, tetrahydrofuran, or the mixture thereof.

8. The compound or pharmaceutically acceptable salts thereof, according to any one of claim 1 to claim 6, wherein said salts are inorganic salts obtainable by reacting corresponding pyrimidinone compound (I) with organic amine in H₂O, alcohols, tetrahydrofuran, or the mixture thereof.

9. A pharmaceutical composition containing a therapeutically effective amount of a compound of the present invention according to claim 1 to claim 6 and pharmaceutical excipient.

10. A compound according to claim 1 to claim 6 useful for cardiovascular diseases.

11. A process for preparing compound (I) which comprises the steps of reacting compound (II) with P₅S₁₀, bis(tricyclohexyltartar) sulfide or Lawesson's reagent in any one selected among benzen, dichloromethane or tetrahydrofuran, (wherein X is S):

\[
\begin{align*}
\text{Compound Formula I} & \quad \text{Compound Formula II} \\
(\text{wherein } R^1, R^2, R^3, R^4, Z, m, n \text{ have the meaning defined in claim 1.})
\end{align*}
\]
12. A process for preparing compound (I) which may be obtained by compound (II) by adding substituted amine after preparation of iminium intermediate by using a reagent such as oxalyl chloride, phosphorous oxychloride or ethyl chloroformate in a solvent selected among benzene, ether or tetrahydrofuran, wherein X is NR³:

\[
\begin{align*}
\text{Compound Formula I} & \quad \text{Compound Formula II} \\
\text{wherein } R¹, R², R³, R⁴, R⁵, Z, m \text{ and } n \text{ have the meaning defined in claim 1.}
\end{align*}
\]
INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 99/00198

A. CLASSIFICATION OF SUBJECT MATTER
IPC®: C 07 D 239/36, 403/10, 403/04; A 61 K 31/505
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)
IPC®: C 07 D 239/00, 403/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
AT, Chem.Abstr.

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Questel: DARC, CAS; EPO:WPI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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* Further documents are listed in the continuation of Box C.  
** See patent family annex.

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Date of the actual completion of the international search
12 August 1999 (12.08.99)

Date of mailing of the international search report
01 September 1999 (01.09.99)

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