PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ^{6} **:**
C07D 239/60, 239/54, A61K 31/505

A1

(11) International Publication Number: **WO 95/18109**

(43) International Publication Date: 6 July 1995 (06.07.95)

(21) International Application Number: PCT/KR94/00178

(22) International Filing Date: 20 December 1994 (20.12.94)

(30) Priority Data:

1993/28908	21 December 1993 (21.12.93)	KR
1993/28909	21 December 1993 (21.12.93)	KR
1994/10262	11 May 1994 (11.05.94)	KR
1994/10263	11 May 1994 (11.05.94)	KR
1994/10264	11 May 1994 (11.05.94)	KR
1994/29388	10 November 1994 (10.11.94)	KR

(71) Applicant *(for all designated States except US)*: KOREA RESEARCH INSTITUTE OF CHEMICAL TECHNOLOGY [KR/KR]; 100, Jang-dong, Youseong-gu, Daejeon 305-343 (KR).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: SON, Jong, Chan [KR/KR]; Hanbit Apartment 131-603, 99, Oun-dong, Yuseong-gu, Daejeon 305-333 (KR). LEE, Ill, Young [KR/KR]; Hanbit Apartment 103-404, 99, Oun-dong, Yuseong-gu, Daejeon 305-333 (KR). BAE, Byung, Il [KR/KR]; 90, Hawolgok-dong, Seongbuk-gu, Seoul 136-130 (KR). HAN, Jeong, Sik [KR/KR]; Hanwool Apartment 105-1501, 160-1, Shinseong-dong, Yuseong-gu, Daejeon 305-345 (KR). CHOI, Joong, Kwon [KR/KR]; Hyundae Apartment 103-604, 431-6, Doryong-dong, Yuseong-ku, Daejeon 305-340 (KR). CHAE, Yung, Bok [KR/KR]; 175-7, Pyoungchang-dong, Jongro-gu, Seoul 110-012 (KR).

(74) Agents: JANG, Seong, Ku et al.; 275, Yangjae-dong, Seocho-gu, Seoul 137-130 (KR).

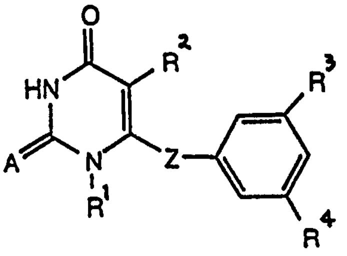
(81) Designated States: AU, CA, JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: NOVEL ANTIVIRAL 2,4-PYRIMIDINEDIONE DERIVATIVES AND PROCESSES FOR THE PREPARATION THEREOF

(57) Abstract

Novel 2,4-pyrimidinedione compounds, and pharmaceutically acceptable salts thereof which possess good antiviral activities, and specifically represented by formula (I) wherein: R^1 represents an unsubstituted or substituted alkyl group represented by $CH_2CH{=}CR^5R^6$ or an unsubstituted or substituted propargyl group represented by $CH_2C{\equiv}CR^7$ wherein R^5, R^6 and R^7 are each independently a hydrogen atom; a methyl group optionally substituted with a halogen atom, or a C_{1-10} carbonyloxy, hydroxy, azido, cyano, optionally substituted amino, optionally substituted phosphonyl, optionally substituted phenyl, C_{3-10} heteroaryl, C_{1-3} alkoxy or benzyloxy radical; a C_{2-10} alkyl or alkenyl group; a cyclopropyl group; an optionally substituted phenyl group; a C_{3-10} heteroaryl group; a C_{1-10} ester group; or an optionally substituted C_{1-10} alkylamide group; R^2 represents a halogen atom, an optionally substituted C_{1-5} alkyl, C_{3-6} cycloalkyl, C_{2-8} alkenyl, C_{2-8} alkynyl group or a benzyl group; R^3 and R^4 represent independently a hydrogen or halogen atom, or a hydroxy, C_{1-3} alkyl, fluoromethyl, C_{1-3} alkoxy, amino, C_{2-6} alkylester or C_{2-7} alkylamide group; A represents an oxygen or sulfur atom; Z represents an oxygen or sulfur atom; a carbonyl group; an amino group; or a methylene group optionally substituted with at least one selected from the group consisting of a halogen atom, and a cyano, hydroxy, azido, amino, C_{1-3} alkylamide, C_{1-4} ester, and nitro groups.



(I)

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria
AU	Australia
BB	Barbados
BE	Belgium
BF	Burkina Faso
BG	Bulgaria
BJ	Benin
BR	Brazil
BY	Belarus
CA	Canada
CF	Central African Republic
CG	Congo
CH	Switzerland
CI	Côte d'Ivoire
CM	Cameroon
CN	China
CS	Czechoslovakia
CZ	Czech Republic
DE	Germany
DK	Denmark
ES	Spain
FI	Finland
FR	France
GA	Gabon
GB	United Kingdom
GE	Georgia
GN	Guinea
GR	Greece
HU	Hungary
IE	Ireland
IT	Italy
JP	Japan
KE	Kenya
KG	Kyrgystan
KP	Democratic People's Republic of Korea
KR	Republic of Korea
KZ	Kazakhstan
LI	Liechtenstein
LK	Sri Lanka
LU	Luxembourg
LV	Latvia
MC	Monaco
MD	Republic of Moldova
MG	Madagascar
ML	Mali
MN	Mongolia
MR	Mauritania
MW	Malawi
NE	Niger
NL	Netherlands
NO	Norway
NZ	New Zealand
PL	Poland
PT	Portugal
RO	Romania
RU	Russian Federation
SD	Sudan
SE	Sweden
SI	Slovenia
SK	Slovakia
SN	Senegal
TD	Chad
TG	Togo
TJ	Tajikistan
TT	Trinidad and Tobago
UA	Ukraine
US	United States of America
UZ	Uzbekistan
VN	Viet Nam

NOVEL ANTIVIRAL 2,4-PYRIMIDINEDIONE DERIVATIVES AND PROCESSES FOR THE PREPARATION THEREOF

Field of the Invention

The present invention relates to novel pyrimidinedione derivatives, which are useful as an antiviral agent, particularly as a treating agent for acquired immunodeficiency syndrome (AIDS), and pharmaceutically acceptable salts thereof. The invention also relates to processes for the preparation of such derivatives and to pharmaceutical compositions containing same as active ingredients.

Description of the Prior Art

Various compounds such as AZT (3'-azido-3'-deoxythymidine); DDC (2',3'-dideoxycytidine), DDI (2',3'-dideoxyinosine) and D4T (3'-deoxy-2',3'-didehydrothymidine) have been reported to have the ability, albeit limited, to inhibit the reproduction of AIDS virus; and they are also known to produce undesirable side effects due to their toxicity.

In order to minimize such problems, therefore, many attempts have been made. For example, 2,4-pyrimidinedione derivatives substituted with an alkoxymethylene group on the N-1 position thereof have been published in J. Med. Chem., <u>35</u>, 4713 (1992); J. Med. Chem., <u>35</u>, 337 (1992); J. Med. Chem., <u>34</u>, 1508 (1991); J. Med. Chem., <u>34</u>, 1394 (1991); J. Med. Chem., <u>34</u>, 349 (1991); Molecular Pharm., <u>39</u>, 805 (1991); Molecular Pharm., <u>44</u>, 694 (1993); EP 0,449,726 A1; EP 0,420,763 A2; and USP 5,318,972 and reported to have an improved activity against human immunodeficiency virus (HIV), while exhibiting a lower toxicity. However, needs have continued to exist for effective compounds with excellent potency against HIV with a lower toxicity.

The present inventors have studied for a long time in search for 2,4-pyrimidinedione compounds which have a strong activity against HIV as well as a lower toxicity, and, as a result, have discovered that 2,4-pyrimidinedione compounds with an allyl or propargyl group in the N-1 position of the 2,4-pyrimidinedione ring exhibit strong antiviral activities against HIV.

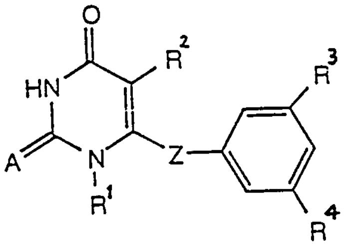
Summary of the Invention

Accordingly, it is a primary object of the present invention to provide novel compounds having superior antiviral activities against HIV with reduced toxicity.

It is another object of the present invention to provide pharmaceutical compositions containing same.

It is a further object of the present invention to provide processes for the preparation of said novel compounds.

In accordance with one aspect of the present invention, there are provided novel 2,4-pyrimidinedione compounds of formula(I):



(I)

wherein:

R^1 represents an unsubstituted or substituted allyl group represented by $CH_2CH=CR^5R^6$ or an unsubstituted or substituted propargyl group represented by $CH_2C\equiv CR^7$ wherein R^5, R^6 and R^7 are each independently a hydrogen atom; a methyl group optionally substituted with a halogen atom, or a C_{1-10} carbonyloxy, hydroxy, azido, cyano, optionally substituted amino, optionally substituted phosphonyl, optionally substituted phenyl, C_{3-10} heteroaryl, C_{1-3} alkoxy or benzyloxy radical; a C_{2-10} alkyl or alkenyl group; a cyclopropyl group; an optionally substituted phenyl group; a C_{3-10} heteroaryl group; a C_{1-10} ester group; or an optionally substituted C_{1-10} alkylamide group;

R^2 represents a halogen atom, an optionally substituted C_{1-5} alkyl, C_{3-6} cycloalkyl, C_{2-8} alkenyl or C_{2-8} alkynyl group, or a benzyl group;

R^3 and R^4 represent independently a hydrogen or halogen atom, or a hydroxy, C_{1-3} alkyl, fluoromethyl, C_{1-3} alkoxy, amino, C_{2-6} alkylester or C_{2-7} alkylamide group;

A represents an oxygen or sulfur atom;

Z represents an oxygen or sulfur atom; a carbonyl group; an amino group; or a methylene group optionally substituted with at least one selected from the group consisting of a halogen, and a cyano, hydroxy, azido, amino, C_{1-3} alkylamide, C_{1-4} ester, and nitro groups.

In accordance with another aspect of the present invention, there are provided pharmaceutically acceptable salts of the compounds of formula(I).

In accordance with a further aspect of the present invention, there are provided pharmaceutical compositions comprising one or more of the 2,4-pyrimidinedione compounds represented by formula(I) and their salts as active ingredients and pharmaceutically acceptable carriers and/or adjuvants.

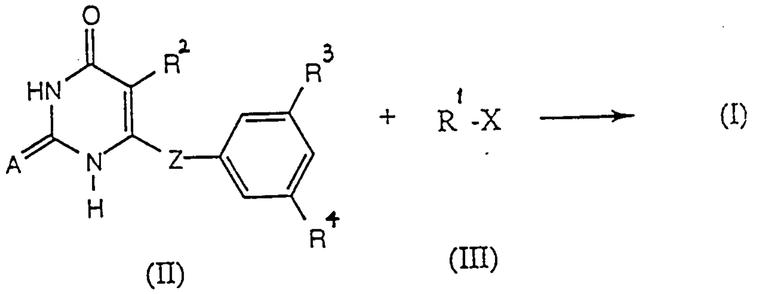
In accordance with still another aspect of the present invention, there are provided with processes for preparing the 2,4-pyrimidinedione compounds.

Detailed Description of the Invention

Among the compounds of the present invention, preferred compounds are those wherein: R^2 is an optionally substituted C_{1-5} alkyl group and/or A is an oxygen atom and/or Z is an oxygen or sulfur atom, or a carbonyl or methylene group.

The 2,4-pyrimidinedione compound of formula(I) of the present invention may be prepared by reacting a compound of formula(II) with a compound of formula(III), as shown in Reaction Scheme (1):

Reaction Scheme (1)



wherein:

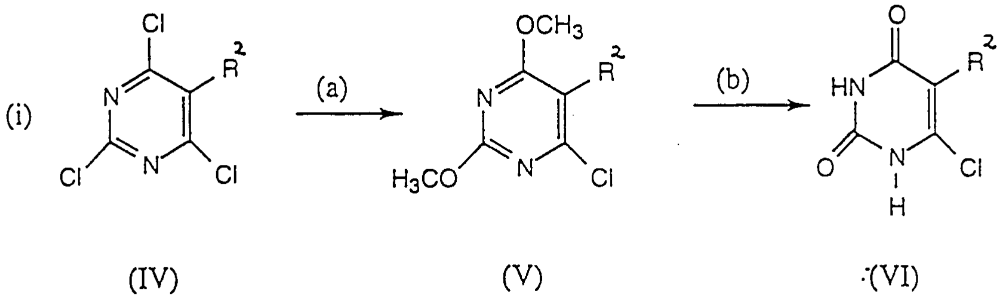
A, R^1, R^2, R^3, R^4 and Z have the same meanings as defined above;

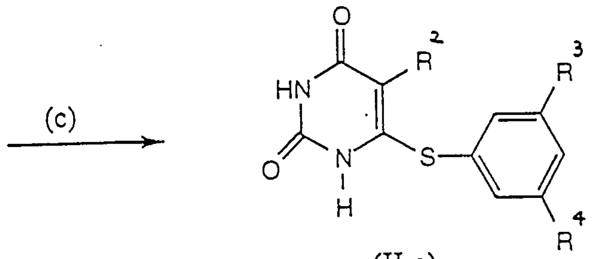
X represents a halogen atom or a sulfonyloxy group.

The above reaction may be conducted in the presence of a base and a solvent at a reaction temperature ranging from 0 to 100 °C under a nitrogen blanket and in a molar ratio of the compound (II) and the compound (III) ranging from 1:0.8 to 1:1.2. Representative of the base include anhydrous potassium carbonate, anhydrous sodium carbonate, potassium tert-butoxide and the like. The solvent is preferably polar and representative thereof include dimethylformamide, dimethylsulfoxide, hexamethylphosphoramide and the like.

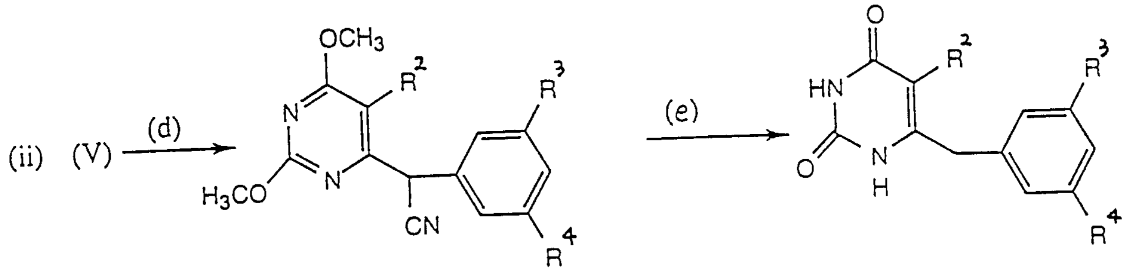
The compounds(II) used as the starting material in the preparation of the 2,4-pyrimidinedione compounds may be prepared by using the methods as shown in Reaction Scheme (2) depending on the Z group.

Reaction Scheme (2)



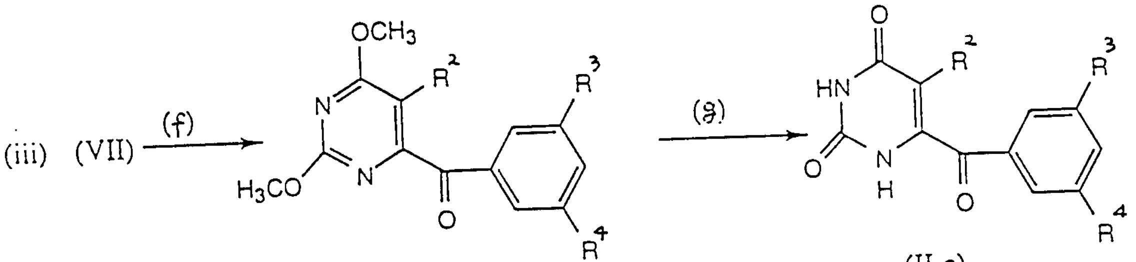


(II-a)



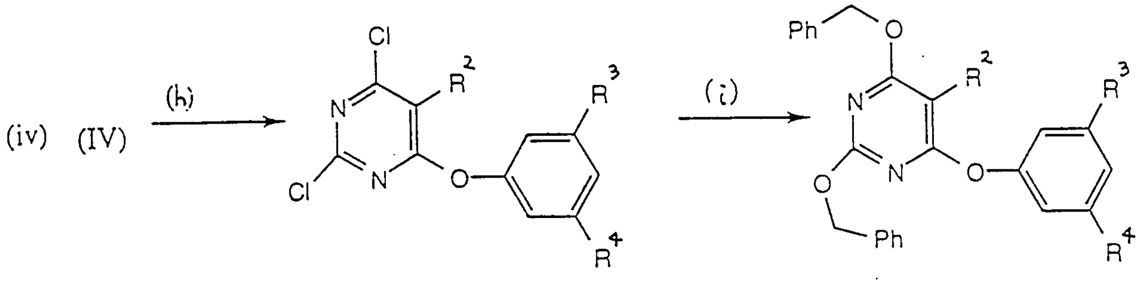
(VII)

(II-b)



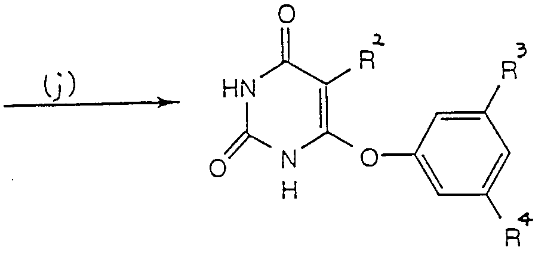
(VIII)

(II-c)



(IX)

(X)



(II-d)

wherein:
R^2, R^3 and R^4 have the same meanings as defined previously.

In accordance with the method (i), a compound of formula (IV) is reacted using a known method disclosed in, e.g., Ber., 52B, 869 (1919) and J. Med. Chem., 7, 808 (1964) to provide a compound of formula (V) (step (a)), which is hydrolyzed with an acid, e.g., hydrochloric acid, to provide a compound of formula (VI) (step (b)). Thereafter, the compound (VI) is reacted with an arylthio compound, e.g., 3,5-dimethylthiophenol, in an alcoholic solvent, e.g., ethanol, in the presence of a base, e.g., potassium hydroxide, to provide a compound of formula (II-a) (step (c)).

In the method (ii), the compound of formula (V) obtained in step (a) above is reacted with an arylacetonitrile compound, e.g., 3,5-dimethylphenylacetonitrile, and a base, e.g.,.sodium hydride, in a polar solvent, e.g., dimethylformamide, under a nitrogen blanket to provide a compound of formula (VII) (step (d)), which is hydrolyzed by the method described in the step (b) above to provide a compound of formula (II-b) (step (e)).

Further, in accordance with the method (iii), the compound of formula (VII) obtained in step (d) above is reacted with a base, e.g., sodium hydride, in a polar solvent, e.g., dimethylformamide, under an oxygen containing atmosphere to provide a compound of formula (VIII) (step (f)), which is hydrolyzed by the method described in the step (b) above to provide a compound of formula (II-c) (step (g)).

In accordance with the method (iv), the compound of formula (IV) is reacted with phenol in a polar solvent, e.g., dimethylformamide, in the presence of a base, e.g., sodium hydride, to provide a compound of formula (IX) (step (h)), which is reacted with an organometallic compound, e.g., sodium benzylate in an aprotic solvent, e.g., toluene, to provide a compound of formula (X) (step (i)). Thereafter, the compound (X) is subjected to a hydrogen addition reaction in an alcoholic solvent, e.g., ethanol in the presence of a palladium catalyst, e.g., 10% palladium-on-carbon, to provide a compound of formula (II-d) (step (j)).

The compounds of formula (III) used in the present invention are commercially available.

Exemplary compounds of formula(I) of the present invention which can be prepared in accordance with the inventive method described are listed below:

1-allyl-5-ethyl-6-phenylthio-2,4-pyrimidinedione;
1-(2-butenyl)-5-ethyl-6-phenylthio-2,4-pyrimidinedione;
1-cinnamyl-5-ethyl-6-phenylthio-2,4-pyrimidinedione;
1-(3-methyl-2-butenyl)-5-ethyl-6-phenylthio-2,4-pyrimidinedione;
1-(4-ethoxy-2-butenyl)-5-ethyl-6-phenylthio-2,4-pyrimidinedione;
1-(4-benyloxy-2-butenyl)-5-ethyl-6-phenylthio-2,4-pyrimidinedione;
1-propargyl-5-ethyl-6-phenylthio-2,4-pyrimidinedione;

1-allyl-5-ethyl-6-(3,5-dimethylphenylthio)-2,4-pyrimidinedione;
1-(2-butenyl)-5-ethyl-6-(3,5-dimethylphenylthio)-2,4-pyrimidinedione;
1-cinnamyl-5-ethyl-6-(3,5-dimethylphenylthio)-2,4-pyrimidinedione;
1-(methoxycarbonylallyl)-5-ethyl-6-(3,5-dimethylphenylthio)-2,4-pyrimidinedione;
1-(carboxyallyl)-5-ethyl-6-(3,5-dimethylphenylthio)-2,4-pyrimidinedione;
1-(4-chloro-2-butenyl)-5-ethyl-6-(3,5-dimethylphenylthio)-2,4-pyrimidinedione;
1-propargyl-5-ethyl-6-(3,5-dimethylphenylthio)-2,4-pyrimidinedione;
1-(2-butynyl)-5-ethyl-6-(3,5-dimethylphenylthio)-2,4-pyrimidinedione;
1-(3-phenyl-2-propynyl)-5-ethyl-6-(3,5-dimethylphenylthio)-2,4-pyrimidinedione;
1-(2-pentenyl)-5-ethyl-6-(3,5-dimethylphenylthio)-2,4-pyrimidinedione;

1-(4-hydroxy-2-butenyl)-5-ethyl-6-(3,5-dimethylphenylthio)-2,4-pyrimidinedione;

1-(2-butenyl)-5-isopropyl-6-(3,5-dimethylphenylthio)-2,4-pyrimidinedione;
1-(2-pentenyl)-5-isopropyl-6-(3,5-dimethylphenylthio)-2,4-pyrimidinedione;
1-cinnamyl-5-isopropyl-6-(3,5-dimethylphenylthio)-2,4-pyrimidinedione;
1-(methoxycarbonylallyl)-5-isopropyl-6-(3,5-dimethylphenylthio)-2,4-pyrimidinedione;
1-(2-butynyl)-5-isopropyl-6-(3,5-dimethylphenylthio)-2,4-pyrimidinedione;
1-(3-phenyl-2-propynyl)-5-isopropyl-6-(3,5-dimethylphenylthio)-2,4-pyrimidinedione;

1-allyl-5-ethyl-6-benzyl-2,4-pyrimidinedione;
1-(2-butenyl)-5-ethyl-6-benzyl-2,4-pyrimidinedione;
1-cinnamyl-5-ethyl-6-benzyl-2,4-pyrimidinedione;

1-allyl-5-ethyl-6-(3,5-dimethylbenzyl)-2,4-pyrimidinedione;
1-(2-butenyl)-5-ethyl-6-(3,5-dimethylbenzyl)-2,4-pyrimidinedione;
1-cinnamyl-5-ethyl-6-(3,5-dimethylbenzyl)-2,4-pyrimidinedione;
1-(3-methyl-2-butenyl)-5-ethyl-6-(3,5-dimethylbenzyl)-2,4-pyrimidinedione;
1-(methoxycarbonylallyl)-5-ethyl-6-(3,5-dimethylbenzyl)-2,4-pyrimidinedione;
1-propargyl-5-ethyl-6-(3,5-dimethylbenzyl)-2,4-pyrimidinedione;
1-(2-butynyl)-5-ethyl-6-(3,5-dimethylbenzyl)-2,4-pyrimidinedione;
1-(3-phenyl-2-propynyl)-5-ethyl-6-(3,5-dimethylbenzyl)-2,4-pyrimidinedione;

1-(2-butenyl)-5-isopropyl-6-(3,5-dimethylbenzyl)-2,4-pyrimidinedione;
1-cinnamyl-5-isopropyl-6-(3,5-dimethylbenzyl)-2,4-pyrimidine-

dione;

1-(3-phenyl-2-propynyl)-5-isopropyl-6-(3,5-dimethylbenzyl)-2,4-pyrimidinedione;

1-allyl-5-ethyl-6-(3,5-dimethylbenzoyl)-2,4-pyrimidinedione;

1-(2-butenyl)-5-ethyl-6-(3,5-dimethylbenzoyl)-2,4-pyrimidinedione;

1-(trans-cinnamyl)-5-ethyl-6-(3,5-dimethylbenzoyl)-2,4-pyrimidinedione;

1-(cis-cinnamyl)-5-ethyl-6-(3,5-dimethylbenzoyl)-2,4-pyrimidinedione;

1-(2-pentenyl)-5-ethyl-6-(3,5-dimethylbenzoyl)-2,4-pyrimidinedione;

1-(3-methyl-2-butenyl)-5-ethyl-6-(3,5-dimethylbenzoyl)-2,4-pyrimidinedione;

1-(methoxycarbonylallyl)-5-ethyl-6-(3,5-dimethylbenzoyl)-2,4-pyrimidinedione;

1-(ethoxycarbonylallyl)-5-ethyl-6-(3,5-dimethylbenzoyl)-2,4-pyrimidinedione;

1-(isopropoxycarbonylallyl)-5-ethyl-6-(3,5-dimethylbenzoyl)-2,4-pyrimidinedione;

1-(4-chloro-2-butenyl)-5-ethyl-6-(3,5-dimethylbenzoyl)-2,4-pyrimidinedione;

1-(4-azido-2-butenyl)-5-ethyl-6-(3,5-dimethylbenzoyl)-2,4-pyrimidinedione;

1-(4-acetoxy-2-butenyl)-5-ethyl-6-(3,5-dimethylbenzoyl)-2,4-pyrimidinedione;

1-(4-hydroxy-2-butenyl)-5-ethyl-6-(3,5-dimethylbenzoyl)-2,4-pyrimidinedione;

1-(4-methoxy-2-butenyl)-5-ethyl-6-(3,5-dimethylbenzoyl)-2,4-pyrimidinedione;

1-propargyl-5-ethyl-6-(3,5-dimethylbenzoyl)-2,4-pyrimidinedione;

1-(2-butynyl)-5-ethyl-6-(3,5-dimethylbenzoyl)-2,4-pyrimidinedione;

1-(3-phenyl-2-propynyl)-5-ethyl-6-(3,5-dimethylbenzoyl)-2,4-pyrimidinedione;

1-(2-butenyl)-5-isopropyl-6-(3,5-dimethylbenzoyl)-2,4-pyrimidinedione;

1-cinnamyl-5-isopropyl-6-(3,5-dimethylbenzoyl)-2,4-pyrimidinedione;

1-(2-pentenyl)-5-isopropyl-6-(3,5-dimethylbenzoyl)-2,4-pyrimidinedione;

1-(methoxycarbonylallyl)-5-isopropyl-6-(3,5-dimethylbenzoyl)-2,4-pyrimidinedione;

1-(4-chloro-2-butenyl)-5-isopropyl-6-(3,5-dimethylbenzoyl)-2,4-pyrimidinedione;

1-(4-azido-2-butenyl)-5-isopropyl-6-(3,5-dimethylbenzoyl)-2,4-pyrimidinedione;

1-(4-acetoxy-2-butenyl)-5-isopropyl-6-(3,5-dimethylbenzoyl)-2,4-pyrimidinedione;

1-(4-hydroxy-2-butenyl)-5-isopropyl-6-(3,5-dimethylbenzoyl)-2,4-pyrimidinedione;

1-(2-butynyl)-5-isopropyl-6-(3,5-dimethylbenzoyl)-2,4-pyrimidinedione;

1-(3-phenyl-2-propynyl)-5-isopropyl-6-(3,5-dimethylbenzoyl)-2,4-pyrimidinedione;

1-allyl-5-ethyl-6-(3,5-dimethylphenoxy)-2,4-pyrimidinedione;

1-(2-butenyl)-5-ethyl-6-(3,5-dimethylphenoxy)-2,4-pyrimidinedione;

1-(trans-cinnamyl)-5-ethyl-6-(3,5-dimethylphenoxy)-2,4-pyrimidinedione;

1-(cis-cinnamyl)-5-ethyl-6-(3,5-dimethylphenoxy)-2,4-pyrimidinedione;

1-(4-hydroxy-2-butenyl)-5-ethyl-6-(3,5-dimethylphenoxy)-2,4-pyrimidinedione;

1-propargyl-5-ethyl-6-(3,5-dimethylphenoxy)-2,4-pyrimidinedione;

1-(3-phenyl-2-propynyl)-5-ethyl-6-(3,5-dimethylphenoxy)-2,4-pyrimidinedione;

1-(2-pentenyl)-5-ethyl-6-(3,5-dimethylphenoxy)-2,4-pyrimidinedione;

1-(methoxycarbonylallyl)-5-ethyl-6-(3,5-dimethylphenoxy)-2,4-

pyrimidinedione;

1-(2-butenyl)-5-isopropyl-6-(3,5-dimethylphenoxy)-2,4-pyrimidinedione;
1-cinnamyl-5-isopropyl-6-(3,5-dimethylphenoxy)-2,4-pyrimidinedione;
1-(methoxycarbonylallyl)-5-isopropyl-6-(3,5-dimethylphenoxy)-2,4-pyrimidinedione;
1-(2-butynyl)-5-isopropyl-6-(3,5-dimethylphenoxy)-2,4-pyrimidinedione; and
1-(3-phenyl-2-propynyl)-5-isopropyl-6-(3,5-dimethylphenoxy)-2,4-pyrimidinedione.

Furthermore, the present invention encompasses, within its scope, those pharmaceutically acceptable salts of the compounds of formula(I). Suitable pharmaceutically acceptable salts of the 2,4-pyrimidinedione compounds(I) may include alkali or alkaline earth metallic salts, e.g., a sodium, potassium, magnesium, calcium salts and the like. Further, in case that any one of R^1, R^3 and R^4 in formula (I) is an amino group, such inorganic acid salts as a hydrochloride, hydrobromide, sulfate, phosphate, nitrate, perchlorate and the like; and such organic carboxylic and sulfonic acid salts as a formate, acetate, propionate, succinate, glycolate, lactate, fumarate, 4-hydroxybenzoate, methanesulfonate, ethanesulfonate and the like are also included within the scope of the pharmaceutically acceptable salts of the present invention.

As described previously, the 2,4-pyrimidinedione compounds(I) of the present invention and their pharmaceutically acceptable salts possess a strong antiviral activity, particularly against HIV.

The present invention also includes within its scope pharmaceutical compositions comprising one or more of the compounds(I) and their above-mentioned salts as active ingredients, in association with pharmaceutically acceptable carriers, excipients or other additives, if necessary.

The pharmaceutical compositions of the invention may be formulated for administration orally or by injection. The composition for oral administration may take various forms such as tablets and gelatin capsules, which may contain conventional additives such as a diluent (e.g., lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine), a lubricant (e.g., silica, talc, stearic acid or its magnesium and calcium salts and polyethylene glycol). In the case of the tablet form, the composition may further comprise a coupling agent (e.g., magnesium aluminum silicate, starch paste, gelatin, tragakans, methyl cellulose, sodium carboxymethyl cellulose and polyvinyl picolidine) and optionally a dusting agent (e.g., starch, agar and alginic acid or its sodium salt), absorbent, colorant, favour, sweetener and the like. The composition for injection may be an isotonic solution or a suspension.

The composition may be sterilized and/or contain an adjuvant such as a preservative, stabilizer, wetting agent, emulsifier, a salt for controlling an osmotic pressure and/or a buffer solution, and other pharmaceutically effective materials.

The pharmaceutical compositions can be prepared by a conventional mixing, granulating or coating method and may comprise preferably about 0.1 to 75 %, more preferably about 1 to 50 % of an active ingredient. The unit dosage of the composition suitable for the administration to human of a weight of about 50 to 70 kg may comprise about 10 to 200mg of the active ingredient.

The following Examples are given for the purpose of illustration only and are not intended to limit the scope of the invention.

In the Examples, unless otherwise specified, the evaporation was conducted under a reduced pressure, preferably under a pressure ranging from about 15 to 100 mmHg, and the flash chromatography was carried out by using Merck Kieselgel 60, 230-400 mesh marketed by Merck.

<u>Preparation 1</u> : Synthesis of 5-ethyl-6-phenylthio-2,4-pyrimidinedione

Step 1) Synthesis of 5-ethyl-6-chloro-2,4-pyrimidinedione

A solution of 32 g (0.16 mol) of 2,4-dimethoxy-5-ethyl-6-chloro-1,3-pyrimidine in 130ml of conc. HCl was refluxed with stirring. After 4 hours, the reaction mixture was cooled to room temperature to give a light yellow precipitate, which was collected by filtration and recrystallized from dichloromethane-methanol(1:1) to afford 18.4 g (yield 67 %) of the title compound as a white solid.

M.p. : 218 to 219 °C

^{1}H-NMR(300MHz, CD_3OD) δ 1.06(3H, t, J=7.5Hz), 2.45(2H, q, J=7.5Hz)

IR(KBr) 3377(w, N-H), 1730 and 1630 cm^{-1}(s, CO)

m/z(EI) 174(M^+, 100%), 159($M-CH_3^+$, 94%)

Step 2) Synthesis of 5-ethyl-6-phenylthio-2,4-pyrimidinedione

To a stirred solution of 3.28 g (58.4 mmol) of potassium hydroxide in 120 ml of anhydrous ethanol were added 10.2 g (58.4 mmol) of the compound obtained from step 1 and 7.2 ml (58.4 mmol) of benzenethiol. The resulting mixture was refluxed for 24 hours and evaporated under reduced pressure to give a white precipitate, which was washed with distilled water and recrystallized from ethanol to afford 18.2 g (yield 84 %) of the title compound as a white solid.

M.p. : 221 to 223 °C

^{1}H-NMR(300MHz, CD_3OD) δ 1.11(3H, t, J=7.5Hz), 2.58(2H, q, J=7.5Hz), 7.49(5H, m)

IR(KBr) 3379(w, N-H), 1703 and 1632 cm^{-1}(s, CO)

m/z(EI) 248(M^+, 63%), 233($M-CH_3^+$, 100%)

<u>Preparation 2</u> : Synthesis of 5-ethyl-6-(3,5-dimethylphenylthio)-2,4-pyrimidinedione

To a stirred solution of 2.02 g (36 mmol) of potassium hydroxide dissolved in 100 ml of anhydrous ethanol were added 6.28 g (36 mmol) of the compound obtained from step 1 of Preparation 1 and 5 g (36 mmol) of 3,5-dimethylthiophenol. The resulting mixture was refluxed for 24 hours and evaporated under reduced pressure to give a white precipitate, which was washed with distilled water and recrystallized from ethanol to afford 7.5 g (yield 75 %) of the title compound as a white solid.

M.p. : 224 to 225 °C

^{1}H-NMR(200MHz, CD_3OD) δ 1.14(3H, t, J=7.5Hz), 2.36(6H, s), 2.55 (2H, q, J=7.5Hz), 7.06(1H, s), 7.16-7.26(3H, m), 9.04(1H, s)

m/z(EI) 276(M^+, 73%), 261($M-CH_3^+$, 100%)

<u>Preparation 3</u> : Synthesis of 5-isopropyl-6-(3,5-dimethylphenylthio-2,4-pyrimidinedione

Step 1) Synthesis of 2,4-dimethoxy-5-isopropyl-6-chloro-1,3-pyrimidine

To 50 ml of anhydrous methanol was added 0.46 g (20 mmol) of sodium to produce sodium methoxide, and then 4.51 g (20 mmol) of 2,4,6-trichloro-5-isopropyl-1,3-pyrimidine was added thereto. The resulting mixture was stirred at room temperature for about 24 hours and evaporated under reduced pressure to give an oily residue, which was purified by flash chromatography using a mixture of ethyl acetate and hexane (1:10) as an eluent to afford 4.11 g (yield 95 %) of the title compound as a colorless oil.

^{1}H-NMR(200MHz, $CDCl_3$) δ 1.23(6H, d, J=7.1Hz), 3.40(1H, m), 3.94(3H, s), 3.97(3H, s)

Step 2) Synthesis of 5-isopropyl-6-chloro-2,4-pyrimidinedione

A solution of 1.00 g (4.619 mmol) of the compound obtained from step 1 in 20 ml of conc. HCl-methanol (1:3) was refluxed with stirring. After about 4 hours, the reaction mixture was evaporated under reduced pressure to give a white solid, which was further purified by recrystallization from chloroform-methanol to afford 581 mg (yield 67 %) of the title compound as a white solid.

M.p. : 250 to 251 °C

^{1}H-NMR(200MHz, $CDCl_3$) δ 1.25(6H, d, J=7.1Hz), 3.13(1H, m)

m/z(EI), 188(M^+, 39%), 173($M-CH_3^+$, 100%)

Step 3) Synthesis of 5-isopropyl-6-(3,5-dimethylphenylthio)-2,4-pyrimidinedione

To a stirred solution of 2 g (10.6 mmol) of the compound obtained from step 2 in 25 ml of ethanol were added 2.2 g (15.9 mmol) of 3,5-dimethylthiophenol and 654 mg (11.7 mmol) of potassium hydroxide. The resulting mixture was refluxed with stirring for 23 hours and evaporated under reduced pressure to give a white solid, which was washed with distilled water and dried under reduced pressure to afford 2.9 g (yield 94 %) of the title compound as a white solid.

M.p. : 225 to 226 °C

^{1}H-NMR(200MHz, $CDCl_3$) δ 1.34(6H, d, J=7.0Hz), 2.35(6H, s), 3.11(1H, m), 7.14(1H, s), 7.16(2H,s), 9.30(1H,s)

<u>Preparation 4</u> : Synthesis of 5-ethyl-6-benzyl-2,4-pyrimidinedione

Step 1) Synthesis of 2,4-dimethoxy-5-ethyl-6-(α-cyanobenzyl)-1,3-pyrimidine

A solution of 20.25 g (0.1 mol) of 2,4-dimethoxy-5-ethyl-6-chloro-1,3-pyrimidine and 14 g (0.12 mol) of phenylacetonitrile in 60ml of dimethylformamide (DMF) was cooled to 0 °C under an atmosphere of nitrogen and 4.4 g (0.11 mol) of 60 % sodium hydride was added with stirring thereto. The resulting mixture was then stirred at room temperature for 16 hours, neutralized with a dil. HCl, extracted with ether, washed with water, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure to give an ivory oily residue. The residue was purified by flash chromatography using a mixture of ethyl acetate and hexane (1:1) as an eluent to afford 17.95 g (yield 63 %) of the title compound as a white solid.

M.p. : 73 to 74 °C

^{1}H-NMR(200MHz, $CDCl_3$) δ 0.95(3H, t, J=7.5Hz), 2.47-2.59(2H, m), 3.97(3H, s), 4.00(3H, s), 5.31(1H, s), 7.26-7.47(5H, m)

Step 2) Synthesis of 5-ethyl-6-benzyl-2,4-pyrimidinedione

A solution of 3.95 g (14.0 mmol) of the compound obtained from step 1 in 100ml of conc. HCl was refluxed with stirring.

After about 45 hours, the reaction mixture was cooled to room temperature to give a white precipitate, which was collected by filtration and recrystallized from methanol to afford 2.64 g (yield 82 %) of the title compound as a white solid.

M.p. : 240 to 241 °C

^{1}H-NMR(200MHz, $CDCl_3$) δ 1.02(3H, t, J=7.5Hz), 2.74(2H, q, J=7.5Hz), 4.15(2H, s), 7.18-7.32(5H, m)

m/z(EI) 230(M^+ , 100%), 215($M-CH_3^+$, 38%)

Preparation 5 : Synthesis of 5-ethyl-6-(3,5-dimethylbenzyl)-2,4-pyrimidinedione

Step 1) Synthesis of 2,4-dimethoxy-5-ethyl-6-(α-cyano-3,5-dimethylbenzyl)-1,3-pyrimidine

A solution of 13.26 g (65.5 mmol) of 2,4-dimethoxy-5-ethyl-6-chloro-1,3-pyrimidine and 11.4 g (78.6 mmol) of 3,5-dimethylphenylacetonitrile in 120ml of DMF was cooled to 0 °C under nitrogen and 3.14 g (78.6 mmol) of 60 % sodium hydride was added portionwise, with stirring, thereto. The resulting mixture was stirred for 14 hours at room temperature, neutralized with acetic acid, and evaporated under reduced pressure to give a brown-colored residue, which was purified by flash chromatography using a mixture of ethyl acetate and hexane (1:10) as an eluent to afford 13.2 g (yield 65 %) of the title compound as a white solid.

M.p. : 86 to 88 °C

^{1}H-NMR(200MHz, $CDCl_3$) δ 0.96(3H, t, J=7.4Hz), 2.87(6H, s), 2.46-2.58(2H, m), 3.97(3H, s), 4.01(3H, s), 5.22(1H, s), 6.94(1H, s), 7.02(2H, s)

Step 2) Synthesis of 5-ethyl-6-(3,5-dimethylbenzyl)-2,4-pyrimidinedione

A solution of 2 g (6.43 mmol) of the compound obtained from step 1 in 20 ml of conc. HCl was refluxed with stirring in an oil bath. After 72 hours, the reaction mixture was cooled to room temperature and evaporated under reduced pressure to give a light yellow residue, which was recrystallized from chloroform-methanol to afford 1.28 g

(yield 77 %) of the title compound as a white solid.
M.p. : 228 to 229 °C
^{1}H-NMR(200MHz, $CDCl_3$) δ 1.02(3H, t, J=7.4Hz), 2.27(6H, s), 2.42(2H, q, J=7.4Hz), 3.74(2H, s), 6.79(2H, s), 6.95(1H, s), 7.72(1H, s), 8.50(1H, s)

Preparation 6 : Synthesis of 5-ethyl-6-(3,5-dimethylbenzoyl)-2,4-pyrimidinedione

Step 1) Synthesis of 2,4-dimethoxy-5-ethyl-6-(3,5-dimethylbenzoyl)-1,3-pyrimidine

To a stirred solution of 2.35 g (7.56 mmol) of the compound obtained from step 1 of Preparation 5 in 50 ml of DMF was added 363 mg (9.07 mmol) of 60 % sodium hydride at room temperature under an atmosphere of nitrogen. The resulting mixture was stirred for 4 hours under an air atmosphere, neutralized with acetic acid, and evaporated under reduced pressure to give a light yellow residue, which was purified by flash chromatography using a mixture of ethyl acetate and hexane (1:9) as an eluent to afford 1.96 g (yield 86 %) of the title compound as a white solid.
M.p. : 97 to 99 °C
^{1}H-NMR(200MHz, $CDCl_3$) δ 1.04(3H, t, J=7.5Hz), 2.33(6H, s), 2.41(2H, q, J=7.5Hz), 3.93(3H, s), 4.04(3H, s), 7.22(1H, s), 7.45(2H, s)

Step 2) Synthesis of 5-ethyl-6-(3,5-dimethylbenzoyl)-2,4-pyrimidinedione

A solution of 600 mg (2 mmol) of the compound obtained from step 1 in 15 ml of conc. HCl-methanol (1:2) was refluxed with stirring for about 16 hours and evaporated under reduced pressure to give a light yellow residue, which was recrystallized from methanol-chloroform (5:1) to afford 480 mg (yield 88 %) of the title compound as a white solid.
M.p. : 249 to 250 °C
^{1}H-NMR(200MHz, $CDCl_3/CD_3OD$) δ 0.97(3H, t, J=7.4Hz), 2.17(2H, q, J=7.4Hz), 2.39(6H, s), 7.32(1H, s), 7.50(2H, s)

m/z(EI) 272(M^+, 42%), 257($M-CH_3^+$, 100%)

Preparation 7 : Synthesis of 5-isopropyl-6-(3,5-dimethylbenzyl)-2,4-pyrimidinedione

Step 1) Synthesis of 2,4-dimethoxy-5-isopropyl-6-(α-cyano-3,5-dimethylbenzyl)-1,3-pyrimidine

To a stirred solution of 2.9 g (13.4 mmol) of the compound obtained from step 1 of Preparation 3 and 2.32 g (16.1 mmol) of 3,5-dimethylphenylacetonitrile in 26 ml of DMF was added 643 mg (16.1 mmol) of 60 % sodium hydride under nitrogen atmosphere. The resulting mixture was stirred for 24 hours at room temperature and neutralized with acetic acid. The mixture was then diluted with ether, washed with water, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure to give a yellow-colored residue, which was purified by flash chromatography using a mixture of ethyl acetate and hexane (1 : 10) as an eluent to afford 2.33 g (yield 54 %) of the title compound as a white solid.

M.p. : 107 to 108 °C

^{1}H-NMR(200MHz, $CDCl_3$) δ 1.11(3H, d, J=7.0Hz), 1.13(3H, d, J=7.0Hz), 2.29(6H, s), 3.07(1H, m), 4.00(3H, s), 4.04(3H, s), 5.37(1H, s), 6.94(1H, s), 7.00(2H, s)

Step 2) Synthesis of 5-isopropyl-6-(3,5-dimethylbenzyl)-2,4-pyrimidinedione

A solution of 2.14 g (6.58 mmol) of the compound obtained from step 1 in 20 ml of conc. HCl was heated to reflux, with stirring, for 48 hours and evaporated under reduced pressure to give a yellow-colored residue, which was recrystallized from chloroform-methanol (1:6) to afford 1.0 g (yield 56 %) of the title compound as a white solid.

M.p. : 268 to 269 °C

^{1}H-NMR(200MHz, $CDCl_3/CD_3OD$) δ 1.24(6H, d, J=7.0Hz), 2.29(6H, s), 2.94(1H, m), 3.73(2H, s), 6.80(2H, s), 6.91(1H, s)

m/z(EI) 272(M^+, 79%), 257($M-CH_3^+$, 100%)

Preparation 8 : Synthesis of 5-isopropyl-6-(3,5-dimethylbenzoyl)-2,4-pyrimidinedione

Step 1) Synthesis of 2,4-dimethoxy-5-isopropyl-6-(3,5-dimethylbenzoyl)-1,3-pyrimidine

To a stirred solution of 198 mg (0.61 mmol) of the compound obtained from step 1 of Preparation 7 in 6 ml of DMF was added 24 mg (0.63 mmol) of 60 % sodium hydride at room temperature under an atmosphere of nitrogen. The resulting mixture was then stirred for about 2 hours under an air atmosphere, diluted with 10 ml of ether, washed with water, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure to give a light yellow-colored residue, which was purified by flash chromatography using a mixture of ethyl acetate and hexane (1:7) as an eluent to afford 190 mg (yield 99 %) of the title compound as a white solid.

M.p. : 149 to 150 °C

^{1}H-NMR(200MHz, $CDCl_3$) δ 1.20(6H, d, J=6.9Hz), 2.37(6H, s), 2.81(1H, m), 3.96(3H, s), 4.08(3H, s), 7.28(1H, s), 7.47(2H, s)

Step 2) Synthesis of 5-isopropyl-6-(3,5-dimethylbenzoyl)-2,4-pyrimidinedione

A solution of 186 mg (0.59 mmol) of the compound obtained from step 1 in 15 ml of conc. HCl-methanol (1:2) was heated to reflux with stirring for about 16 hours and evaporated under reduced pressure to give a light yellow-colored residue, which was recrystallized from chloroform-hexane (1:1) to afford 130 mg (yield 77 %) of the title compound as a white solid.

M.p. : 238 to 239 °C

^{1}H-NMR(200MHz, $CDCl_3/CD_3OD$) δ 1.16(6H, d, J=6.9Hz), 2.35-2.49 (7H, m), 7.35(1H, s), 7.53(2H, s)

m/z(EI) 286(M^+, 100%), 271($M-CH_3^+$, 32%)

Preparation 9 : Synthesis of 5-ethyl-6-(3,5-dimethylphenoxy)-2,4-pyrimidinedione

Step 1) Synthesis of 2,4-dichloro-5-ethyl-6-(3,5-dimethylphenoxy)-1,3-pyrimidine

To a stirred solution of 10 g (47.6 mmol) of 5-ethyl-2,4,6-trichloro-1,3-pyrimidine in 150ml of DMF were added 5.8 g (47.6 mmol) of 3,5-dimethylphenol and 1.9 g (47.6 mmol) of 60 % sodium hydride under nitrogen. The resulting mixture was stirred for about 26 hours at room temperature and neutralized with acetic acid. The mixture was then diluted with ether, washed with water, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure to give a yellow-colored residue, which was purified by flash chromatography using a mixture of ethyl acetate and hexane (1:30) as an eluent to afford 13 g (yield 92 %) of the title compound as a white solid.

M.p. : 91 to 92 °C

^{1}H-NMR(200MHz, $CDCl_3$) δ 1.25(3H, t, J=7.5Hz), 2.35(6H, s), 2.84(2H, q, J=7.5Hz), 6.74(2H, s), 6.92(1H, s)

Step 2) Synthesis of 5-ethyl-6-(3,5-dimethylphenoxy)-2,4-pyrimidinedione

To a stirred solution of 1.84 g (17 mmol) of benzyl alcohol in 20 ml of toluene was added 0.39 g (17 mmol) of sodium under nitrogen. After stirring for about 6 hours at room temperature, 2.52 g (11.9 mmol) of the compound obtained from step 1 was added and the stirring was continued for another 11 hours at room temperature. The mixture was then evaporated under reduced pressure to give a light yellow residue, which was purified by flash chromatography using a mixture of ethyl acetate and hexane (1:9) as an eluent to afford 2.6 g of 2,4-dibenzyloxy-5-ethyl-6-(3,5-dimethylphenoxy)-1,3-pyrimidine as a colorless oil.

A solution of 2 g (4.5 mmol) of the benzylated compound in 20 ml of ethanol was stirred under an atmosphere of hydrogen in the presence of 10 % palladium on charcoal at room temperature for 6 hours. The reaction mixture was filtered through Cellite pad and evaporated under reduced pressure to give a light yellow residue, which was recrystallized from methanol-chloroform to afford 420 mg (yield 36 %) of the title compound as a white solid.

M.p. : 221 to 222 °C

^{1}H-NMR(200MHz, CD_3OD) δ 0.90(3H, t, J=7.4Hz), 2.17-2.25(8H, m), 6.62(2H, s), 6.78(1H, s)

m/z(EI) 260(M^+, 69%), 245($M-CH_3^+$, 100%)

Preparation 10 : Synthesis of 5-isopropyl-6-(3,5-dimethylphenoxy)-2,4-pyrimidinedione

Step 1) Synthesis of 2,4-dichloro-5-isopropyl-6-(3,5-dimethylphenoxy)-1,3-pyrimidine

To a stirred solution of 2.26 g (10 mmol) of 5-isopropyl-2,4,6-trichloro-1,3-pyrimidine in 150ml of DMF were added 1.28 g (10.5 mmol) of 3,5-dimethylphenol and 420 mg (10.5 mmol) of 60 % sodium hydride under nitrogen. The reaction mixture was stirred for about 17 hours at room temperature and neutralized with acetic acid. The mixture was diluted with ether, washed with water, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure to give a light yellow-colored oil, which was purified by flash chromatography using a mixture of ethyl acetate and hexane (1:30) as an eluent to afford 3 g (yield 96 %) of the title compound as a white solid.

M.p. : 91 to 92 °C

^{1}H-NMR(200MHz, $CDCl_3$) δ 1.39(6H, d, J=7.0Hz), 2.33(6H, s), 3.56(1H, m), 6.70(2H, s), 6.89(1H, s)

Step 2) Synthesis of 5-isopropyl-6-(3,5-dimethylphenoxy)-2,4-pyrimidinedione

To a stirred solution of 2.2 g (20 mmol) of benzyl alcohol in 20 ml of toluene was added 513 mg (22 mmol) of sodium under nitrogen. After stirring for about 5 hours at room temperature, 3 g (9.7 mmol) of the compound obtained from step 1 was added and the stirring was continued for another 10 hours at room temperature. The mixture was then evaporated under reduced pressure to give a light yellow residue, which was purified by flash chromatography using a mixture of ethyl acetate and hexane (1:9) as an eluent to afford 3 g of 2,4-dibenzyloxy-5-isopropyl-6-(3,5-dimethylphenoxy)-1,3-pyrimidine as a colorless oil.

A solution of 2.8 g (6.17 mmol) of the benzylated compound in 20 ml of ethanol was stirred under an atmosphere of hydrogen in the presence of 10 % palladium on charcoal at room temperature for 5 hours. The reaction mixture was filtered through Cellite pad and evaporated under reduced pressure to give a light yellow residue, which was recrystallized from methanol-chloroform to afford 1.06 g (yield 63 %) of the title compound as a white solid.

M.p. : 229 to 230 °C

^{1}H-NMR(200MHz, CD_3OD) δ 1.20(6H, d, J=7.1Hz), 2.33(6H, s), 3.35(1H, m), 6.64(2H, s), 6.83(1H, s)

Example 1 : Synthesis of 1-propargyl-5-ethyl-6-phenylthio-2,4-pyrimidinedione

To a stirred solution of 248 mg (1 mmol) of the compound obtained from Preparation 1 and 138 mg (1 mmol) of anhydrous potassium carbonate in 5 ml of DMF was added 130 μl (1.2 mmol) of propargyl bromide. The reation mixture was stirred for about 24 hours at room temperature and evaporated under reduced pressure to give a yellow residue, which was purified by flash chromatography using a mixture of ethyl acetate and hexane (1:2) as an eluent to afford 120 mg (yield 42 %) of the title compound as a white solid.

M.p. : 132 °C

^{1}H-NMR(200MHz, $CDCl_3$) δ 1.10(3H, t, J=7.5Hz), 2.21(1H, t, J=2.4 Hz), 2.27(2H, q, J=7.5Hz), 4.82(2H, d, J=2.4Hz), 7.25-7.43(5H, m), 9.49(1H, s)

IR(KBr) 3200(w, NH), 1700, 1650 cm^{-1}(s, CO)

Example 2 : Synthesis of 1-(trans-2-pentenyl)-5-ethyl-6-(3,5-dimethylphenylthio)-2,4-pyrimidinedione

To a stirred solution of 166 mg (0.6 mmol) of the

compound obtained from Preparation 2 and 83 mg (0.6 mmol) of anhydrous potassium carbonate in 5 ml of DMF was added 89 μl (0.6 mmol) of 1-bromo-2-pentene. The reaction mixture was stirred at room temperature for about 24 hours and then evaporated under reduced pressure to give a yellow residue, which was purified by flash chromatography using a mixture of ethyl acetate and hexane (1:2) as an eluent to afford 178 mg (yield 86 %) of the title compound as a white solid.
M.p. : 129 to 130 °C
^{1}H-NMR(200MHz, $CDCl_3$) δ 0.91(3H, t, J=7.5Hz), 1.04(3H, t, J=7.5 Hz), 1.94(2H, q, J=7.5Hz), 2.28(6H, s), 2.70(2H, q, J=7.5Hz), 4.54-4.59(2H, m), 5.31-5.68(2H, m), 6.76(2H, s), 6.87(1H, s), 8.90(1H, s)

<u>Example 3</u> : Synthesis of 1-(3-phenyl-2-propynyl)-5-isopropyl-6-(3,5-dimethylphenylthio)-2,4-pyrimidinedione

To a stirred solution of 203 mg (0.7 mmol) of the compound obtained from Preparation 3 in 5 ml of DMF were added 110 mg (0.8 mmol) of anhydrous potassium carbonate, 116 mg (0.8 mmol) of 1-chloro-3-phenyl-2-propyn, and 471 mg (0.35 mmol) of lithium iodide. The reaction mixture was stirred for about 16 hours at room temperature and evaporated under reduced pressure to give a light yellow-colored residue, which was purified by flash chromatography using a mixture of ethyl acetate and hexane (1:3) as an eluent to afford 156 mg (yield 55 %) of the title compound as a white solid.
M.p. : 113 to 115 °C
^{1}H-NMR(200MHz, $CDCl_3$) δ 1.22(6H, d, J=7.0Hz), 2.22(6H, s), 3.50 (1H, m), 5.06(2H, s), 6.82(1H, s), 6.86(2H, s), 7.19-7.31(5H, m), 8.77(1H, s)

<u>Example 4</u> : Synthesis of 1-allyl-5-ethyl-6-benzyl-2,4-pyrimidinedione

To a stirred solution of 460 mg (2 mmol) of the compound obtained from Preparation 4 and 276 mg (2 mmol) of anhydrous potassium carbonate in 10 ml of DMF was added 174 μl (2 mmol) of allyl bromide at room temperature. After 48 hours, the mixture was evaporated under reduced pressure to give a yellow-colored residue, which was purified by flash chromatography using a mixture of ethyl acetate and hexane (2:5) as an eluent to afford 35 mg (yield 6 %) of the title compound as a white solid.

M.p. : 164 to 165 °C

^{1}H-NMR(200MHz, $CDCl_3$) δ 1.06(3H, t, J=7.5Hz), 2.48(2H, q, J=7.5 Hz), 3.99(2H, s), 4.28-4.31(2H, m), 5.04-5.24(2H, m), 5.85(1H, m), 7.09-7.41(5H, m), 9.37(1H, s)

<u>Example 5</u> : Synthesis of 1-(trans-2-butenyl)-5-ethyl-6-(3,5-dimethylbenzyl)-2,4-pyrimidinedione

To a stirred solution of 258 mg (1 mmol) of the compound obtained from Preparation 5 in 5 ml of DMF were added 138 mg (1 mmol) of anhydrous potassium carbonate and 121 μl (1 mmol) of 85% trans-crotyl bromide at room temperature. After 45 hours, the reaction mixture was then evaporated under reduced pressure to give a yellow-colored residue, which was purified by flash chromatography using a mixture of ethyl acetate and hexane (1:1) as an eluent to afford 43 mg (yield 14 %) of the title compound as a white solid.

M.p. : 145 to 146 °C

^{1}H-NMR(200MHz, $CDCl_3$) δ 1.06(3H, t, J=7.5Hz), 1.70(3H, d, J=5.1 Hz), 2.30(6H, s), 2.46(2H, q, J=7.5Hz), 3.92(6H, s), 4.20-4.23 (2H, m), 5.48-5.62(2H, m), 6.69(2H, s), 6.91(1H, s), 9.23(1H, s)

<u>Example 6</u> : Synthesis of 1-(trans-cinnamyl)-5-isopropyl-6-(3,5-dimethylbenzyl)-2,4-pyrimidinedione

To a stirred solution of 408 mg (1.5 mmol) of the compound obtained from Preparation 7 in 5 ml of DMF were added 248 mg (1.8 mmol) of anhydrous potassium carbonate and 296 mg (1.5 mmol) of cinnamyl bromide at room temperature. After 36 hours, the reaction mixture was then evaporated under reduced pressure to give a yellow-colored residue, which was purified

by flash chromatography using a mixture of ethyl acetate and hexane (1:2) as an eluent to afford 88 mg (yield 15 %) of the title compound as a white solid.
M.p. : 180 to 181 °C
^{1}H-NMR(200MHz, $CDCl_3$) δ 1.31(6H, d, J=7.0Hz), 2.31(6H, s), 2.85 (1H, m), 3.99(2H, s), 4.47(2H, d, J=4.4Hz), 6.17(1H, m), 6.40 (1H, d, J=16.1Hz), 6.73(2H, s), 6.93(1H, s), 7.22-7.40(5H, m), 8.79(1H, s)

<u>Example 7</u> : Synthesis of 1-(3-methyl-2-butenyl)-5-ethyl-6-(3,5-dimethylbenzoyl)-2,4-pyrimidinedione

To a stirred solution of 272 mg (1 mmol) of the compound obtained from Preparation 6 in 5 ml of DMF were added 138 mg (1 mmol) of anhydrous potassium carbonate and 115 μl (1 mmol) of 1-bromo-3-methyl-2-butene at room temperature. After 16 hours; the reaction mixture was evaporated under reduced pressure to give a yellow-colored residue, which was purified by flash chromatography using a mixture of ethyl acetate and hexane (1:2) as an eluent to afford 248 mg (yield 72 %) of the title compound as a white solid.
M.p. : 255 to 260 °C
^{1}H-NMR(200MHz, $CDCl_3$) δ 0.96(3H, t, J=7.4Hz), 1.37(3H, s), 1.46 (3H, s), 2.03(1H,m), 2.26(1H,m), 2.40(6H, s), 4.23-4.27(2H, m), 4.99(1H, m), 7.33(1H, s), 7.52(2H, s), 8.71(1H, s)

<u>Example 8</u> : Synthesis of 1-(methoxycarbonylallyl)-5-ethyl-6-(3,5-dimethylbenzoyl)-2,4-pyrimidinedione

To a stirred solution of 272 mg (1 mmol) of the compound obtained from Preparation 6 and 138 mg (1 mmol) of anhydrous potassium carbonate in 5 ml of DMF was added 138 μl (1 mmol) of 85% methyl 4-bromocrotonate at room temperature. After 4 hours, the reaction mixture was evaporated under reduced pressure to give a yellow-colored residue, which was purified by flash chromatography using a mixture of ethyl acetate and hexane (3:1) as an eluent to afford 151 mg (yield 41 %) of the title compound as a white solid.

M.p. : 201 to 202 °C
^{1}H-NMR(200MHz, $CDCl_3$) δ 0.96(3H, t, J=7.4Hz), 2.00-2.31(2H, m), 2.37(6H, s), 3.67(3H, s), 4.22-4.38(2H, m), 5.69(1H, m), 6.67 (1H, m), 7.32(1H, s), 7.49(2H, s)

Example 9 : Synthesis of 1-(4-chloro-trans-2-butenyl)-5-isopropyl-6-(3,5-dimethylbenzoyl)-2,4-pyrimidinedione

To a stirred solution of 1.43 g (5 mmol) of the compound obtained from Preparation 8 in 10 ml of DMF were added 690 mg (5 mmol) of anhydrous potassium carbonate and 525 μl (5 mmol) of 1,4-dichloro-trans-2-butene at room temperature. After 42 hours, the reaction mixture was diluted with ether, washed with water, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure to give a yellow-colored residue, which was purified by flash chromatography using a mixture of ethyl acetate and hexane (1:2) as an eluent to afford 860 mg (yield 46 %) of the title compound as a white solid.
M.p. : 178 to 179 °C
^{1}H-NMR(200MHz, $CDCl_3$) δ 1.12(3H, d, J=6.9Hz), 1.20(3H, d, J=6.9 Hz), 2.31(1H, m), 2.39(6H, s), 3.83(2H, d, J=6.5Hz), 4.08(1H, m), 4.25(1H, m), 5.46-5.72(2H, m), 7.33(1H, s), 7.51(2H, s), 9.41(1H, s)

Example 10 : Synthesis of 1-(trans-2-butenyl)-5-ethyl-6-(3,5-dimethylphenoxy)-2,4-pyrimidinedione

To a stirred solution of 260 mg (1 mmol) of the compound obtained from Preparation 9 in 5 ml of DMF were added 138 mg (1 mmol) of anhydrous potassium carbonate and 121 μl (1 mmol) of 85 % trans-crotyl bromide at room temperature. After 16 hours, the reaction mixture was evaporated under reduced pressure to give a yellow-colored residue, which was purified by flash chromatography using a mixture of ethyl acetate and hexane (1:2) as an eluent to afford 188 mg (yield 60 %) of the title compound as a white solid.
M.p. : 149 to 150 °C

^{1}H-NMR(200MHz, $CDCl_3$) δ 0.94(3H, t, J=7.5Hz), 1.61(2H, d, J=6.0 Hz), 2.14-2.30(8H, m), 4.23-4.26(2H, m), 5.40-5.60(2H, m), 6.53(2H, s), 6.77(1H, s), 8.88 (1H, s)

Example 11 : Synthesis of 1-(2-butynyl)-5-isopropyl-6-(3,5-dimethylphenoxy)-2,4-pyrimidinedione

To a stirred solution of 274 mg (1 mmol) of the compound obtained from Preparation 10 in 5 ml of DMF were added 152 mg (1.1 mmol) of anhydrous potassium carbonate and 163 mg (1.1 mmol) of 1-methylsulfonyl-2-butyn at room temperature. After 15 hours, the reaction mixture was diluted with ether, washed with water, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure to give a yellow-colored residue, which was purified by flash chromatography using a mixture of ethyl acetate and hexane (1:4) as an eluent to afford 175 mg (yield 54 %) of the title compound as a white solid.
M.p. : 158 to 160 °C
^{1}H-NMR(200MHz, $CDCl_3$) δ 1.15(6H, d, J=7.0Hz), 1.69(3H, t, J=2.2 Hz), 2.32(6H, s), 2.80(1H, m), 3.73(3H, s), 4.43(2H, q, J=2.2 Hz), 6.60(2H, s), 6.78(1H, s), 8.55(1H, s)

Similarly to Examples above, various 2,4-pyrimidinedione derivatives of the present invention were prepared and a list of them is represented in Table 1.

Table 1.

Ex.No.	R^1	R^2	R^3	R^4	Z	^{1}H-NMR(200MHz, $CDCl_3$)δ	M.P.(°C)
12	CH_2=CH-CH_2-	CH_3CH_2-	H	H	S	1.02(3H, t, J=7.5Hz), 2.70 (2H, q, J=7.5Hz), 4.58-4.62(2H, m), 5.03-5.15(2H, m), 7.14-7.38 (5H, m), 9,49(1H, s)	133-134
13	trans CH_3CH=CH-CH_2-	CH_3CH_2-	H	H	S	1.01(3H, t, J=7.4Hz), 1.57 (3H, dd, J=1.2Hz, 6.2Hz), 2.68(2H, q, J=7.4Hz), 4.50 -4.59(2H, m), 5.25-5.65 (2H, m), 7.10-7.36(5H, m), 9.28(1H, s)	132-133
14	trans PhCH=CH-CH_2-	CH_3CH_2-	H	H	S	1.04(3H, t, J=7.5Hz), 2.72 (3H, q, J=7.5Hz), 4.74-4.77(2H, m), 5.91-6.11 (2H, m), 6.46(1H, d, J=15.9Hz), 7.15-7.38(10H, m), 9.37(1H, s)	180-181
15	$(CH_3)_2$C=CH-CH_2-	CH_3CH_2-	H	H	S	1.04(3H, t, J=7.4Hz), 1.61 (3H, s), 1.67(3H, s), 2.70 (2H, q, J= 7.4Hz), 4.56-4.59(2H, m), 4.98-5.05(1H, m), 7.13-7.38(5H, m), 9.24 (1H, s)	162-163

Ex.No.	R^1	R^2	R^3	R^4	Z	^{1}H-NMR(200MHz, $CDCl_3$)δ	M.P.(°C)
16	cis $CH_3CH_2OCH_2CH=CH-CH_2-$	CH_3CH_2-	H	H	S	1.02(3H, t, J=7.4Hz), 1.16 (3H, t, J=7.0Hz), 2.69(2H, q, J=7.4Hz), 3.45(2H, q, J=7.0Hz), 4.05(2H, dd, J= 1.4Hz, 6.2 Hz), 4.62(2H, m), 5.35(1H, m), 5.64(1H, m), 7.13-7.38(5H, m), 8.89(1H, s)	103-104
17	cis $PhCH_2OCH_2CH=CH-CH_2-$	CH_3CH_2-	H	H	S	1.03(3H, s, J=7.5Hz), 2.69 (2H, q, J=7.5Hz), 4.13(1H, m), 4.49 (2H, s), 4.61(2H, m), 5.40(1H, m), 5.67(1H, m), 7.08-7.36(10H, m), 8.98(1H, s)	105-106
18	$CH_2=CH-CH_2-$	CH_3CH_2-	CH_3	CH_3	S	1.04(3H, t, J=7.5Hz), 2.28 (6H, s), 2.70(2H, q, J= 7.5Hz), 4.58-4.61(2H, m), 5.03-5.17(2H,m), 5.75(1H, m), 6.75(2H, s), 6.87(1H, s),9.40(1H,s)	164-165
19	trans $CH_3CH=CH-CH_2-$	CH_3CH_2-	CH_3	CH_3	S	1.04(3H, t, J=7.5Hz), 1.62 (3H, dd, J=1.3Hz, 6.2Hz), 2.29(6H, s), 2,70(2H, q, J=7.5Hz), 4.52-4.55(2H, m), 5.37-5.66(2H, m), 6.76 (2H, s), 6.88(1H, s), 9.08 (1H,s)	158-159

Ex.No.	R^1	R^2	R^3	R^4	Z	^{1}H-NMR(200MHz, $CDCl_3$)δ	M.P.(°C)
20	trans PhCH=CH-CH_2-	CH_3CH_2-	CH_3	CH_3	S	1.03(3H, t, J=7.4Hz), 2.23 (6H, s), 2.70(2H, q, J=7.5 Hz), 4.73-4.76 (2H, m), 6.04-6.10(1H, m), 6.42(1H, d, J=15.8 Hz), 6.78(2H, s), 6.82 (1H, s), 7.22(5H, m), 9.11(1H, s)	160-162
21	trans CH_3O_2CCH=CH-CH_2-	CH_3CH_2-	CH_3	CH_3	S	1.06(3H, t, J=7.3Hz), 2.26 (6H, s), 2.70(2H, q, J=7.3 Hz), 3.68(3H, s), 4.73(2H, dd, J=1.7 Hz, 5.0Hz), 5.62 (1H, m), 6.67(1H, m), 6.75 (2H, s), 6.85(1H, s), 9.07 (1H, s)	210-211
22	trans $ClCH_2CH$=CH-CH_2-	CH_3CH_2-	CH_3	CH_3	S	1.04(3H, t, J=7.3Hz), 2.27 (6H, s), 2,70(2H, q, J=7.3 Hz), 3.91-3.93(2H, m), 4.58-4.60(2H, m), 5.64-5.69(2H, m), 6.75(2H, m), 6.87(1H, s), 8.86(1H,s)	164
23	cis $ClCH_2CH$=CH-CH_2-	CH_3CH_2-	CH_3	CH_3	S	1.08(3H, t, J=7.4Hz), 2.28 (6H, s), 2,71(2H, q, J=7.4 Hz), 4.15(2H, d, J=7.3Hz), 4.64(2H, d, J=7.3Hz), 5.42 (1H, m), 5.71(1H, m), 6.75 (2H, s), 6.88(1H, s), 9.82 (1H, s)	152-153
24	HC≡CCH_2-	CH_3CH_2-	CH_3	CH_3	S	1.06(3H, t, J=7.5Hz), 2.20 (1H, t, J=2.4Hz), 2.29(6H, s), 2.73(2H, q, J=7.5Hz), 4.76(2H, d, J=2.4Hz), 6.82 (2H, s), 6.90(1H, s), 9.44 (1H, s)	180-181

Ex.No.	R^1	R^2	R^3	R^4	Z	^{1}H-NMR(200MHz, $CDCl_3$)δ	M.P.(°C)
25	$H_3CC\equiv CCH_2$-	CH_3CH_2-	CH_3	CH_3	S	1.03(3H, t, J=7.5Hz), 1.69 (3H, t, J=2.4Hz), 2.27(6H, s), 2.70(2H, q, J=7.5Hz), 4.70-4.72 (2H, m), 6.81 (2H, s), 6.86(1H, s), 9.74 (1H,s)	186-187
26	$PhC\equiv CCH_2$-	CH_3CH_2-	CH_3	CH_3	S	1.03(3H, t, J=7.4Hz), 2.22 (6H, s), 2.70(2H, q, J=7.4 Hz), 5.00(2H, s), 6.82-7.33(8H, m), 8.95(1H, s)	178-180
27	trans $CH_3CH=CH-CH_2$-	$(CH_3)_2CH$-	CH_3	CH_3	S	1.22(6H, d, J=7.0Hz), 1.61 -1.67(3H, m), 2.26 (6H, s), 3.50(1H, m), 3.58-4.60 (2H, m), 5.40-5.67(2H,m), 6.76(2H, s), 6.87(1H, s)	166-167
28	trans $CH_3CH_2CH=CH-CH_2$-	$(CH_3)_2CH$-	CH_3	CH_3	S	0.89(3H, t, J=7.5Hz), 1.21 (6H, d, J=7.0Hz),1.87-2.02 (2H, m), 2.25 (6H, s), 3.47(1H, m), 4.61(2H, d, J=5.2Hz), 5.40(1H, m), 5.64(1H, m), 6.74(2H, s), 6.84 (1H, s), 10.14(1H, s)	122-123
29	trans $PhCH=CH-CH_2$-	$(CH_3)_2CH$-	CH_3	CH_3	S	1.23(6H, d, J=6.7Hz), 2.23 (6H, s), 3.52(1H, m), 4.80 -4.83(2H, m), 6.09(1H, m), 6.46(1H, d, J=15.9Hz), 6.79(2H, s), 6.83(1H, s), 7.17- 7.25(5H, m)	133-134
30	trans $CH_3O_2CCH=CH-CH_2$-	$(CH_3)_2CH$-	CH_3	CH_3	S	1.29(6H, d, J=7.0Hz), 2.29 (6H, s), 3.56(1H, m), 3.71 (3H, s), 4.78-4.82(2H, m), 5.68(1H, m), 6.83-6.87 (4H, m)	147-148

Ex.No.	R^1	R^2	R^3	R^4	Z	^{1}H-NMR(200MHz, $CDCl_3$)δ	M.P.(°C)
31	$H_3CC{\equiv}CCH_2$-	$(CH_3)_2CH$-	CH_3	CH_3	S	1.24(6H, d, J=7.0Hz), 1.72 (3H, t, J=2.3Hz), 2.30(6H, s), 3.51(1H, m), 4.78-4.81 (2H, m), 6.85 (2H, s), 6.89(1H, s), 8.87(1H, s)	165-166
32	trans $CH_3CH{=}CH{-}CH_2$-	CH_3CH_2-	H	H	CH_2	1.06(3H, t, J=7.4Hz), 1.69 (3H, d, J=4.8Hz), 2.47(2H, q, J=7.4Hz), 4.01(2H, s), 4.21-4.23(2H, m), 5.47-5.54(2H, m), 7.10-7.40(5H, m), 9.10(1H, s)	132-133
33	trans PhCH=CH-CH_2-	CH_3CH_2-	H	H	CH_2	1.05(3H, t, J=7.4Hz), 2.48 (2H, q, J=7.4Hz), 4.03(2H, s), 4.42-4.45(2H, m), 6.12 (1H, m), 6.38(1H, d, J= 15.1Hz), 7.12-7.44(10H, m), 9.38(1H, s)	159-160
34	$CH_2{=}CH{-}CH_2$-	CH_3CH_2-	CH_3	CH_3	CH_2	1.09(3H, t, J=7.5Hz), 2.28 (6H, s), 2.51(2H, q, J=7.5 Hz), 3.71 (2H, s), 4.49 (2H, dd, J= 1.3Hz, 5.8 Hz), 5.12-5.27(2H, m), 5.85(1H, m), 6.80 (2H, s), 6.92(1H, s), 8.55(1H, s)	129-130
35	trans PhCH=CH-CH_2-	CH_3CH_2-	CH_3	CH_3	CH_2	1.07(3H, t, J=7.4Hz), 2.31 (6H, s), 2.48(2H, q, J=7.4 Hz), 3.97 (2H, s), 4.44-4.47(2H, m), 6.09-6.43(2H, m), 6.73(2H, s), 6.93 (1H, s), 7.25-7.34(5H, m), 8.26 (1H, s)	223-224

Ex.No.	R^1	R^2	R^3	R^4	Z	^{1}H-NMR(200MHz, $CDCl_3$)δ	M.P.(°C)
36	$(CH_3)_2C=CH-CH_2-$	CH_3CH_2-	CH_3	CH_3	CH_2	1.07(3H, t, J=7.5Hz), 1.64 (3H, s), 1.72(3H, s), 2.30 (6H, s), 2.46 (2H, q, J= 7.5Hz), 3.91 (2H, s), 4.28 (2H, d, J=6.2Hz), 5.08 (1H, m), 6.70(2H, s), 6.92 (1H, s), 9.46(1H, s)	169-170
37	trans $CH_3O_2CCH=CH-CH_2-$	CH_3CH_2-	CH_3	CH_3	CH_2	1.11(3H, t, J=7.5Hz), 2.30 (6H, s), 2.52(2H, q, J=7.5 Hz), 3.71(3H, s), 3.73(2H, s), 4.63-4.67(2H, m), 5.89 (1H, m), 6.81-6.95(4H, m), 8.13(1H, s)	105-106
38	$HC\equiv CCH_2-$	CH_3CH_2-	CH_3	CH_3	CH_2	1.07(3H, t, J=7.5Hz), 2.28 (6H, s), 2.34(1H, t, J=2.4 Hz), 2.48(2H, q, J=7.5Hz), 4.08(2H, s), 4.42(2H, d, J=2.4 Hz), 6.70(2H, s), 6.90(1H, s), 9.03(1H, s)	163-164
39	$H_3CC\equiv CCH_2-$	CH_3CH_2-	CH_3	CH_3	CH_2	1.08(3H, t, J=7.5Hz), 1.82 (3H, t, J=2.3Hz), 2.39(6H, s), 2.45(2H, q, J=7.5Hz), 4.09(2H, s), 4.38(2H, d, J=8.4 Hz), 6.72(2H, s), 6.90 (1H, s), 9.40(1H, s)	179-180
40	$PhC\equiv CCH_2-$	CH_3CH_2-	CH_3	CH_3	CH_2	1.09(3H, t, J=7.5Hz), 2.29 (6H, s), 2.50(2H, q, J= 7.5Hz), 4.16(2H, s), 4.67 (2H, s), 6.75 (2H, s), 6.91(1H, s), 7.01-7.60(5H, m), 9.51 (1H, s)	187-189

Ex.No.	R^1	R^2	R^3	R^4	Z	^{1}H-NMR(200MHz, $CDCl_3$)δ	M.P.(°C)
41	trans $CH_3CH=CH-CH_2-$	$(CH_3)_2CH-$	CH_3	CH_3	CH_2	1.28(6H, d, J=7.0Hz), 1.70 (3H, d, J=4.8Hz), 2.29 (6H, s), 2.83(1H, m), 3.92(2H, s), 4.22 (2H, s), 5.48-5.56(2H, m), 6.69(2H, s), 6.91 (1H, s), 8.77(1H, s)	187-188
42	$PhC\equiv CCH_2-$	$(CH_3)_2CH-$	CH_3	CH_3	CH_2	1.32(6H, d, J=7.0Hz), 2.31 (6H, s), 2.89(1H, m), 4.20 (2H, s), 4.69 (2H, s), 6.77(2H, s), 6.93(1H, s), 7.27-7.48 (5H, m)	149-150
43	$CH_2=CH-CH_2-$	CH_3CH_2-	CH_3	CH_3	$\begin{matrix}O\\ \|\\ C\end{matrix}$	0.97(3H, t, J=7.4Hz), 2.07 (1H, m), 2.29(1H, m), 2.39(6H, s), 3.98 (1H, m), 4.37(1H, m), 4.98-5.13(2H, m), 5.69 (1H, m), 7.34(1H, s), 7.52(2H, s),9.42(1H,s)	177-178
44	trans $CH_3CH=CH-CH_2-$	CH_3CH_2-	CH_3	CH_3	$\begin{matrix}O\\ \|\\ C\end{matrix}$	0.98(3H, t, J=7.4Hz), 1.51 (3H, d, J=4.8Hz), 1.97-2.36(2H, m), 2.42(6H, s), 4.03-4.25(2H, m), 5.35-5.49(2H, m), 7.34(1H, s), 7.53(2H, s), 9.69(1H, s)	151-152
45	trans $PhCH=CH-CH_2-$	CH_3CH_2-	CH_3	CH_3	$\begin{matrix}O\\ \|\\ C\end{matrix}$	0.95(3H, t, J=7.4Hz), 1.97 -2.27(8H, m), 4.21-4.47 (2H, m), 5.97(1H, m), 6.16 (1H, d, J=16.0Hz), 7.07-7.49(8H, m), 8.99(1H, s)	171-172

Ex.No.	R^1	R^2	R^3	R^4	Z	^{1}H-NMR(200MHz, $CDCl_3$)δ	M.P.(°C)
46	trans $CH_3CH_2CH{=}CH{-}CH_2{-}$	CH_3CH_2-	CH_3	CH_3	$\overset{\overset{O}{\|}}{C}$	0.80(3H, t, J=7.5Hz), 0.95 (3H, t, J=7.5Hz), 1.84(2H, q, J=7.5Hz), 2.04(1H, m), 2.29(1H, m), 2.39(6H, s), 4.14 (2H, m), 5.24-5.49 (2H, m), 7.32(1H, s), 7.50 (2H, s), 9.14(1H, s)	163-164
47	trans $ClCH_2CH{=}CH{-}CH_2{-}$	CH_3CH_2-	CH_3	CH_3	$\overset{\overset{O}{\|}}{C}$	0.95(3H, t, J=7.5Hz), 2.04 (1H, m), 2.30(1H, m), 2.39 (6H, s), 3.84 (2H, d, J= 5.3Hz), 4.15 (2H, m), 5.60 (2H, m), 7.33(1H, s), 7.50 (2H, s), 9.03(1H, s)	158-159
48	$HC{\equiv}CCH_2-$	CH_3CH_2-	CH_3	CH_3	$\overset{\overset{O}{\|}}{C}$	0.96(3H, t, J=7.4Hz), 2.03 -2.34(3H, m), 2.40 (6H,s), 4.36-4.45(2H, m), 7.35(1H, s), 7.60 (2H, s), 9.19(1H, s)	214-215
49	$H_3CC{\equiv}CCH_2-$	CH_3CH_2-	CH_3	CH_3	$\overset{\overset{O}{\|}}{C}$	0.92(3H, t, J=7.3Hz), 1.44 (3H, t, J=2.3Hz), 1.96-2.28(2H, m), 2.37 (6H, s), 4.12(1H, m), 4.59(1H, m), 7.29(1H, s), 7.58(2H, s), 9.85 (1H, s)	202-203
50	$PhC{\equiv}CCH_2-$	CH_3CH_2-	CH_3	CH_3	$\overset{\overset{O}{\|}}{C}$	0.95(3H, t, J=7.4Hz), 2.06 -2.25(8H, m), 4.40 (1H, d, J=17.9Hz), 5.09 (1H, d, J= 17.9Hz), 6.98 -7.30(6H, m), 7.61(2H, s), 9.42(1H, s)	194-195

Ex.No.	R^1	R^2	R^3	R^4	Z	^{1}H-NMR(200MHz, $CDCl_3$)δ	M.P.(°C)
51	trans $CH_3CH{=}CH{-}CH_2{-}$	$(CH_3)_2CH{-}$	CH_3	CH_3	O ‖ C	1.14(3H, d, J=6.8Hz), 1.23 (3H, d, J=6.8Hz), 1.50 (3H, d, J=4.9Hz), 2.27-2.42(7H, m), 3.99-4.24 (2H, m), 5.25-5.47(2H, m), 7.35(1H, s), 7.55(2H, s), 8.96(1H,s)	195-196
52	trans $PhCH{=}CH{-}CH_2{-}$	$(CH_3)_2CH{-}$	CH_3	CH_3	O ‖ C	1.14(3H, d, J=6.8Hz), 2.24 (3H, d, J=6.8Hz), 2.29-2.39(7H, m), 4.28-4.51 (2H, m), 5.98(1H, m), 6.16 (1H, d, J=16.0Hz), 7.08-7.27(6H, m), 7.53 (2H, s), 9.74(1H, s)	187-189
53	trans $CH_3CH_2CH{=}CH{-}CH_2{-}$	$(CH_3)_2CH{-}$	CH_3	CH_3	O ‖ C	0.78(3H, t, J=7.5Hz), 1.11 (3H, d, J=6.8Hz), 1.20(3H, d, J=6.8Hz), 1.73-1.88(2H, m), 2.30 (1H, m), 2.38(6H, s), 4.11(2H, d, J=6.2Hz), 5.20-5.43(2H, m), 7.31 (1H, s), 7.51(2H, s), 8.59 (1H, s)	168-169
54	trans $CH_3O_2CCH{=}CH{-}CH_2{-}$	$(CH_3)_2CH{-}$	CH_3	CH_3	O ‖ C	1.15(3H, d, J=6.9Hz), 1.22 (3H, d, J=6.9Hz), 2.28-2.39(7H, m), 3.68 (3H, s), 4.11-4.45(2H, m), 5.70(1H, m), 6.66 (1H, m), 7.50(1H, s), 7.52(2H, s), 8.65(1H, s)	188-189

Ex.No.	R^1	R^2	R^3	R^4	Z	^{1}H-NMR(200MHz, $CDCl_3$)δ	M.P.(°C)
55	$H_3CC{\equiv}CCH_2$-	$(CH_3)_2CH$-	CH_3	CH_3	$\overset{O}{\overset{\|}{C}}$	1.11(3H, d, J=6.8Hz), 1.19 (3H, d, J=6.8Hz), 1.45(3H, t, J=2.4Hz), 2.26-2.40 (7H, m), 4.15(1H, m), 4.61 (1H, m), 7.31(1H, s), 7.61 (2H, s), 8.82(1H, s)	191-192
56	$PhC{\equiv}CCH_2$-	$(CH_3)_2CH$-	CH_3	CH_3	$\overset{O}{\overset{\|}{C}}$	1.11(3H, d, J=6.8Hz), 1.20 (3H, d, J=6.8Hz), 2.25-2.37(7H, m), 4.36 (1H, d, J=17.9Hz), 5.05 (1H, d, J=17.9Hz), 6.95-7.28(6H, m), 7.62 (2H, s), 8.75(1H, s)	183-185
57	$CH_2{=}CH{-}CH_2$-	CH_3CH_2-	CH_3	CH_3	O	0.94(3H, t, J=7.4Hz), 2.16 -2.30(8H, m), 4.31-4.34 (2H, m), 5.09-5.18(2H, m), 5.79(1H, m), 6.54(2H, s), 6.77(1H, s), 9.32 (1H, s)	184-186
58	$CH_3C{\equiv}C{-}CH_2$-	CH_3CH_2-	CH_3	CH_3	O	0.94(3H, t, J=7.5Hz), 1.69 (3H, t, J=2.4Hz), 2.22 (2H, q, J=7.5Hz), 4.49(2H, q, J=2.4Hz), 6.62(2H, s), 6.79 (1H, s), 8.93(1H, s)	152-154
59	trans $PhCH{=}CH{-}CH_2$-	CH_3CH_2-	CH_3	CH_3	O	0.94(3H, t, J=7.5Hz), 2.16 -2.25(8H, m), 4.47-4.50 (2H, m), 6.12(1H, m), 6.38 (1H, d, J=15.8Hz), 6.55 (2H, s), 6.42(1H, s), 7.20 -7.30(5H, m), 9.39(1H, s)	174-175
60	$HC{\equiv}CCH_2$-	CH_3CH_2-	CH_3	CH_3	O	0.96(3H, t, J=7.4Hz), 2.19 -2.33(9H, m), 4.54 (2H, d, J=2.4Hz), 6.63(2H, s), 6.81(1H, s), 9.04(1H, s)	178-179

Ex.No.	R^1	R^2	R^3	R^4	Z	^1H-NMR(200MHz, $CDCl_3$)δ	M.P.(°C)
61	$PhC\equiv CCH_2$-	CH_3CH_2-	CH_3	CH_3	O	0.93(3H, t, J=7.4Hz), 2.15 -2.24(8H, m), 4.78(2H, s), 6.65(2H, s), 6.75(1H, s), 7.20-7.29(5H, m), 8.79 (1H, s)	128-129
62	trans CH_3CH_2CH=CH-CH_2-	CH_3CH_2-	CH_3	CH_3	O	0.87-0.99(6H, m), 1.98(2H, q, J=7.4Hz), 2.21 (2H, q, J=7.4Hz), 2.31 (6H, s), 4.25-4.30(2H, m), 5.31-5.65(2H, m), 6.55(2H, s), 6.78(1H, s), 8.25(1H, s)	145-146
63	trans CH_3O_2CCH=CH-CH_2-	CH_3CH_2-	CH_3	CH_3	O	0.96(3H, t, J=7.4Hz), 2.17 -2.73(8H, m), 3.73(3H, s), 4.46-4.49(2H, m), 5.83(1H, m), 6.53 (2H, s), 6.77-6.85 (2H,m)	188-189
64	trans CH_3CH=CH-CH_2-	$(CH_3)_2CH$-	CH_3	CH_3	O	1.13(6H, d, J=7.0Hz), 1.59 (3H, d, J=5.0Hz), 2.29(6H, s), 2.78(1H, m), 4.20(2H, d, J=5.5Hz), 5.34-5.61(2H, m), 6.51(2H, s), 6.75(1H, s), 8.75(1H, s)	141-143
65	trans PhCH=CH-CH_2-	$(CH_3)_2CH$-	CH_3	CH_3	O	1.15(6H, d, J=7.0Hz), 2.27 (6H, s), 2.79(1H, m), 4.46 (2H, d, J=6.2 Hz), 6.11 (1H, m), 6.37 (1H, d, J=15.9Hz), 6.56(2H, s), 6.75 (1H, s), 7.21-7.32(5H, m)	157-158

Ex.No.	R^1	R^2	R^3	R^4	Z	^{1}H-NMR(200MHz, $CDCl_3$)δ	M.P.(°C)
66	trans $CH_3O_2CCH=CH-CH_2-$	$(CH_3)_2CH-$	CH_3	CH_3	O	1.15(6H, d, J=7.0Hz), 2.30 (6H, s), 2.81(1H, m), 3.73 (3H, s), 4.44(2H, d, J=5.5 Hz), 5.78(1H, d, J=15.8 Hz), 6.52(2H, s), 6.72-6.86(2H, m), 9.34(1H, s)	187-188
67	$PhC{\equiv}CCH_2-$	$(CH_3)_2CH-$	CH_3	CH_3	O	1.15(6H, d, J=7.0Hz), 2.26 (6H, s), 2.79(1H, m), 4.75 (2H, s), 6.44(2H, s), 6.76 (1H, s), 7.21-7.33(5H, m), 8.82 (1H, s)	186-187

Example 68 : Synthesis of 1-(cis-2-butenyl)-5-ethyl-6-(3,5-dimethylbenzoyl)-2,4-pyrimidinedione

To a solution of 49 mg (0.15 mmol) of the compound obtained from Example 49 in 1 ml of methanol were added 3 ml of pyridine, a drop of quinoline, and 3 mg of palladium on barium sulfate. The reaction mixture was then stirred for about 2 hours at room temperature under an atmosphere of hydrogen, filtered through Cellite pad, and evaporated under reduced pressure to give a light brown oil, which was purified by flash chromatography using a mixture of ethyl acetate and hexane (1:2) as an eluent to afford 22 mg (yield 45 %) of the title compound as a white solid.

M.p. : 199 to 200 °C

^{1}H-NMR(200MHz, $CDCl_3$) δ 0.96(3H, t, J=7.3 Hz), 1.43(3H, dd, J=7.0 Hz, 1.8Hz), 2.02(1H, m), 2.30(1H, m), 2.40(6H, s), 4.09(1H, m), 4.43(1H, m), 5.23-5.54(2H, m), 7.34(1H, s), 7.52(2H, s), 8.45(1H, s)

Example 69 : Synthesis of 1-(cis-cinnamyl)-5-ethyl-6-(3,5-dimethylbenzoyl)-2,4-pyrimidinedione

To a solution of 40 mg (0.1 mmol) of the compound obtained from Example 50 in 1 ml of methanol were added 3 ml of pyridine, a drop of quinoline, and 4 mg of palladium on barium sulfate. The reaction mixture was then stirred for about 2 hours at room temperature under an atmosphere of hydrogen, filtered through Cellite pad, and evaporated under reduced pressure to give a light brown oil, which was purified by flash chromatography using a mixture of ethyl acetate and hexane (1:3) as an eluent to afford 28 mg (yield 69 %) of the title compound as a white solid.

M.p. : 98 to 99 °C

^{1}H-NMR(200MHz, $CDCl_3$) δ 0.95(3H, t, J=7.3 Hz), 1.99(1H, m), 2.17-2.39(7H, m), 4.35(1H, m), 4.65(1H, m), 5.56(1H, m), 6.43(1H, d, J=11.6Hz), 6.90-6.94(2H, m), 7.12-7.27(6H, m), 9.40(1H, s)

Example 70 : Synthesis of 1-(cis-2-butenyl)-5-ethyl-6-(3,5-dimethylphenoxy)-2,4-pyrimidinedione

To a solution of 40 mg (0.13 mmol) of the compound obtained from Example 58 in 1 ml of methanol were added 3 ml of pyridine, a drop of quinoline, and 4 mg of palladium on barium sulfate. The reaction mixture was then stirred for about 2 hours at room temperature under an atmosphere of hydrogen, filtered through Cellite pad, and evaporated under reduced pressure to give a light brown oil, which was purified by flash chromatography using a mixture of ethyl acetate and hexane (1:3) as an eluent to afford 32 mg (yield 80 %) of the title compound as a white solid.

M.p. : 181 to 182 °C

^{1}H-NMR(200MHz, $CDCl_3$) δ 0.94(3H, t, J=7.5 Hz), 1.61(3H, dd, J=7.0Hz, 1.5Hz), 2.20(2H, q, J=7.5 Hz), 2.30(6H, s), 4.39(2H, d, J=7.0Hz), 5.33-5.66(2H, m), 6.55(2H, s), 6.77(1H, s), 8.91(1H, s)

Example 71 : Synthesis of 1-(cis-2-butenyl)-5-isopropyl-6-(3,5-dimethylphenoxy)-2,4-pyrimidinedione

To a solution of 33 mg (0.1 mmol) of the compound obtained from Example 11 in 1 ml of methanol were added 3 ml of pyridine, a drop of quinoline, and 4 mg of palladium on barium sulfate. The reaction mixture was then stirred for about 2 hours at room temperature under an atmosphere of hydrogen, filtered through Cellite pad, and evaporated under reduced pressure to give a light brown oil, which was purified by flash chromatography using a mixture of ethyl acetate and hexane (1:3) as an eluent to afford 25 mg (yield 76 %) of the title compound as a white solid.

M.p. : 141 to 142 °C

^{1}H-NMR(200MHz, $CDCl_3$) δ 1.13(6H, d, J=7.0Hz), 1.61(3H, dd, J=6.9Hz, 1.4Hz), 2.31(6H, s), 2.79(1H, m), 4.35(2H, d, J=6.8Hz), 5.38(1H, m), 5.60(1H, m), 6.54(2H, s), 6.77(1H, s)

Example 72 : Synthesis of 1-(ethoxycarbonylallyl)-5-ethyl-6-(3,5-dimethylbenzoyl)-2,4-pyrimidinedione

To a solution of 100 mg (0.27 mmol) of the compound obtained from Example 8 in 10 ml of anhydrous ethanol was added 20 mg of p-toluenesulfonic acid monohydrate. The reaction mixture was refluxed with stirring for about 48 hours, neutralized with sodium bicarbonate, and evaporated under reduced pressure to give a light brown residue, which was purified by flash chromatography using a mixture of ethyl acetate and hexane (1:2) as an eluent to afford 60 mg (yield 58 %) of the title compound as a white solid.
M.p. : 157 to 158 °C
^{1}H-NMR(200MHz, $CDCl_3$) δ 0.98(3H, t, J=7.4Hz), 1.22(3H, t, J=7.0 Hz), 2.07(1H, m), 2.27(1H, m), 2.39(6H, s), 4.08-4.37(4H, m), 5.66(1H, m), 6.66(1H, m), 7.33(1H, s), 7.51(2H, s), 9.24(1H, s)

Example 73 : Synthesis of 1-(isopropoxycarbonylallyl)-5-ethyl-6-(3,5-dimethylbenzoyl)-2,4-pyrimidinedione

To a stirred solution of 100 mg (0.27 mmol) of the compound obtained from Example 8 in 10 ml of isopropyl alcohol was added 20 mg of p-toluenesulfonic acid monohydrate. The reaction mixture was refluxed with stirring for about 24 hours, neutralized with sodium bicarbonate, and evaporated under reduced pressure to give a light brown residue, which was purified by flash chromatography using a mixture of ethyl acetate and hexane (1:1) as an eluent to afford 40 mg (yield 37 %) of the title compound as a white solid.
M.p. : 175 to 176 °C
^{1}H-NMR(200MHz, $CDCl_3$) δ 0.95(3H, t, J=7.4Hz), 1.19(6H, d, J=6.0 Hz), 2.07(1H, m), 2.25(1H, m), 2.38(6H, s), 4.25-4.32(2H, m), 4.96(1H, m), 5.60(1H, m), 6.61(1H, m), 7.30(1H, s), 7.48(2H, s), 9.74(1H, s)

Example 74 : Synthesis of 1-(4-azido-trans-2-butenyl)-5-isopropyl-6-(3,5-dimethylbenzoyl)-2,4-pyrimidinedione

To a stirred solution of 187 mg (0.5 mmol) of the compound obtained from Example 9 in 5 ml of DMF was added 98 mg (1.5 mmol) of sodium azide at room temperature. After 24 hours, the reaction mixture was diluted with ether, washed with water, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure to give a yellow oil, which was purified by flash chromatography using a mixture of ethyl acetate and hexane (1:2) as an eluent to afford 180 mg (yield 94 %) of the title compound as a white solid.

M.p. : 126 to 127 °C

^{1}H-NMR(200MHz, $CDCl_3$) δ 1.14(3H, d, J=6.8 Hz), 1.21(3H, d, J=6.8 Hz), 2.31(1H, m), 2.39(6H, s), 3.60(2H, d, J=5.4Hz), 4.03(1H, m), 4.31(1H, dd, J=15.8Hz, 6.6Hz), 5.40-5.70(2H, m), 7.34(1H, s), 7.53(2H, s), 9.91(1H,s)

Example 75 : Synthesis of 1-(4-acetoxy-trans-2-butenyl)-5-isopropyl-6-(3,5-dimethylbenzoyl)-2,4-pyrimidinedione

To a solution of 187 mg (0.5 mmol) of the compound obtained from Example 9 in 5 ml of DMF was added 410 mg (5 mmol) of sodium acetate. The reaction mixture was then stirred for about 48 hours at 100 °C, and evaporated under reduced pressure to give a yellow-colored residue, which was purified by flash chromatography using a mixture of ethyl acetate and hexane (1:2) as an eluent to afford 140 mg (yield 70 %) of the title compound as a colorless syrup.

^{1}H-NMR(200MHz, $CDCl_3$) δ 1.22(3H, d, J=6.9Hz), 1.27(3H, d, J=6.8Hz), 2.03(3H, s), 2.29(1H, m), 2.40(6H, s), 4.15(2H, m), 4.35(2H, d, J=4.7Hz), 5.45-5.60(2H, m), 7.34(1H, s), 7.53(2H, s), 8.88(1H, s)

Example 76 : Synthesis of 1-(4-hydroxy-trans-2-butenyl)-5-isopropyl-6-(3,5-dimethylbenzoyl)-2,4-pyrimidinedione

To a stirred solution of 80 mg (0.2 mmol) of the compound obtained from Example 75 in 5 ml of methanol was added 20 mg

(0.37 mmol) of sodium methoxide at room temperature. After 1 hour, the reaction mixture was neutralized with acetic acid and evaporated under reduced pressure to give a yellow-colored residue, which was purified by flash chromatography using a mixture of ethyl acetate and hexane (4:1) as an eluent to afford 60 mg (yield 82 %) of the title compound as a colorless syrup.

^{1}H-NMR(200MHz, $CDCl_3$) δ 1.12(3H, d, J=6.8 Hz), 1.19(3H, d, J=6.8Hz), 2.26-2.38(7H, m), 3.94-4.05(3H, m), 4.26(1H, dd, J=14.9Hz, 4.4Hz), 5.53-5.60(2H, m), 7.33(1H, s), 7.52(2H, s), 9.56(1H, s)

<u>Example 77</u> : Synthesis of 1-(carboxyallyl)-5-ethyl-6-(3,5-dimethylphenylthio)-2,4-pyrimidinedione

To a stirred solution of 561 mg (1.5 mmol) of the compound obtained from Example 21 in 11 ml of methanol-water (10:1) was added 120 mg (3 mmol) of sodium hydroxide. The reaction mixture was then refluxed for about 2 hours, acidified with dil. hydrochloric acid, and evaporated under reduced pressure to give a yellow residue, which was purified by flash chromatography using a mixture of methanol and chloroform (1:9) as an eluent to afford 100 mg (yield 19 %) of the title compound as a foam.

^{1}H-NMR(200MHz, $CDCl_3$) δ 1.08(3H, t, J=7.5Hz), 2.28(6H, s), 2.75(2H, q, J=7.5Hz), 4.75-4.77(2H, m), 5.62(1H, d, J=15.8Hz), 6.73-6.87(4H,m), 10.02(1H, s)

<u>Example 78</u> : Synthesis of 1-(4-hydroxy-trans-2-butenyl)-5-ethyl-6-(3,5-dimethylphenylthio)-2,4-pyrimidinedione

With stirring, a solution of 112 mg (0.3 mmol) of the compound obtained from Example 21 in 3 ml of THF was cooled to -78 °C under nitrogen and then 440 µl (0.66 mmol) of 1.5 M solution of diisobutyl aluminum hydride in toluene was added. The resulting mixture was then warmed to room temperature over about 1 hour and stirred for 2 hours at room temperature. The excess hydride was then decomposed by addition of methanol and the solvent was removed under reduced pressure to give an oily residue, which was purified by flash chromatography using a mixture of methanol and chloroform (1:10) as an eluent to afford 47 mg (yield 45 %) of the title compound as a white solid.

M.p. : 157 to 158 °C

^{1}H-NMR(200MHz, $CDCl_3$) δ 1.05(3H, t, J=7.4Hz), 2.28(6H, s), 2.71(2H, q, J=7.4Hz), 4.03-4.09(2H, m), 4.59-4.62(2H, m), 5.62-5.70(2H, m), 6.76(2H, s), 6.88(1H, s), 9.17(1H, s)

Example 79 : Synthesis of 1-(4-azido-trans-2-butenyl)-5-ethyl-6-(3,5-dimethylbenzoyl)-2,4-pyrimidinedione

To a stirred solution of 200 mg (0.55 mmol) of the compound obtained from Example 47 in 5 ml of DMF was added 108 mg (1.66 mmol) of sodium azide at room temperature. After 18 hours, the reaction mixture was diluted with ether, washed with water, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure to give a yellow-colored residue, which was purified by flash chromatography using a mixture of ethyl acetate and hexane (1:2) as an eluent to afford 184 mg (yield 90 %) of the title compound as a white solid.

M.p. : 119 to 120 °C

^{1}H-NMR(200MHz, $CDCl_3$) δ 0.96(3H, t, J=7.4Hz), 2.04(1H, m), 2.29(1H, m), 2.40(6H, s), 3.63(2H, d, J=5.5Hz), 4.06(1H, m), 4.36(1H, m), 5.41-5.68(2H, m), 7.35(1H, s), 7.52(2H, s), 9.44(1H, s)

Example 80 : Synthesis of 1-(4-acetoxy-trans-2-butenyl)-5-ethyl-6-(3,5-dimethylbenzoyl)-2,4-pyrimidinedione

To a solution of 180 mg (0.5 mmol) of the compound obtained from Example 47 in 5 ml of DMF was added 410 mg (5 mmol) of sodium acetate. The reaction mixture was then stirred for about 40 hours at 100 °C and evaporated under reduced pressure to give a yellow residue, which was purified

by flash chromatography using a mixture of ethyl acetate and hexane (1:2) as an eluent to afford 110 mg (yield 57 %) of the title compound as a white solid.
M.p. : 152 to 153 °C
^{1}H-NMR(200MHz, $CDCl_3$) δ 0.94(3H, t, J=7.4Hz), 1.94-2.15(4H, m), 2.23(1H,m), 2.37(6H, s), 4.00-4.35(4H, m), 5.44-5.65(2H, m), 7.32(1H, s), 7.49(2H, s), 9.67(1H,s)

Example 81 : Synthesis of 1-(4-hydroxy-trans-2-butenyl)-5-ethyl-6-(3,5-dimethylbenzoyl)-2,4-pyrimidinedione

To a stirred solution of 50 mg (0.13 mmol) of the compound obtained from Example 80 in 5 ml of methanol was added 20 mg (0.37 mmol) of sodium methoxide at room temperature. After 1 hour, the reaction mixture was neutralized with acetic acid and evaporated under reduced pressure to give a yellow-colored residue, which was purified by flash chromatography using a mixture of ethyl acetate and hexane (4:1) as an eluent to afford 26 mg (yield 56 %) of the title compound as a white solid.
M.p. : 172 to 173 °C
^{1}H-NMR(200MHz, $CDCl_3$) δ 0.96(3H, t, J=7.4Hz), 2.01(1H, m), 2.31(1H, m), 2.40(6H, s), 3.94-4.37(4H, m), 5.57-5.62(2H, m), 7.34(1H, s), 7.52(2H, s), 9.46(1H,s)

Example 82 : Synthesis of 1-(4-methoxy-trans-2-butenyl)-5-ethyl-6-(3,5-dimethylbenzoyl)-2,4-pyrimidinedione

To a stirred solution of 60 mg (0.17 mmol) of the compound obtained from Example 47 in 2 ml of methanol was added 50 mg (2.17 mmol) of sodium under nitrogen at room temperature. After 48 hours, the reaction mixture was neutralized with acetic acid and evaporated under reduced pressure to give a yellow-colored residue, which was purified by flash chromatography using a mixture of ethyl acetate and hexane (1:1) as an eluent to afford 30 mg (yield 50 %) of the title compound as a white solid.
M.p. : 142 to 143 °C

^{1}H-NMR(200MHz, $CDCl_3$) δ 0.95(3H, t, J=7.5Hz), 2.01(1H, m), 2.27(1H, m), 2.39(6H, s), 3.24(3H, s), 3.73(2H, d, J=4.4Hz), 4.07(1H, m), 4.32(1H, m), 5.45-5.64(2H, m), 7.33(1H, s), 7.51(2H, s)

Example 83 : Synthesis of 1-(4-hydroxy-trans-2-butenyl)-5-ethyl-6-(3,5-dimethylphenoxy)-2,4-pyrimidinedione

With stirring, a solution of 179 mg (0.53 mmol) of the compound obtained from Example 63 in 5 ml of THF was cooled to -78 °C under nitrogen and 1 ml (1.5 mmol) of 1.5 M solution of diisobutyl aluminum hydride in toluene was added. The reaction mixture was then warmed to room temperature over about 2 hours, then stirred for 14 hours at room temperature. The excess hydride was then decomposed by addition of methanol and the solvent was removed under reduced pressure to give an oily residue, which was purified by flash chromatography using ether as an eluent to afford 66 mg (yield 40 %) of the title compound as a white solid.
M.p. : 125 to 126 °C
^{1}H-NMR(200MHz, $CDCl_3$) δ 0.94(3H, t, J=7.4Hz), 2.15-2.30(8H, m), 4.04-4.06(2H, m), 4.33-4.35(2H, m), 5.67-5.72(2H, m), 6.54(2H, s), 6.77(1H, s), 9.06(1H,s)

Antiviral Activity and Toxicity Test

The anti-HIV assays were based on the inhibition of the virus-induced cytopathic effect in MT-4 cells as described in J. Virol. Methods, 16, 171 (1987). Briefly, MT-4 cells were suspended in culture medium at 2.5 x 10^5 cells/ml and infected with 1000 $CCID_{50}$ (50% cell culture infective dose) of HIV. Immediately, after virus infection, 100 μl of the cell suspension was brought into each well of a flat-bottomed microtiter tray containing various concentrations of the test compounds. After a 4 or 5 day incubation at 37 °C, the number of viable cells was determined by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) method, as disclosed in J. Virol. Methods, 20, 309 (1988).

The cytotoxicity of the compounds of the present invention was assessed in parallel with their antiviral activity. It was based on the viability of mock-infected host cells as determined by the MTT methods (see J. Virol. Methods, 20, 309 (1988)).

The results of the tests are shown in Table 2.

Table 2

Ex.No.	CD_{50}(μg/ml)	ED_{50}(μg/ml)	S.I.(CD_{50}/ED_{50})
1	14.85	< 0.32	> 46
2	8.73	< 0.32	> 29
3	7.94	< 0.009	> 882
4	52.5	< 0.32	> 164
5	48.59	< 0.032	> 1,518
6	8.03	< 0.009	> 892
7	27.84	< 0.33	> 84
8	27.24	< 0.19	> 143
9	6.38	< 0.009	> 708
10	19.39	< 0.01	> 1,939
11	39.87	< 0.32	> 124
12	17.48	< 0.32	> 54
13	16.17	< 0.32	> 50
14	5.77	< 0.032	> 180
15	11.26	0.36	31
16	19.03	2.78	6.85
17	5.79	3.68	1.57
18	3.9	< 0.032	> 121
19	8.74	< 0.009	> 971
20	5.21	< 0.009	> 578
21	41.42	< 0.32	> 129
22	33.8	< 0.36	> 93
23	38.2	< 0.93	> 41

Ex.No.	CD_{50}(μg/ml)	ED_{50}(μg/ml)	S.I.(CD_{50}/ED_{50})
24	1.81	< 0.032	> 56
25	62.5	< 0.69	> 90
26	4.93	< 0.009	> 547
27	6.66	< 0.009	> 740
28	5.79	< 0.009	> 643
29	37.15	< 0.023	> 1,615
30	17.7	< 0.009	> 1,966
31	16.94	< 0.32	> 52
32	32.36	< 0.32	> 101
33	8.58	< 0.032	> 268
34	12.33	< 0.32	> 38
35	5.78	< 0.009	> 642
36	22.07	< 0.33	66
37	12.47	1.64	7.6
38	24.15	< 0.32	> 75
39	8.65	< 0.049	> 176
40	5.02	< 0.009	> 557
41	21.04	< 0.01	> 2,104
42	7.42	< 0.009	> 824
43	54.51	< 0.17	> 320
44	34.39	< 0.01	> 3,439
45	5.97	< 0.009	> 663
46	9.14	< 0.009	> 1,015
47	6.7	< 0.009	> 774
48	36.38	< 0.39	> 93
49	5.2	< 0.032	> 162
50	4.34	< 0.009	> 482
51	22.26	< 0.01	> 2,473
52	9.75	< 0.009	> 1,083
53	5.99	< 0.009	> 665
54	30.05	< 0.01	> 3,005
55	41.66	< 0.32	> 130

Ex.No.	CD$_{50}$(μg/ml)	ED$_{50}$(μg/ml)	S.I.(CD$_{50}$/ED$_{50}$)
56	6.76	< 0.009	> 751
57	42.39	< 0.32	> 132
58	48.9	< 0.34	> 143
59	38.56	< 0.23	> 167
60	15.76	< 0.62	> 25
61	9.3	< 0.009	> 1,033
62	8.05	< 0.032	> 251
63	7.17	< 0.032	> 224
64	9.89	< 0.009	> 1,098
65	8.04	< 0.009	> 893
66	78.64	< 0.32	> 245
67	7.6	< 0.009	> 844
68	8.21	< 0.032	> 162
69	8.67	< 0.032	> 270
70	73.81	< 0.01	> 7,381
71	7.71	< 0.0155	> 497
72	6.85	< 0.01	> 685
73	4.85	< 0.01	> 485
74	8.59	< 0.009	> 954
75	58.39	< 0.009	> 6,487
76	41.98	< 0.025	> 1,679
77	68.34	< 0.902	> 75
78	28.97	< 0.97	> 29
79	8.2	< 0.009	> 911
80	44.4	< 0.033	> 1,345
81	55.44	< 0.009	> 6,160
82	43.1	< 0.32	> 134
83	25.5	< 0.81	> 31
Ref.1	44.66	< 0.009	> 4,962
Ref.2	6.05	< 0.009	> 672

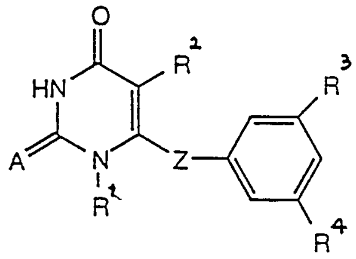
Foot note:

ED_{50}: Effective concentration for the inhibition of the proliferation of HIV by 50%
CD_{50}: Cytotoxic concentration that causes death of cells by 50 %
S.I.: Selectivity index (CD_{50}/ED_{50})
Ref.1: 1-ethoxymethyl-5-ethyl-6-(3,5-dimethylbenzyl)-2,4-pyrimidinedione
Ref.2: 1-benzyloxymethyl-5-ethyl-6-(3,5-dimethylphenylthio)-2,4-pyrimidinedione

While the invention has been described in connection with the above specific embodiments, it should be recognized that various modifications and changes may be made to the present invention and also fall within the scope of the invention as defined by the claims that follow.

What is claimed is:

1. A 2,4-pyrimidinedione compound of formula(I):



(I)

wherein:

R^1 represents an unsubstituted or substituted allyl group represented by $CH_2CH=CR^5R^6$ or an unsubstituted or substituted propargyl group represented by $CH_2C\equiv CR^7$ wherein R^5, R^6 and R^7 are each independently a hydrogen atom; a methyl group optionally substituted with a halogen atom, or a C_{1-10} carbonyloxy, hydroxy, azido, cyano, optionally substituted amino, optionally substituted phosphonyl, optionally substituted phenyl, C_{3-10} heteroaryl, C_{1-3} alkoxy or benzyloxy radical; a C_{2-10} alkyl or alkenyl group; a cyclopropyl group; an optionally substituted phenyl group; a C_{3-10} heteroaryl group; a C_{1-10} ester group; or an optionally substituted C_{1-10} alkylamide group;

R^2 represents a halogen atom, an optionally substituted C_{1-5} alkyl, C_{3-6} cycloalkyl, C_{2-8} alkenyl, C_{2-8} alkynyl group or a benzyl group;

R^3 and R^4 represent independently a hydrogen or halogen atom, or a hydroxy, C_{1-3} alkyl, fluoromethyl, C_{1-3} alkoxy, amino, C_{2-6} alkylester or C_{2-7} alkylamide group;

A represents an oxygen or sulfur atom;

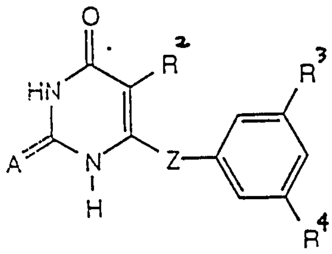
Z represents an oxygen or sulfur atom; a carbonyl group; an amino group; or a methylene group optionally substituted with at least one selected from the group consisting of a halogen atom, and a cyano, hydroxy, azido, amino, C_{1-3} alkylamide, C_{1-4} ester, and nitro groups, or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1 wherein A is an oxygen atom and Z is an oxygen or sulfur atom, or a carbonyl or methylene group, or a pharmaceutically acceptable salt thereof.

3. The compound of claim 2 wherein R^2 is a C_{1-5} alkyl group, or a pharmaceutically acceptable salt thereof.

4. The compound of claim 3 wherein R^2 is an ethyl or isopropyl group, R^3 and R^4 are independently a hydrogen or halogen atom, or a hydroxy, C_{1-3} alkyl, fluoromethyl or C_{1-3} alkoxy group, or a pharmaceutically acceptable salt thereof.

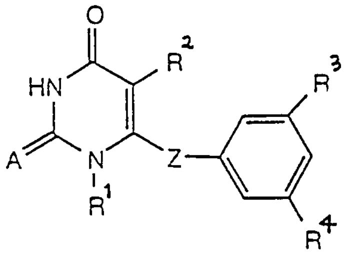
5. A process for the preparation of the compound of formula (I) defined in claim 1 comprising reacting a compound of formula (II) with a compound of formula (III):



(II)

R_1-X

(III)



(I)

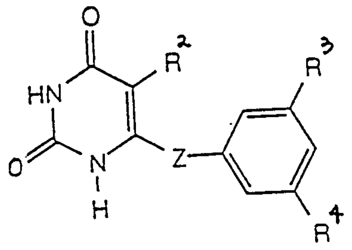
wherein:

A, R^1, R^2, R^3, R^4 and Z have the same meanings as defined in claim 1;

X is a halogen atom or a sulfonyloxy group.

6. The process of claim 5 wherein the reaction is carried out in the presence of a base and a polar solvent under a nitrogen blanket and at a reaction temperature ranging from 0 to 100 °C in a molar ratio of the compound (II) to the compound (III) ranging from 1:0.8 to 1:1.2.

7. A compound having the formula (II):



(II)

wherein:

R^2 is an ethyl or isopropyl group,

R^3 and R^4 are each a methyl group,

Z is an oxygen or sulfur atom, or a carbonyl or methylene group.

8. A pharmaceutical composition comprising an antivirally effective amount of the 2,4-pyrimidinedione compound or a pharmaceutically acceptable salt thereof defined in claim 1 as an active ingredient, and pharmaceutically acceptable carrier and/or adjuvants.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/KR94/00178

A. CLASSIFICATION OF SUBJECT MATTER

IPC^6: C07D 239/60, 239/54; A61K 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^6: C07D 239/60, 239/54; A61K 31/505

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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 484843 A1 (E.R. SQUIBB & SONS, INC) 13 May 1992 (13.05.92), claims 1,3; --	1,8
A	EP 420763 A2 (MISUBISHI KASEI CORPORATION) 03 April 1991 (03.04.91), cited in the application, claims 1,7,8,9,11; --	1,4,8
P	US 5318972 A (MIYASAKA et al .) 07 June 1994 (07.06.94), cited in the application, claims 1,7; --	1,8
A	US 4730001 A (SHEALY et al .) 08 March 1988 (08.03.88), claims 1,11. ----	1,8

☐ 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 31 May 1995 (31.05.95)	Date of mailing of the international search report 13 June 1995 (13.06.95)
Name and mailing address of the ISA/ AT AUSTRIAN PATENT OFFICE Kohlmarkt 8-10 A-1014 Vienna Facsimile No. 1/53424/535	Authorized officer Lux e.h. Telephone No. 1/5337058/31

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/KR 94/00178

Im Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
EP A1 484843	13-05-92	CA AA 2053730	06-05-92
		JP A2 4300872	23-10-92
		US H1 1142	02-02-93
EP A2 420763	03-04-91	JP A2 3279366	10-12-91
		AU A1 63262/90	11-04-91
		AU B2 642906	04-11-93
		CA AA 2026226	30-03-91
		DD A5 299297	09-04-92
		EP A3 420763	18-09-91
		HU A0 906019	28-03-91
		HU A2 55006	29-04-91
		HU B 205917	28-07-92
		ZA A 9007701	31-07-91
US A 5318972	07-06-94	CA AA 2039039	30-09-91
		EP A1 449726	02-10-91
		JP A2 3284624	16-12-91
		JP A2 3284670	16-12-91
		JP B4 7005465	25-01-95
		JP B4 7005570	25-01-95
US A 4730001	08-03-88	keine - none - rien	