CASTELLANOS & CO LTDA
ABOGADOS
Calle 94 A No. 7 A-09
Bogotá, D.C. – COLOMBIA

696

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 06-096752- -00006-0000
Fecha: 2008-05-15 14:40:55 Dep: 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 538 PETICION Folios: 2

Señor

Jefe de la División de Nuevas Creaciones

Superintendencia de Industria y Comercio

Ministerio de Comercio, Desarrollo, Industria y Turismo

E. S. D.

Re.: Expediente No. **06.096.752**

Solicitud del examen de patentabilidad correspondiente a la Patente PCT Entrada en Fase Nacional, para:

"COMPUESTO 8-OXOADENINA 9-SUSTITUIDO"

Solicitante: **DAINIPPON SUMITOMO PHARMA CO., LTD y ASTRAZENECA AKTIEBOLAG**

SOLICITUD EXAMEN DE PATENTABILIDAD

(CAPITULO I)

Yo, **MARGARITA CASTELLANOS ABONDANO**, mayor de edad, identificada y domiciliada como aparece al pié de mi firma, obrando en mi calidad de apoderada de la sociedad solicitante, atentamente me permito solicitar a Ud. que se realice el examen de patentabilidad de la invención arriba citada, para lo cual anexo el comprobante de pago **No. 08- 38.521** de **Mayo 14 de 2008,** correspondiente a la tasa establecida para dicha solicitud.

En consecuencia, atentamente solicito a Ud. se anexe este memorial junto con el comprobante de pago al expediente correspondiente a esta solicitud de Patente PCT Entrada en Fase Nacional, y se continúe con su tramitación.

Señor Jefe,

Margarita Castellanos Abondano
C.C. No. **39.779.654** de Usaquén
T.P.A. No. **70.819** del C. S. J.
Calle 94 A No. 7 A-09 - Bogotá, D.C.
Teléfono (PBX): 610 7420

Bogotá,
MCA/gcb/P1399 (6064-FNPCT)

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693

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 06-096752- -00006-0000

Fecha: 2008-05-15 14:40:55 Dep. 2020 NUECREACIONE
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 38,521
FECHA : MAYO 14 DE 2008

06-096752

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	[illegible]	FECHA PGO	Vr. PAGO
ALVARO CASTELLANOS	CONSIGNACION	BANCO DE BOGOTA	062754387	106619	14/05/2008	6,964,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	85	EXAMEN DE PATENTABILIDAD DE INVEN	420,000.00
			TOTAL : $	420,000.00

SON: CUATROCIENTOS VEINTE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

2

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694

Industria y Comercio
SUPERINTENDENCIA

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 06-96752

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCIÓN**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **583** DE

FECHA **18 DE DICIEMBRE DE 2007** EL TÉRMINO HÁBIL SEÑALADO POR LA

LEY EXPIRA EL **14 DE MARZO DE 2008**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____ NO ___X___

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

202012
Bogotá, D.C., 26 de febrero de 2010

Apoderado: Margarita Castellanos Abondano

ASUNTO	Radicación	06-96752
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	3171
	Folios	

Patente de Invención ⊗

Vía PCT (fase nacional) ⊗ Cap.I ⊗ Cap. II ☐

No. Sol. Internacional PCT/JP2005/005401
Fecha de Presentación Internal. 24/mar/2005

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados

1.1. Descripción: Folios:196 a 408 Como se radicó inicialmente.
Folios 466 a 664 Modificación.

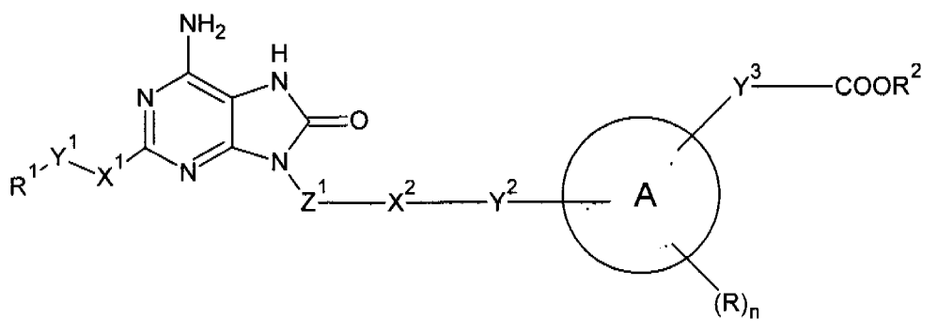
1.2. Reivindicaciones: Folios 409 a 422 Como se radicó inicialmente
Folios 665 a 676 Modificación.
Folios 681 a 691 Modificación.

1.3. Prioridad: Folio 1: JP2004-093672, 26/mar/2004

2. Objeto de la invención

Título de la solicitud: COMPUESTO 8-OXOADENINA 9-SUSTITUIDO.

El objeto de la invención son los derivados de 6-amino- 7,9-dihidro-8H-purin-8-ona-2,9-disustituido que tienen la fórmula Markush (I):



(I)

Reivindicaciones 1–11, 20: Un compuesto de la fórmula (I)
Reivindicación 12: Composiciones que los contienen
Reivindicación 13:Un inmuno-modulador.
Reivindicación 14: Un agente terapéutico.
Reivindicación 15: Medicamento
Reivindicación 16: Un proceso para preparar los compuestos de formula (I).
Reivindicación 17: Un compuesto de fórmula (10)
Reivindicación 18: Proceso.
Reivindicación 19: Compuesto de fórmula (11).

Se catalogó la invención, según la Clasificación Internacional de Patentes (IPC.). C07D473/18, A61K31/522, 31/5377, A61P31/12, 35/00, 37/02, 37/08

3. De la solicitud de Patente

3.1. Reivindicaciones *(artículo 30 D 486 de la C.A.N.)*

-La reivindicación 1 no es clara, donde se rotulan los sustituyentes con denominaciones genéricas tales como por ejemplo "*R es un grupo alquilo, un grupo hidroxi alquilo, un grupo haloalquilo, un grupo alcoxi, un grupo hidroxialcoxi, un grupo haloalcoxi ....*" O, "*...Z^1 un grupo alquileno sustituido o no sustituido o un grupo cicloalquileno sustituido o no sustituido...*" o "*...un grupo holoalquilo, un grupo alquileno..*" etc., no aparece sustento de todas las posibles estructuras que se encierran esas denominaciones y menos para el incalculable número de posibilidades de sus permutaciones. En las reivindicaciones no se aceptan los términos ambiguos, indeterminados o que causan confusión respecto al alcance exacto de la invención, o sea, esos términos no delimitan claramente el alcance de la invención; no se aceptan expresiones genéricas e ilimitadas para definir una invención.
Por lo tanto las reivindicaciones no cumplen con el requisito de claridad, concisión o sustento por la descripción de acuerdo al art. 30 de la Decisión 486.
-Las reivindicaciones 13 y 14 reclaman nuevamente la materia reclamada como compuestos de formula (I), pero con un adjetivo distinto al de compuesto.
-la reivindicación 15 es redundante con la reivindicación 12, ambas son una "composición" que comprende un principio activo "compuesto de fórmula (I)" .

4. Determinación del Estado de la Técnica

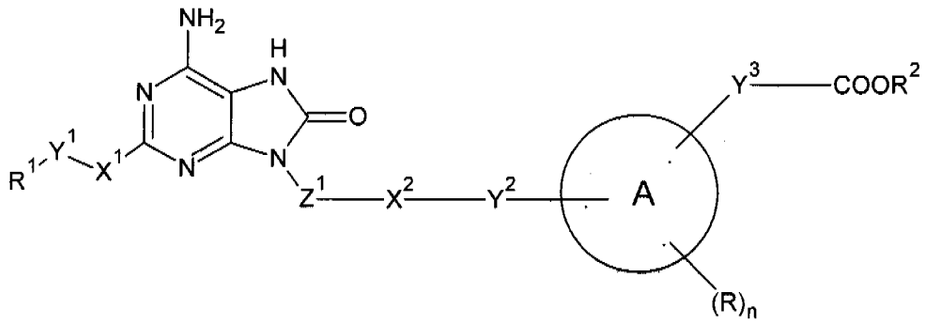
La fecha que se ha tenido en cuenta para determinar el estado de la técnica fecha de presentación de la solicitud de la cual se reclama prioridad, 26/mar/2004.
Teniendo en cuenta la fecha indicada se realizó la búsqueda del estado de la técnica, en bases de datos donde esta oficina tiene acceso libre, para búsqueda de documentos relacionados con la materia que se reclama como nueva e inventiva en presente solicitud, encontrándose los siguientes documentos más relevantes:

N°	Documento	Título	Fecha de Publicación*
D1	EP1035123	Novel heterociclic compounds	10/jun/1999

5. Análisis de patentabilidad (artículo 14 D486 de la C.A.N.)

5.1. Novedad *(artículo 16 D486 de la C.A.N.)*

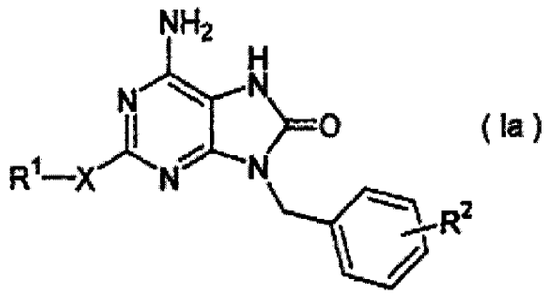
La solicitud en estudio reclama los compuestos derivados de 6-amino- 7,9-dihidro-8H-purin-8-ona-2,9-disustituido que tienen la fórmula Markush (I):



(I)

-El estado de la técnica D1[EP1035123] enseña, derivado de de 6-amino- 7,9-dihidro-8H-purin-8-ona-2,9-disustituido que tienen la fórmula Markush (I):

[0050] The compound (I) of the present invention forms an equilibrium mixture with a tautomer represented by the following formula (Ia):



(Ia)

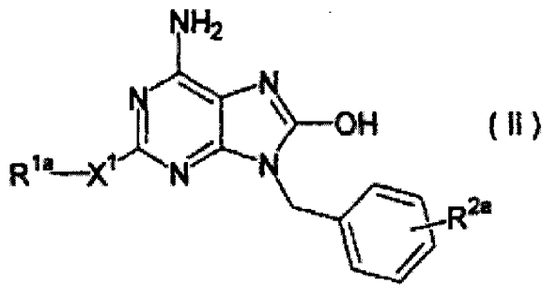
[0051] The compound (I) of the present invention may forms a salt with an acid.

[0052] The preferable acids are pharmaceutically acceptable acids, including inorganic acids, such as hydrochloric acid, sulfuric acid, hydrobromic acid, etc., organic acids, such as acetic acid, oxalic acid, citric acid, malic acid, tartaric acid, fumaric acid, maleic acid, etc.

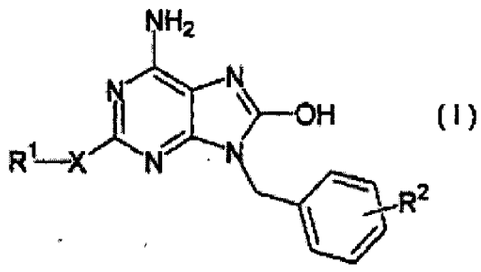
such as sodium or potassium, or organic bases, such as triethylamine or pyridine.

[0055] Preferable embodiments among the compounds (I) of the present invention are as follows.

(a) A heterocyclic compound of the formula (II):



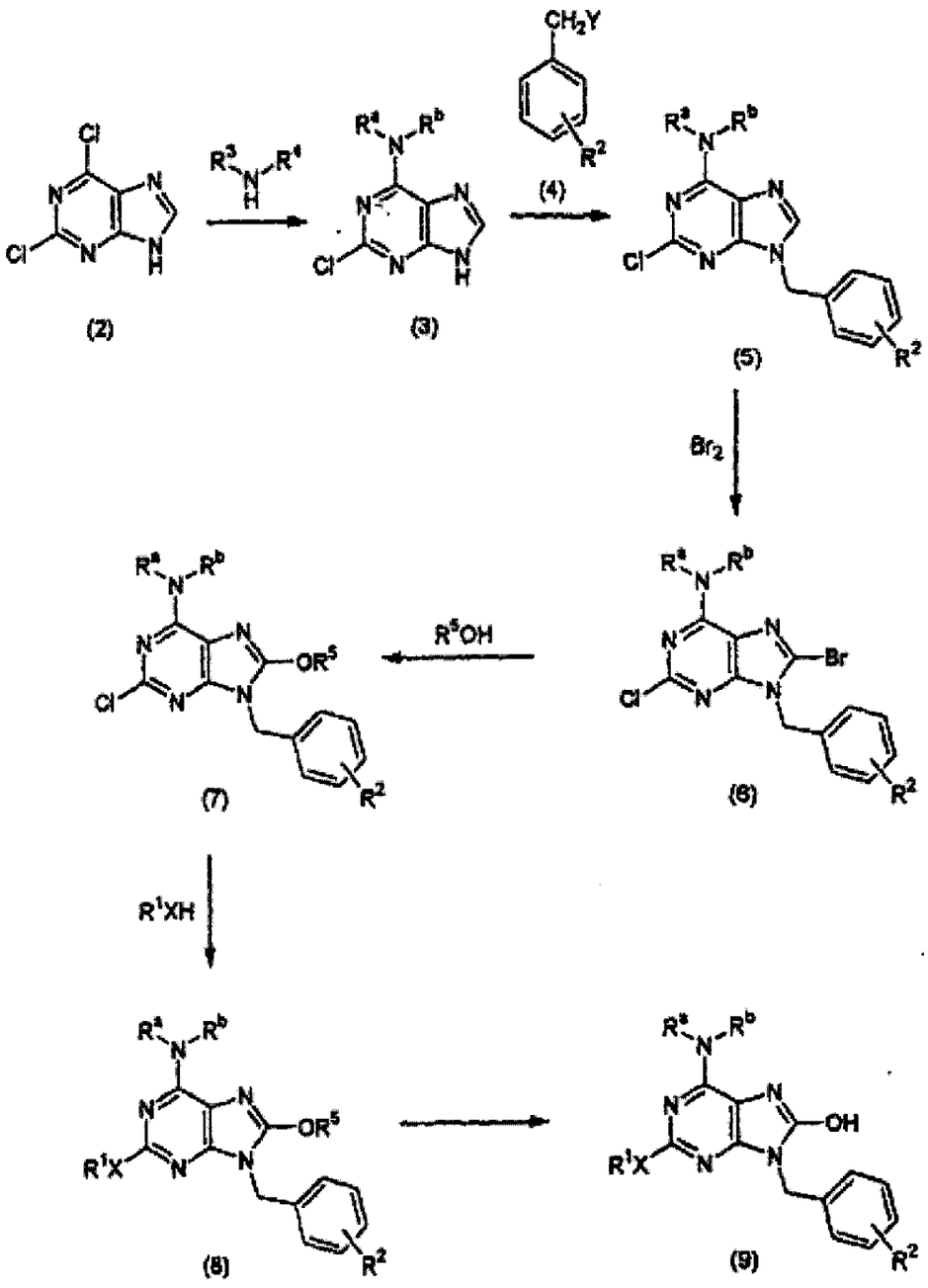
(II)



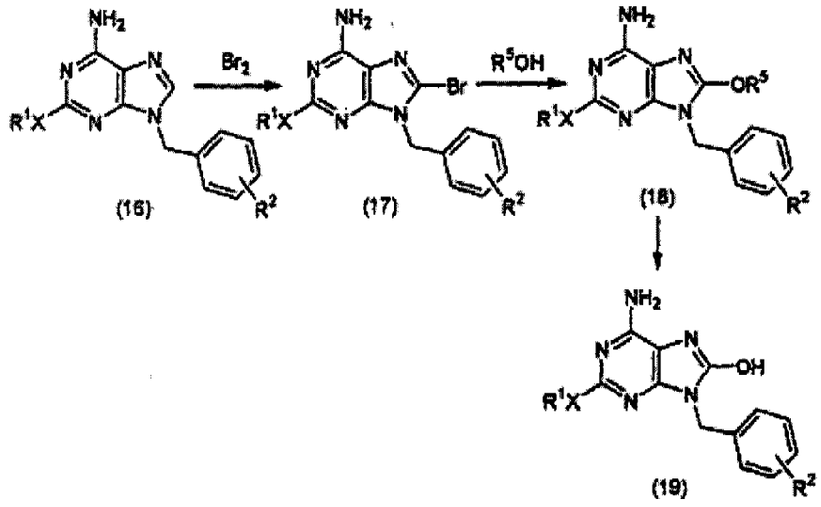
(I)

El proceso donde aparece el intermediario reclamado mediante la fórmula (10) y el proceso:

Process 1.



-Proceso reclamado en la reivindicación 18 y compuesto reclamado mediante la fórmula (11).



-El elemento característico son los derivados de 6-amino- 7,9-dihidro-8H-purin-8-ona-2,9-disustituido, ya eran conocidos en D1, al igual que los esquemas de reacción, o procesos para preparar los esos derivados. Véase todo D1, especialmente todo lo relacionado con los compuestos de fórmula (Ia) y (I), y la reivindicación 1, porque los compuestos carbonílicos que tienen átomos de hidrógenos en sus carbonos alfa se interconvierten en forma rápida con sus correspondientes enoles (*eno* + *ol*, alcohol insaturado). Esta rápida interconversión entre dos especies químicamente distintas es una clase especial de isomería conocida como tautomería. A los isómeros individuales se les llama **tautómeros**. En el equilibrio, la mayoría de los compuestos carbonílicos existen casi exclusivamente en la forma ceto (formula (Ia)) como los reclamados en la solicitud, y suele ser difícil aislar el enol (formula (I)) en forma pura. Eso quiere decir que al momento de obtener los compuestos de fórmula (I) en (D1), se obtiene inmediatamente y en mayor cantidad los compuestos de fórmula (Ia), que es la forma ceto, compuestos que son reclamados en la presente solicitud, así las cosas, la solicitud en estudio no cumple con lo exigido en el artículo 16 D486 de la C.A.N

6. Conclusión:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

**Una solicitud que no cumple con el requisito de novedad obviamente no posee nivel inventivo.*

Documento N°		Reivindicaciones Afectadas	Requisito que Afecta
D1	EP1036123	1-20	Novedad

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de notificación de la presente comunicación. En caso

de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el artículo 8 de la resolución reglamentaria No. 00210 del 15 de enero de 2001, advirtiendo que contra él no procede recurso alguno en la vía gubernativa.

ALIX CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista, de fecha 05 Feb. 2010

CONCEPTO TECNICO No.	**EXAMINADOR TECNICO** Código No.202012

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 035 123 A1

(12) EUROPEAN PATENT APPLICATION

published in accordance with Art. 158(3) EPC

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13.09.2000 Bulletin 2000/37

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(51) Int. Cl.[7]: **C07D 473/16**, C07D 473/18, C07D 473/24, A61K 31/52, A61K 31/535

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PCT/JP98/05318

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WO 99/28321 (10.06.1999 Gazette 1999/23)

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(30) Priority: **28.11.1997 JP 34742297**
11.12.1997 JP 36745197
17.12.1997 JP 36744997

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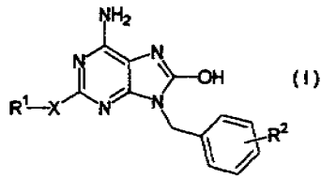
(54) NOVEL HETEROCYCLIC COMPOUNDS

(57) The present invention relates to a heterocyclic compound of the following general formula (I):



(I)

wherein

X is sulfur atom, oxygen atom or -NR^3- (R^3 may form a heterocyclic ring or a substituted heterocyclic ring with R^1 via the nitrogen atom),
R^1 is alkyl group, substituted alkyl group, aryl group, substituted aryl group, heterocyclic group or substituted heterocyclic group, and
R^2 is hydrogen atom, halogen atom etc.;
or its pharmaceutically acceptable salt and interferon inducers, antiviral agents, anticancer agents and therapeutic agents for immunologic diseases comprising the compound (I) or its pharmaceutically acceptable salt as active ingredients.

EP 1 035 123 A1

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2.16.7 (HRS)/3.6

Description

TECHNICAL FIELD

[0001] The present invention relates to novel heterocyclic compounds having inducing activity for biosynthesis of interferon. The heterocyclic compounds of the present invention induce biosynthesis of endogenous interferon in a living body, and are useful for medicines, such as antiviral agents, anticancer agents and therapeutic agents for immunologic diseases.

BACKGROUND OF THE ART

[0002] It has been recently cleared that endogenous interferon plays not only central role to bio-defensive mechanism against virus infections and microbial infections, but also important role on antitumor and immune modulator. Mass production of interferon is established. Namely, it is possible to be available of natural interferon by cell culture and also to produce a large amount of recombinant interferon from E. coli transferred with a gene of interferon and therefore, many research achievements on these interferons have accumulated.. For example, many kinds of biological activity on interferon, such as antiviral activity, prevention of cell growth and immune modulation have been confirmed and interferon is practiced on clinics as treating agents for virus infected diseases, such as hepatitis C and hepatitis B, anticancer agents and therapeutic agents for immunologic disease. Furthermore, it is suggested that interferon will prevent carcinogenesis by hepatitis C and hepatitis B.

[0003] Since there is no therapeutic method for almost of the above diseases, interferon is especially made much of.

DISCLOSURE OF INVENTION

[0004] The object of the present invention is to provide novel low molecular compounds having inducing activity for biosynthesis of interferon, and interferon inducers, antiviral agents, anticancer agents and therapeutic agents for immunologic diseases comprising these compounds as active ingredients.

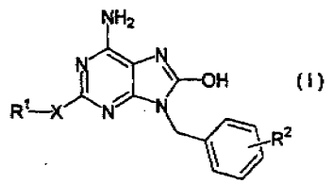
[0005] Viruses of many kinds of animals, microbes such as mycobacteria and protozoa, extracts of them, mitogen, specific antigens and immunopotenciators are known as inducers for biosynthesis of interferon. It is known that for example, many kinds of natural double strand RNAs, synthesized double strand RNAs such as poly-I:C, and anionic high molecular compounds such as polyacrylic acid and oxyamylose oxidized with chlorite have inductive activity of interferon.

[0006] On the other hand, among low molecular compounds have been found fluorenones, pyrimidine derivatives, anthraquinones, acridines and so on having inductive activity of interferon (Stringfellow, D. A.: Methods in Enzymology, 1981, 78, 262).

[0007] However, when these compounds are used in clinical trial, their inducing activity of interferon is unexpectedly low and these compounds have side effects or by administering them repeatedly, their inducing activity of interferon decreases and therefore, development on these compounds have not succeeded. Furthermore, imidazoquinolines are known as interferon inducers among low molecular compounds. However, it is known that these compounds are inferior in selective interferon inducing activity and simultaneously induce cytokines such as IL-6, TNF-α, etc (Testerman, T. L., et al.: J. Leukocyte Biol., 1995, 58, 365).

[0008] As the result of extensive investigation of interferon biosynthesis inducers among low molecules, the present inventors have found that the heterocyclic compounds of the present invention have excellent interferon biosynthesis inducing activity.

[0009] The present invention relates to a heterocyclic compound of the following general formula (I):



(I)

wherein

X is sultur atom, oxygen atom, -NR^3- (in which R^3 is hydrogen atom, alkyl group or substituted alkyl, or may form a heterocyclic ring or a substituted heterocyclic ring together with R^1 via the nitrogen atom),
R^1 is alkyl group, substituted alkyl group, aryl group, substituted aryl group, heterocyclic group or substituted heterocyclic group, and
R^2 is hydrogen atom, or one or more substituents on the benzene ring, and said substituent is the same or different and is hydroxy group, lower alkyl group, substituted lower alkyl group, lower alkoxy group, substituted lower alkoxy group, lower alkanoyl group, substituted lower alkanoyl group, aroyl group, substituted aroyl group, carboxyl group, lower alkoxycarbonyl group, substituted lower alkoxycarbonyl group, amino group, lower alkylamino group, di(lower alkyl)amino group, carbamoyl group, lower alkylcarbamoyl group, di(lower alkyl)carbamoyl group, halogen atom, nitro group or cyano group; or a pharmaceutically acceptable salt thereof.

[0010] Further, the present invention relates to a pharmaceutical composition comprising a heterocyclic compound of the above formula (I) or its pharmaceutically acceptable salt as an active ingredient.

[0011] Further, the present invention relates to an interferon inducer, an antiviral agent, an anticancer agent and a therapeutic agent for immunologic diseases comprising a heterocyclic compound of the above formula (I) or its pharmaceutically acceptable salt as an active ingredient.

[0012] Furthermore, the present invention relates to a process for preparing a heterocyclic compound of the above formula (I) or its pharmaceutically acceptable salt.

[0013] Groups R^1, R^2 and R^3 in the formula (I) are explained below.

[0014] In R^1 alkyl group includes straight or branched C_{1-10} alkyl group (e.g. methyl, ethyl, propyl, butyl, pentyl, isopropyl, isobutyl, 1-methylpropyl, 3-methylbutyl or hexyl), C_{3-7} cycloalkyl group (e.g. cyclopropyl, cyclopentyl, cyclohexyl or cycloheptyl), and alkyl-substituted C_{3-7} cycloalkyl group, preferably straight or branched C_{1-6} alkyl group (e.g. methyl, ethyl, propyl, butyl or pentyl), and C_{5-7} cycloalkyl group (e.g. cyclopentyl or cyclohexyl).

[0015] In R^1 substituted alkyl group means the above alkyl substituted by the same or different and one or more substituents.

[0016] Said substituents include cycloalkyl group (C_{3-6} cycloalkyl group, such as cyclopropyl, cyclopentyl or cyclohexyl), hydroxy group, lower alkoxy group (C_{1-6} alkoxy such as methoxy, ethoxy, propoxy, butoxy or pentoxy), substituted lower alkoxy group (substituted C_{1-6} alkoxy group, such as methoxyethoxy, ethoxyethoxy, hydroxyethoxy or chloroethoxy), amino group, alkylamino group, cyano group, nitro group, acyl group, carboxyl group, lower alkoxycarbonyl group (C_{2-7} alkoxycarbonyl group, such as methoxycarbonyl or ethoxycarbonyl), halogen atom, such as fluorine atom, chlorine atom or bromine atom, mercapt group, lower alkylthio group (C_{1-6} alkylthio group, such as methylthio, ethylthio, propylthio or butylthio), substituted lower alkylthio group (substituted C_{1-6} alkylthio group, such as methoxyethylthio, methylthioethylthio, hydroxyethylthio or chloroethylthio), aryl group (C_{6-10} monocyclic or fused cyclic aryl group, such as phenyl or naphthyl), substituted aryl group (substituted C_{6-10} monocyclic or fused cyclic aryl group, such as 4-hydroxyphenyl, 4-methoxyphenyl, 4-fluorophenyl, 4-chlorophenyl or 3,4-dichlorophenyl), and heterocyclic group (5-6 membered saturated heterocyclic group containing nitrogen atoms from 0-2 and oxygen atoms from 0-2, such as piperidyl, piperazinyl, morpholinyl, tetrahydrofuranyl, pyrrolidinyl, pyrazolinyl or 1,3-dioxolanyl, 5-6 membered unsaturated heterocyclic group, such as furyl, pyrrolyl, pyrazolyl, imidazolyl, thiazolyl, thienyl, pyridyl or pyrimidinyl, or bicyclic unsaturated heterocyclic group, such as indolyl, isoindolyl, quinolyl, benzothiazolyl, chromanyl, benzofuranyl or phthalimino).

[0017] In R^1 aryl group means C_{6-10} monocyclic or fused cyclic aryl group, such as phenyl or naphthyl.

[0018] In R^1 substituted aryl group means the above aryl group substituted by the same or different and one or more substituents.

[0019] Said substituent includes lower alkyl group (C_{1-6} alkyl group, such as methyl, ethyl, propyl, butyl, cyclopentyl or cyclohexyl), hydroxy lower alkyl group (hydroxy C_{1-6} alkyl group, such as hydroxymethyl, 2-hydroxyethyl or 3-hydroxypropyl), lower alkoxy lower alkyl group (C_{1-6} alkoxy C_{1-6} alkyl group, such as 2-methoxyethyl, 2-ethoxyethyl or 3-methoxypropyl), hydroxy group, lower alkoxy group (C_{1-6} alkoxy group, such as methoxy, ethoxy, propoxy, butoxy or pentoxy), cyano group, amino group, substituted amino group, lower alkoxycarbonyl group (C_{2-7} alkoxycarbonyl group, such as methoxycarbonyl, ethoxycarbonyl or propoxycarbonyl), acyl group, nitro group, halogen atom, such as fluorine atom, chlorine atom or bromine atom, aryl group (C_{6-10} monocyclic or fused cyclic aryl group, such as phenyl or naphthyl), substituted aryl group (substituted C_{6-10} monocyclic or fused cyclic aryl group, such as 4-hydroxyphenyl, 4-methoxyphenyl, 4-chlorophenyl or 3,4-dichlorophenyl), and heterocyclic group (alicyclic or aromatic heterocyclic group containing nitrogen atoms from 1-2 and oxygen atom from 0-1, such as pyrrolidinyl, piperidyl, piperazinyl or morpholinyl).

[0020] In R^1 heterocyclic group means monocyclic saturated heterocyclic group, or unsaturated monocyclic or fused heterocyclic group containing at least one heteroatom, that is, 0-3 nitrogen atoms, 0-1 oxygen atom and 0-1 sulfur atom.

[0021] Said saturated monocyclic heterocyclic group includes 5 or 6 membered saturated heterocyclic group, such as tetrahydrofuranyl, pyrrolidinyl, morpholinyl, piperidyl, piperazinyl or pyrazolidinyl. Said unsaturated monocyclic heterocyclic group means 5 or 6 membered unsaturated heterocyclic group, such as furyl, pyrrolyl, pyrazolyl, imidazolyl, thiazolyl, thienyl, pyridyl or pyrimidinyl. Said unsaturated fused heterocyclic group means unsaturated bicyclic heterocyclic group, such as indolyl, isoindolyl, quinolyl, benzothizolyl, chromanyl or benzofuranyl.

[0022] In R^1 substituted heterocyclic group means the above heterocyclic group substituted by the same or different and one or more substituents.

[0023] Said substituents include lower alkyl group (C_{1-6} alkyl group, such as methyl, ethyl, propyl, butyl, cyclopentyl or cyclohexyl), hydroxy lower alkyl group (hydroxy C_{1-6} alkyl group, such as hydroxymethyl, 2-hydroxyethyl or 3-hydroxypropyl), lower alkoxy lower alkyl group (C_{1-6} alkoxy C_{1-6} alkyl group, such as 2-methoxyethyl, 2-ethoxyethyl or 3-methoxypropyl), hydroxy group, lower alkoxy group (C_{1-6} alkoxy group such as methoxy, ethoxy, propoxy, butoxy or pentoxy), cyano group, nitro group, halogen atom, such as fluorine atom, chlorine atom or bromine atom, amino group, substituted amino group, lower alkoxycarbonyl group (C_{2-7} alkoxycarbonyl group, such as methoxycarbonyl, ethoxycarbonyl or propoxycarbonyl), acyl group, aryl group (C_{6-10} monocyclic or fused cyclic aryl group, such as phenyl or naphthyl), substituted aryl group (substituted C_{6-10} monocyclic or fused cyclic aryl group, such as 4-hydroxyphenyl, 4-methoxyphenyl, 4-chlorophenyl or 3,4-dichlorophenyl), and heterocyclic group (alicyclic or aromatic heterocyclic group containing nitrogen atoms from 1-2 and oxygen atom from 0-1, such as pyrrolidinyl, piperidyl, piperazinyl or morpholinyl).

[0024] In R^2 lower alkyl group includes C_{1-6} alkyl group (e.g. methyl, ethyl, propyl, 1-methylethyl, butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 2,2-dimethylpropyl).

[0025] In R^2 substituted lower alkyl group means the above alkyl substituted by the same or different and one or more substituents.

[0026] Said substituents include hydroxy group, lower alkoxy group (for example, C_{1-6} alkoxy group, such as methoxy, ethoxy or propoxy), carboxyl group, lower alkoxycarbonyl group (for example, C_{2-7} alkoxycarbonyl group, such as methoxycarbonyl, ethoxycarbonyl or propoxycarbonyl) and halogen atom, such as fluorine atom, chlorine atom or bromine atom.

[0027] In R^2 lower alkoxy group means C_{1-6} alkoxy group, such as methoxy, ethoxy or propoxy.

[0028] In R^2 substituted lower alkoxy group means the above alkoxy group substituted by the same or different and one or more substituents.

[0029] Said substituents include hydroxy group, lower alkoxy group (C_{1-6} alkoxy group, such as methoxy, ethoxy or propoxy), carboxyl group, lower alkoxycarbonyl group (C_{2-7} alkoxy-carbonyl group, such as methoxycarbonyl, ethoxycarbonyl group or propoxycarbonyl) and halogen atom, such as fluorine atom, chlorine atom or bromine atom.

[0030] In R^2 lower alkanoyl group means C_{1-6} alkanoyl group, such as formyl, acetyl, propanoyl, butanoyl, pentanoyl or hexanoyl.

[0031] In R^2 substituted lower alkanoyl group means the above alkanoyl group substituted by the same or different and one or more substituents.

[0032] Said substituents include hydroxy group, lower alkoxy group (C_{1-6} alkoxy group, such as methoxy, ethoxy or propoxy), carboxyl group, lower alkoxycarbonyl group (C_{2-7} alkoxycarbonyl group, such as methoxycarbonyl or propoxycarbonyl) and halogen atom, such as fluorine atom, chlorine atom or bromine atom.

[0033] In R^2 aroyl group means C_{7-11} aroyl group, such as benzoyl or naphthoyl.

[0034] In R^2 substituted aroyl group means the above aroyl group substituted by the sane or different and one or more substituents.

[0035] Said substituents include hydroxy group, lower alkoxy group (C_{1-5} alkoxy group, such as methoxy, ethoxy or propoxy), carboxyl group, lower alkoxycarbonyl group (C_{2-7} alkoxycarbonyl group, such as methoxycarbonyl, ethoxycarbonyl or propoxycarbonyl) and halogen atom, such as fluorine atom, chlorine atom or bromine atom.

[0036] In R^2 lower alkoxycarbonyl group means C_{2-7} alkoxycarbonyl group, such as methoxycarbonyl, ethoxycarbonyl or propoxycarbonyl.

[0037] In R^2 substituted lower alkoxycarbonyl group means the above alkoxycarbonyl group substituted by the same or different and one or more substituents.

[0038] Said substituents include hydroxy group, lower alkoxy group (C_{1-6} alkoxy group, such as methoxy, ethoxy or propoxy), carboxyl group, lower alkoxycarbonyl group (C_{2-7} alkoxycarbonyl group, such as methoxycarbonyl, ethoxycarbonyl or propoxycarbonyl) and halogen atom, such as fluorine atom, chlorine atom or bromine atom.

[0039] In R^2 lower alkylamino group means amino group substituted by C_{1-6} alkyl group (e.g. methylamino, ethylamino, propylamino, butylamino).

[0040] In R^2 di(lower alkyl)amino group means amino group substituted by the same or different and C_{1-6} alkyl group (e.g. dimethylamino, diethylamino, ethylmethylamino).

[0041] In R^2 lower alkylcarbamoyl group means carbamoyl group substituted by C_{1-6} alkyl group (e.g. methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, butylcarbamoyl).

[0042] In R^2 di(lower alkyl)carbamoyl group means carbamoyl group substituted by the same or different and C_{1-6} alkyl group (e.g. dimethylcarbamoyl, diethylcarbamoyl, ethylmethylcarbamoyl).

[0043] In R^2 halogen atom means halogen atom such as fluorine atom, chlorine atom, bromine atom or iodine atom.

[0044] In R^3 alkyl group includes straight or branched C_{1-10} alkyl group (e.g. methyl, ethyl, propyl, butyl, pentyl, hexyl) and C_{3-7} cycloalkyl group (e.g. cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl), preferably straight or branched C_{1-6} alkyl group (e.g. methyl, ethyl, propyl, butyl, pentyl), and C_{5-7} cycloalkyl group (e.g. cyclopentyl, cyclohexyl).

[0045] In R^3 substituted alkyl group means the above alkyl group substituted by the same or different and one or more substituents.

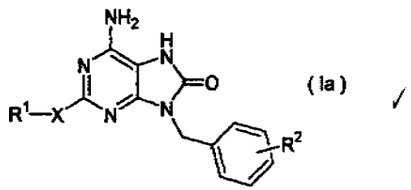
[0046] Said substituents include cycloalkyl group (C_{3-6} cycloalkyl group, such as cyclopropyl, cyclopentyl or cyclohexyl), hydroxy group, lower alkoxy group (C_{1-6} alkoxy, such as methoxy, ethoxy, propoxy, butoxy or pentoxy), amino group, cyano group, aryl group such as phenyl, substituted aryl group, such as 4-hydroxyphenyl, 4-methoxyphenyl, 4-chlorophenyl or 3,4-dichlorophenyl, nitro group and halogen atom, such as fluorine atom, chlorine atom or bromine atom.

[0047] Heterocyclic ring formed together with R^3 and R^1 via the nitrogen atom means 5 or 6 membered saturated heterocyclic ring, such as 1-pyrrolidinyl, 4-morpholinyl, 1-piperidyl, 1-piperazinyl or 1-pyrazolidinyl, and 5 or 6 membered unsaturated heterocyclic ring such as 1-imidazolyl.

[0048] Substituted heterocyclic ring formed together with R^3 and R^1 via the nitrogen atom means the above heterocyclic ring formed together with R^3 and R^1 via the nitrogen atom alkyl substituted by the same or different and one or more substituents.

[0049] Said substituents include lower alkyl group (C_{1-6} alkyl group, such as methyl, ethyl, propyl, butyl, cyclopentyl or cyclohexyl), hydroxy lower alkyl group (hydroxy C_{1-6} alkyl, such as hydroxymethyl, 2-hydroxyethyl or 3-hydroxypropyl), lower alkoxy lower alkyl group (C_{1-6} alkoxy C_{1-6} alkyl, such as 2-methoxyethyl, 2-ethoxyethyl or 3-methoxypropyl), hydroxy group, lower alkoxy group (C_{1-6} alkoxy, such as methoxy, ethoxy, propoxy, butoxy or pentoxy) and cyano group.

[0050] The compound (I) of the present invention forms an equilibrium mixture with a tautomer represented by the following formula (Ia):



(Ia)

[0051] The compound (I) of the present invention may forms a salt with an acid.

[0052] The preferable acids are pharmaceutically acceptable acids, including inorganic acids, such as hydrochloric acid, sulfuric acid, hydrobromic acid, etc., organic acids, such as acetic acid, oxalic acid, citric acid, malic acid, tartaric acid, fumaric acid, maleic acid, etc.

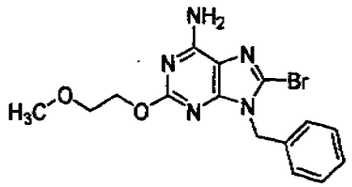
[0053] Further, in case of the compound (I) having an acidic substituent, the compound may form a salt with a base.

[0054] The preferable bases are pharmaceutically acceptable bases, including inorganic bases like alkali metals,

Reference Example 114

6-Amino-9-benzyl-8-bromo-2-(2-methoxyethoxy)purine

[0617]



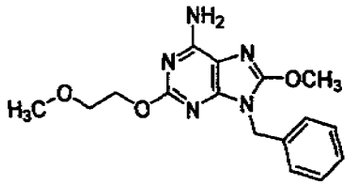
[0618] 6-Amino-9-benzyl-2-(2-methoxyethoxy)purine (93mg, 0.31 mmol) and bromine (1ml) were dissolved in methylene chloride (100ml). The solution was stirred at room temperature for 1 hour. Aqueous sodium thiosulfate was added to the reaction mixture. The organic layer was separated, dried on sodium sulfate and concentrated in vacuo to dryness. The residue was purified with silica gel chromatography (1%methanol/chloroform) to give the subject compound (75mg, yield 64%).

^{1}H-NMR(DMSO-d_6) δ:7.46(2H, br s), 7.38-7.23(5H, m), 5.25(2H, s), 4.33(2H, t, J = 4.6Hz), 3.61(2H, t, J = 4.6Hz), 3.28(3H, s).

Reference Example 115

6-Amino-9-benzyl-8-methoxy-2-(2-methoxyethoxy)purine

[0619]



[0620] 6-Amino-9-benzyl-8-bromo-2-(2-methoxyethoxy)purine (69mg, 0.18mmol) in methanol (50ml) was dissolved in 28% sodium methoxide/methanol (1ml) and the mixture was refluxed on heating under stirring for 5 hours. The reaction mixture was concentrated in vacuo to dryness, and to the residue was added water. The solution was extracted with chloroform and the organic layer was dried on sodium sulfate and concentrated in vacuo to dryness. The residue was purified with silica gel chromatography (3%methanol/chloroform) to give the subject compound (26mg, yield 43%).

^{1}H-NMR(DMSO-d_6) δ:7.36-7.23(5H, m), 6.88(2H, br s), 5.04(2H, s), 4.29(2H, t, J = 4.6Hz), 4.04(3H, s), 3.60(2H, t, J = 4.6Hz), 3.28(3H, s).

INDUSTRIAL APPLICABILITY

[0621] According to the present invention an interferon inducer containing a compound of the present invention as an active agent is provided. The interferon inducer of the present invention has inducing and activating activity for biosynthesis of interferon and therefore, is useful as therapeutic agents based on biological activities of interferon, such as antiviral activity, preventing activity of cell growth, immune modulation etc., that is, therapeutic agents for virus infected diseases (e.g. hepatitis C, hepatitis B), anticancer agents and agents for immunologic diseases.

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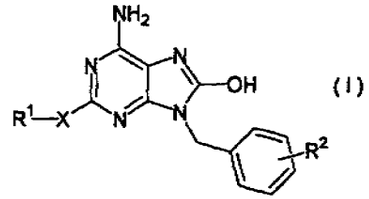
Claims

1. A heterocyclic compound of the following general formula (I)

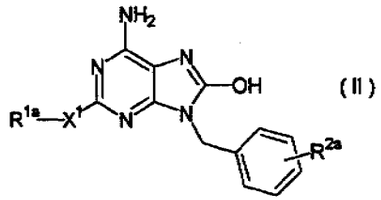


(I)

wherein

X is sulfur atom, oxygen atom, -NR^3- (in which R^3 is hydrogen atom, alkyl group or substituted alkyl, or may form a heterocyclic ring or a substituted heterocyclic ring together with R^1 via the nitrogen atom),
R^1 is alkyl group, substituted alkyl group, aryl group, substituted aryl group, heterocyclic group or substituted heterocyclic group, and
R^2 is hydrogen atom, or one or more substituents on the benzene ring, and said substituent is the same or different and is hydroxy group, lower alkyl group, substituted lower alkyl group, lower alkoxy group, substituted lower alkoxy group, lower alkanoyl group, substituted lower alkanoyl group, aroyl group, substituted aroyl group, carboxyl group, lower alkoxycarbonyl group, substituted lower alkoxycarbonyl group, amino group, lower alkylamino group, di(lower alkyl)amino group, carbamoyl group, lower alkylcarbamoyl group, di(lower alkyl)carbamoyl group, halogen atom, nitro group or cyano group, or a pharmaceutical acceptable salt thereof

2. A heterocyclic compound of the formula (II) or its pharmaceutically acceptable salt:



(II)

wherein

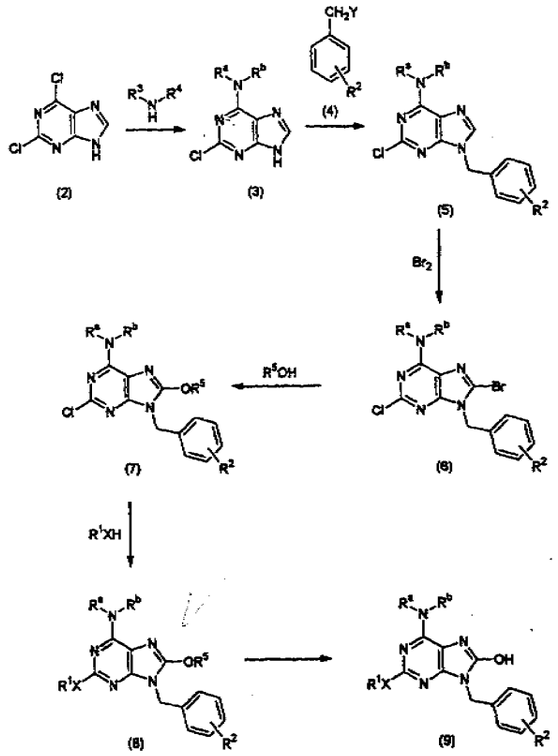
X^1 is sulfur atom, oxygen atom or -NR^{3a} - in which R^{3a} is hydrogen, C_{1-6} alkyl group, or substituted C_{1-6} alkyl group, or may form a heterocyclic ring or a substituted heterocyclic ring together with R^{1a} via the nitrogen atom,
R^{1a} is C_{1-6} alkyl group, substituted C_{1-6} alkyl group, aryl group, substituted aryl group, a heterocyclic group or a substituted heterocyclic group, and
R^{2a} is hydrogen atom, or one or more substituent on the benzene ring, and said substituent is the same or different and is halogen atom, C_{1-6} alkoxy group, nitro group or hydroxy group.

3. The heterocyclic compound of claim 1 or 2, wherein X or X^1 is sulfur atom, or its pharmaceutically acceptable salt.

4. The heterocyclic compound of claim 1 or 2, wherein X or X^1 is oxygen atom, or its pharmaceutically acceptable salt.

5. The heterocyclic compound of claim 1 or 2, wherein X or X^1 is -NH-, or its pharmaceutically acceptable salt.

Process 1.



wherein R^1, X and R^2 are the same as definition in the formula (I), Y is leaving group such as halogen atom (e.g. chlorine atom, bromine atom), R^5 is alkyl group, and R^a and R^b are hydrogen atom, or mean amino protective group because they are protected by amino protective group on the way of reaction, if necessary.

[0071] Compound (3) is prepared by reacting compound (2) with NHR^aR^b in an aqueous solution or in an organic solvent.

[0072] NHR^aR^b can be used about equal molar or large excess amount to compound (2).

[0073] Organic solvents are alcohols, such as methanol, ethanol, propanol or butanol, ethers such as tetrahydrofuran, 1,4-dioxane or diglyme, or aprotic solvents, such as dimethylformamide, dimethyl sulfoxide, acetonitrile or hexamethylphosphoroustriamide $[(CR_3)_2N)_3P]$.

[0074] The reaction temperature is selected from the range between room temperature and about 200°C.

[0075] Reaction vessels such as autoclave etc. may be used in the reaction, if necessary.

[0076] Compound (5) is prepared by reacting compound (3) and compound (4) in the presence of a base in an organic solvent.

[0077] Compound (4) can be used about equal molar or several molars to compound (3).

[0078] Bases are inorganic bases such as alkali metal carbonates (e.g. sodium carbonate, potassium carbonate), or organic bases, such as tertiary amines (e.g. triethylamine, diisopropylethylamine) or pyridines (e.g. 4-dimethylaminopyridine, pyridine). The base is preferably used about equal molar to compound (4)

[0079] The organic solvents are halogenated hydrocarbons such as tetrachloromethane, chloroform or methylene chloride, ethers such as diethyl ether, tetrahydrofuran or 1,4-dioxane, or aprotic solvents, such as dimethylformamide, dimethyl sulfoxide, acetonitrile or hexamethylphosphoroustriamide.

[0080] The reaction temperature is selected from the range between about 0°C and around boiling point of the solvent.

[0081] Compound (6) is prepared by reacting compound (5) with Br_2 in an organic solvent.

[0082] A reaction promoter such as sodium acetate may be added to reaction mixture.

[0083] Br_2 is used from equal molar to several molars to compound (5), preferably from equal molar to one and half molars.

[0084] The organic solvents are halogenated hydrocarbons, such as tetrachloromethane, chloroform or methylene chloride, ethers, such as diethyl ether, acetic acid, or carbon disulfide.

[0085] The reaction temperature is selected from the range between about 0°C and around boiling point of the solvent.

[0086] Compound (7) is prepared by reacting compound (6) and an alcohol such as methanol in the presence of a base in an organic solvent.

[0087] The base are alkali metals, such as sodium or potassium, alkali metal hydrides, such as sodium hydride or potassium hydride, organometalic compounds, such as methyl lithium, butyl lithium or lithium diisopropylamide.

[0088] The base is preferably used from about equal molar to about two times as much to compound (6).

[0089] The organic solvents are ethers, such as diethyl ether, tetrahydrofuran or 1,4-dioxane, or aprotic solvents, such as dimethylformamide, dimethyl sulfoxide, acetonitrile or hexamethylphosphoroustriamide. The alcohol as the reagent, such as methanol, ethanol, propanol or butanol may be served as a solvent.

[0090] The reaction temperature is selected from the range between about room temperature and around boiling point of the solvent.

[0091] Compound (8) is prepared by reacting compound (7) with R^1XH in an organic solvent.

[0092] R^1XH is used from about equal molar to several molars to compound (7).

[0093] When X is oxygen atom or sulfur atom, the reaction is preferably carried out in the presence of a base.

[0094] The bases are alkali metals, such as sodium or potassium, alkali metal hydrides, such as sodium hydride or potassium hydride, organometalic compounds, such as methyl lithium, butyl lithium or lithium diisopropylamide. The base is preferably used about equal molar to R^1XH.

[0095] The organic solvents are aprotic solvents, such as dimethylformamide, acetonitrile or hexamethylphosphoroustriamide, or ethers such as diethyl ether, tetrahydrofuran or 1,4-dioxane or diglyme.

[0096] The reaction temperature is selected from the range between about room temperature and around boiling point of the solvent.

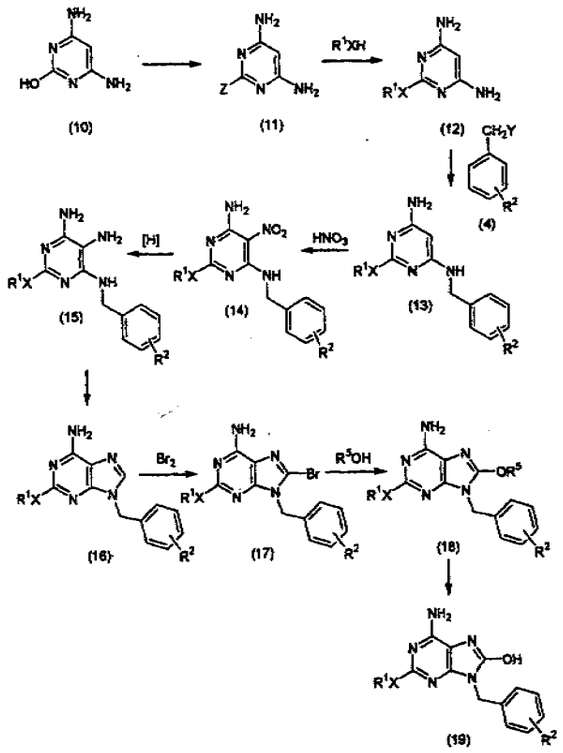
[0097] Compound (9) is prepared by treating compound (8) with an acid in water or a mixture of water and an organic solvent.

[0098] The acids are inorganic acids, such as hydrochloric acid or hydrobromic acid, or organic acids such as trifluoroacetic acid.

[0099] The organic solvents are ethers, such as diethyl ether or tetrahydrofuran, aprotic solvents such as dimethylformamide, alcohols, such as methanol, ethanol or propanol, or acetic acid.

[0100] The reaction temperature is selected from the range between about room temperature and around boiling point of the solvent.

Process 2.



wherein R^1, X and R^2 are the same as definition in the formula (I), Z is halogen atom such as chlorine atom or bromine atom, or leaving group such as methanesulfonyloxy or p-toluenesulfonyloxy, and Y and R^5 are the same as defined above.

[0101] Compound (11) is prepared by a method known by the skilled person. For instance, when Z is chlorine atom, compound (11) is prepared by reacting compound (10) with phosphorusoxychloride.

[0102] The reaction temperature is selected from the range between room temperature and reflux temperature of the reaction solvent. When Z is methanesulfonyloxy, compound (11) is prepared by reacting compound (10) with methanesulfonyl chloride in the presence of a base in an organic solvent, and if necessary, NH_2 group on compound (10) is protected and then deprotected.

[0103] The bases are inorganic bases such as alkali metal carbonates (e.g. potassium carbonate), or organic bases, such as triethylamine, diisopropylethylamine, 4-dimethylaminopyridine or pyridine.

[0104] The organic solvents are halogenated hydrocarbons such as methylene chloride, ethers, such as diethyl ether or tetrahydrofuran, or aprotic solvents such as dimethylformamide, etc.

[0105] The reaction temperature is selected from the range between about 0°C and around boiling point of the solvent.

[0106] Compound (12) is prepared by reacting compound (11) with R^1XH in an organic solvent.

[0107] When X is oxygen atom or sulfur atom, the reaction is preferably carried out in the presence of a base. The bases are alkali metals, such as sodium or potassium, alkali metal hydrides, such as sodium hydride or potassium hydride, or organometalic compounds, such as methyl lithium, butyl lithium or lithium diisopropylamide.

[0108] The organic solvents are aprotic solvents, such as dimethylformamide, acetonitrile or hexamethylphosphoroustriamide, or ethers, such as diethyl ether, tetrahydrofuran 1,4-dioxane or diglyme.

[0109] The reaction temperature is selected from the range between about room temperature and around boiling point of the solvent.

[0110] Compound (13) is prepared by reacting compound (12) and compound (4) in the presence of a base in an organic solvent.

[0111] The bases are inorganic bases such as alkali metal carbonates (e.g. sodium carbonate, potassium carbonate), or organic bases, such as tertiary amines (e.g. triethylamine, diisopropylethylamine) or pyridines (e.g. dimethylaminopyridine, pyridine).

[0112] The organic solvents are halogenated hydrocarbons such as methylene chloride etc., ethers, such as diethyl ether or tetrahydrofuran, or aprotic solvents, such as dimethylformamide, dimethyl sulfoxide or acetonitrile.

[0113] The reaction temperature is selected from the range between about room temperature and around boiling point of the solvent.

[0114] Compound (14) is prepared by nitrating compound (13) in an organic solvent, for example by adding nitric acid thereto in an organic solvent such as acetic acid.

[0115] The reaction temperature is selected from the range between about -20°C and around boiling point of the solvent.

[0116] Compound (15) is prepared by reducing nitro group on compound (14) in an organic solvent.

[0117] The reducing agents are hydrogen, sodium borohydride or lithium aluminum hydride.

[0118] The organic solvents are alcohols, such as methanol or ethanol, esters such as ethyl acetate, etc., or ethers, such as diethyl ether or tetrahydrofuran.

[0119] The reaction temperature is selected from the range between about 0°C and around boiling point of the solvent.

[0120] Compound (16) is prepared by reacting compound (15) with formic acid or trimethyl orthoformate in the presence of an acid.

[0121] The acids are inorganic acids such as hydrochloric acid, or organic acids, such as p-toluenesulfonic acid or camphor sulfonic acid.

[0122] The reaction temperature is selected from the range between about room temperature and around boiling point of the solvent.

[0123] Compound (17) is prepared by reacting compound (16) and Br_2 in an organic solvent.

[0124] A reaction promoter such as sodium acetate may be added in this reaction.

[0125] The organic solvents are halogenated hydrocarbons, such as tetrachloromethane, methylene chloride or dichloroethane, ethers such as diethyl ether, acetic acid, or carbon disulfide.

[0126] The reaction temperature is selected from the range between about 0°C and around boiling point of the solvent.

[0127] Compound (18) is prepared by reacting compound (17) and R^5OH in the presence of a base in an organic solvent.

[0128] The bases are alkali metals, such as sodium or potassium, alkali metal hydrides, such as sodium hydride or potassium hydride, or organometalic compounds, such as methyl lithium, butyl lithium or lithium diisopropylamide.

[0129] The organic solvents are ethers, such as diethyl ether or tetrahydrofuran, or aprotic solvents, such as dimethylformamide or acetonitrile. The alcohol used as the reagent, such as methanol, ethanol, propanol or butanol may be served as a solvent.

[0130] The reaction temperature is selected from the range between about room temperature and around boiling point of the solvent.

[0131] Compound (19) is prepared by treating compound (18) with an acid in water or a mixture of water and an organic solvent.

[0132] The acids are inorganic acids, such as hydrochloric acid or hydrobromic acid, or organic acids such as trifluoroacetic acid, etc.

[0133] The organic solvents are ethers, such as diethyl ether or tetrahydrofuran, aprotic solvents, such as dimethylformamide or acetonitrile, alcohols, such as methanol, ethanol or propanol, or acetic acid.

[0134] The reaction temperature is selected from the range between about room temperature and around boiling point of the solvent.