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SENORES
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO DIVISION DE NUEVAS CREACIONES
E.S.D.

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ASUNTO: SOLICITUD EXAMEN DE PATENTABILIDAD

DILIA RODRIGUEZ D’ALEMAN identificada como aparece al pie de ml firma, domiciliada en Bogota, en la Carrera 11 No. 86-53, piso 6, obrando como apoderada
de la sociedad solicitarite, pido a usted que Se proceda a examinar si Is invenciôn,
cuya patente se tramita en el expediente de la referencia, es patentable.

Adjunto al presente memorial el recibo No. 09-13.344 de 18 de febrero de 2009 por la suma de $452.000.00, COfl 10 cual queda cubierta la tasa oficial correspondiente a dicho estudio.

SeæorSuperintendente,

DILIA RODRK\LJEZ DALEMAN
CC. 41.654.88 de Bogota
T.P. 20824 del C.S.J.

P-998 -.------

SUF’ERINTENDENCIA DE INDUSTRiA Y COMERCIO

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FECHA 31 DE OCTUBRE DE 2008 EL TRMINO HABIL SEI1ALADO POR LA

LEY EXPIRA EL 02 DE FEBRERO DE 2009

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

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI NO X

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(54) ’111k’: VIRAL POLIMURASE INI-ILBItfORS

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ojreNoteson Codes andAbbreviations " appearing at the begin-
ning of regular issue of the PCT Gazetie.

(57) Abstract: An isomer, enanti ci riser, diu.stereoisonier or tautunrer sf a corn-
pound, iepresenresi by formula (1): wherein wherein A, B, R2, B), L. Ml, M2,
Ml, Ml. Yl, TI). Z and Spare as delired in claim 1. or salt thereof, in an
inhibitor of IICV NS51I polynierase.

EXAMPLE 33

Methyl 2bromo..3cyc1ohexyJ1HindOfe-5-CarbOXY1afe:

H

Br

5 Using the same series of reactions described in example 2 but starting from indole 5-

carboxylic acid, the title compound of example 33 was obtained. This compound is a

starting material for The synthesis of compounds according to the general formula 1.4, whereby the methods as described hereinbefore e.g. 4 to 8 and/or in combination

with 9 to 32, can be employed in an analogous manner.

10

EXAMPLE 34

acid methyl

ester
OH

s.COOMe

HO
COOMe

OH

COOMeHo
COOMe

[’7 O..,rizz’...
’trCoOMe H2N’)’tu’COOMe....

15 Methyl 4..hydroxybenzoate(20.00g, 131 rnmol) was dissolved in DMF(350mL)and

K2CO3 (24.19 g, 175 was added. The mixture stirred for 30 min and

crotyl bromide (85%,16.47 mL, 160 mrnol) was added dropwise over 4 mm. The

resulting amber suspension was stirred for 4 h at room temperature. It was then

poured into 0CM and the solution washed with water and brine. The extract was

20 dned (MgSO4) and evaporated to a pale yellow oil consisting of a mixture of two

isomeric ally] ether (4:1 ratio). Upon standing at room temperature, the oil partially crystallized. The supernatant was decanted and tha crystals washed with hexane to

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114

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Example 5
H

CDOtOu

General procedure for the Stile cross -coupling of aryl and N.- COOMe

DMF _ N
1

COOMe

heferoa,ylstannanes with 2-bromoindole derivatives:

BrCHC0OtBu

/ "

Cross-coupling of aromatic/heteroarcmatic stannane derivatives with 2-bromoindoles
5 such as the ones described in examples 2 and 3 can be performed using any
variations of the standard metal-catalyzed Stille cross-coupling reaction as described COOH
in the literature and well known to those skilled in the art. The folowing example COOMe NI
serves to illustrate such a process and is non-limiting. TFA 0
3-Cyclohexjl-2-thiophen-2-y[-IH-indole-6-carboxylic acid methyl ester:

COOMe \N SnMe3 COOMe
Br S

QP Methyl 1-tert-butoxycarbonylmethy!-3-cyclohexyl-2-furan-3-yI4H-ifldOle-6-

PdCl2(PPhJ2 carboxylate:
THF 180 C The indole derivative from example 4 (18.50 g, 57.4 mmol) was dissolved in
10 5 anhydrous D M F (120 mL) and the solution was cooled in an ice bath under an argon
A IL flask equipped with a reflux condenser was charged with 2- atmosphere. NaH (60 % oil dispersion 2.88 g, 72 mmol) was added in 3 portions
trimethyistannylthiophene (11.16g. 45 mmol), the 2-bromoin dole of example 2 (7.00 and the mixture stirred I h at 0 °C. tert-Butylbromoacetate (13.88g. 71 mmol, 1.24
g, 21 mmol) and anhydrous TI-IF (300 mL). The solution was degassed by bubbling equiv.) was added dropwise over 10 min and then the ice bath was removed. The
argon through the solution fort h. The catalyst, dichioro- reaction mixture was stirred overnight at room temperature. It was then diluted with
15 bis(triphenyLphosphine)paLladium (1.76 g, 2.5 mmol) was added and the mixture was 10 TBME (1500 ml) and washed with 10 % HCI (2 x 250 ml), water (3 x 500 mL) and
stirred at 80 C under an argon atmosphere for 24 h. The reaction mixture was brine (1 x 400 mL). After drying (N4a2SO4), the solvent was removed under reduced
cooled to room temperature, filtered to remove solids and concentrated under pressure to give a white solid. The solid was triturated with hexane (300 ml), filtered
reduced pressure. The residue was purified by flash chromatography using 9: 1 and triturated a second time with hexane (500 mL). Filtration followed by drying
hexane -. EtOAc as eluent, to give the desired 2-(2-thiophene)indole product of under vacuum gave the desired tert-butyl ester as a white solid (21.6 g, 86 % yield).
20 example 5 (7.10 g, 99% yield). 15 Methyl 1-cathoxymethyl-3-cyclohexyl-2-furan4-yl-lH4ndole-6-carboxylate:
The tert-butyl ester from above (21.5 g, 49 mmol) was dissolved in dichioromethane
EXAMPLE 6 - (90 mL) and TFA (65.6 mL) was added dropwise to the solution which was stirred for
General procedure forN-alkylation ofindole derivatives to give N- 5 h at room temperature. Volatiles were removed under reduced pressure, the
(methylcarbaxy)indoles: residue was co-evaporated 3 x with DCM and then dried under vacuum. The crude
25 The following example serves to illustrate such a process and is non-Limiting. 20 product was triturated with a mixture of hexane (200 mL) and 0CM (20 mL), filtered
and dried under vacuum to give the title compound of example 6 as a white solid
Methyl 1-ca boxymethyl-3-cyclohexyl-2-furan-3-yl-IH-indo!e-6-carboxylate: (1862 g, 99 % yield)

EXAMPLE 7

25 Methyl 1carboxymethy13cyclopenty!-2-furan-3-yl-1H-indole-6-carbOXYIate.

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(5.1) 111k: VIRAL POLYMERASE LNI1IBI’LIJRS

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(57) Abstract: An isomer, ettantissrscr, diasteresisumei-. or toutsmer ut
a cotupaunsi, represented by Litnitula (l/,wherhtlA is 0,.1, NB), sr CR,
ss]arl-c’in R, is drOned herein; rcp,tseisIs’ritherasitigLe sirs dstuh1chend;R5

A-,_,.,.,_,,.M.. z (I) is ’selected tons IL halogen, R, OR,5K5, (Ot)IC,b)cNIRtrO,

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VIRAL POLYMERASE INHIBITORS

TECHNICAL FIELD OF THE INVENTION

The invention relates to inhibitors of RNA dependent ANA polymerases,

5 particularly Those polymerases within the Flaviviridae family, more particularly

to HCV polymurase.

About 30,000 new cases of hepatitis C virus (HCV) infection are estimated to

10 occur in the United States each year (Ko(ykhalov, A.A.; Mihalik, K; Feinstone.

SM.; Rice, G.M.; 2000; J. Virol. 74-.204&-2051). HCV is not easily cleared by the

hosts’ immunological defences; as many as 85% of the people infected With HCV

become chronically infected. Many of these persistent infections result in chronic iverdisease, including cirrhosis and hepato’cellular carcinoma (Hoofnagle, J.H.;

15 1997; Hepato/ogy 26: 1 5S-20S). There are an estimated 170 million HCV carriers

world-wide, and HCV-associated end-stage liver disease is now the leading

cause of liver transplantation. In the United States alone, hepatitis C is

responsible for 8,000 to 10,000 deaths annually. Without effective intervention,

the number is expected to triple in the next 10 to 20 years. There is no vaccine to

20 prevent HCV infection. Prolonged treatment of chronically infected patients with

interferon or interferon and ribavirin is the only currently approved therapy, but it

achieves a sustained response in fewer than 50°!a of cases (Lindsay, K.L,; 1997; Hepaf&ogy26: 71S-77S, and Reichard, 0.; Schvarcz, R.; Weiland, 0,; 1997 -

belongs the Flaviviridae, genus which three

genera enveloped positive-strand viruses

"FIavivin’dae: the their replication"; in

Fields, Knipe, Publishers,

Philadelphia genome long open reading

frame non-translated regions The

length and functions ribosorne entry site

cap-independent translation initiation (Lemon,

The cleaved and post-translationally

into polypeptides

WO 03/010140

21

0

R2 13

(Ill)
wherein, preferably, B is NW.

PCTICAO2/,

Wth respect to compounds of formula (II) and (ill), preferably, M, K and L is CH
5 or N. More preferably, M, K and L is CH,

More preferably, compounds of the present invention have the following formulae:
0

ha

10

0

RTJO

lIla

R

R24Q
n3

JIb lb

N

or

lId

15 R1:

Preferably R1 is selected from the group consisting of: H or (C1)alkyL More preferably, R1 is I-I, CH2, isopropA or isobutyl. Even more preferably. R1 is H or CH3. Most preferably, R1 is CH,.

20 R2:

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22

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Preferably, R2 is selected from: H, halogen, (02)aikenyI, (C)cycloalkenyl, 6 or 10-membered aryl or Met; wherein (C24alkenyl, (C7)cycloalkenyl, aryl or Het is optonally substftuted with R, wherein R2° is defined as:
- 1 to 4 substituents selected from: halogen, NO2, cyanc, azido,
5 C(=NH)NH2, C(=NH)NF-l(C1)alkyl or C(NR)NHCO(C1)alkf, or
- t14 substituents selected from:

a) (C1) alkyl or haloakyl, (C7)cycEoa1kyI, (C2)alkenyt, (C,)alkynyl, (C1) akyl-(037)cycloalkyl, all of which optionally substituted with R1°;
b) OR1114 wherein R’°4 is H, (Catkyl), (C37)cydoalkyl, or (C)alkyl-(C
10 7)cycloalkyl, aryl, Het, (C1atkyl)aryi or (C1alkyl)Het, said alkyl, cycloalkyl,
aryl, Het, (C1aIkyl)aryb or (C16a1ky1)Het being optionally substituted with

c) 000R105 wherein R’D5 is (C14alkyl, (C7)cycloalkyl, (C1)alkyl-(C3
4cycloatkyl, Het, (C1alkyl)aryl or (C1alkyl)Het, said alkyl, cycloalkyl, aryl,
15 Het, (Ca1kyl)aryl or (C1aIkyl)Het being optionally substituted with R;
d) SR108, SO2N(R1°)2 or SO2N(R108)CO)1R108 wherein each R is
independently H, (C1)alkyl, (C37)cycloalkyl or (C)aIky1-(C37)cycloalkyl,
aryl, Het, (C14alkyl)aryl or (C1.alky1)Flet or both R100 are covalently bonded
together and to the nitrogen to which they are attached to form a 5, 6 or 7-
20 membered saturated heterocycle, said alkyl, cycloalkyl, aryl, Het, (C1
6alkyl)aryl or (Calkyl)Het or heterocycle being optionally substituted with

e) NR111R"2 wherein R’1’ is H, (C1)alkyl, (C37)cycloalkyl or C1)alkyl-(C37)cycloalkyl, aryl, Het, (Ca1ky1)ar1 or (C15alkyl)Het. and R112 is H,
25 CN, (C1)alkyl, (C37)cycloalkyl or (C1.)alkyl-(C37)cycloalkyl, aryl, Het, (01.
8aIkyl)aryl, (Calky1)Het1 C00R115 or S02R115 wherein 13115 is (Cl)alkyl, (C37)cycloalkyf, or (Cl)aIkyl-(C7)cycloatkyl, aryl, Ret, (C1alkyl)aryl or
(C1.6alkyl)Het, or both R111 and R112 are covalently bonded together and to
the nitrogen to which they are attached to form a 5, 6 or 7-membered
30 saturated heterocycle, said alkyl, cycloalkyl, aryl, Het, (C1alkyl)aryL or (C1.
4alkyl)Het, or heterocycle being optionally substituted with Rlso;
0 NR5COR"7wherein R6 and R117 is each H, (Ci.)aLky, (C
7)cycloakyl, (C1)alkyl-(C7)cycloa1kyt, aryl, Het, (CaIkyl)atyl or (C1.
alkyl)Het, said (C1)alkyl, (C7)cycloalkyl. (C)alkyl-(C37)cycloalkyl, aryl,

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5

PCT/CAO2/

23

Wet. (C16a)ky])aryl or (Calky!)Het being optionally substituted with R150; g) NR118CON19R10, wherein 1318, F1119 and A° is each H, (C1)alkyl. (C37)cycloalkyl, (C1)alkyl-(C7)cycFoalkyl, aryl, Wet, (Calky1)aryl or (C1 6alkyl)Het, or H is covalentiy bonded to R19 and to the nitrogen to Which they are attached to form a 5, 6 or 7-membered saturated heterocycle;
or R119 and R° are c valently bonded together and to the nitrogen to
which they are attached to form a 5, 6 or 7-mernttered saturated
heterocycle;
said alkyl, cycloalkyl, (C1)alkyl-(C)cycloalkyl aryl, Wet, (C1a1kyi)aryI or
10 (C,aalkyl)Het or heterocycle being optionally substituted with R°;
h) NR121 GOGOR’22 wherein R121 and R122 is each H, (C,)alkyl, (C3-
7)cycloalkyl, (Cl)alkyl-(C7)cycloalkyl, a 6- or 10-membered aryl, Het, (C
alkyl)aryl or (C16alkyl)Het, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, Het, (Calkyl)aryI or (Ca(kyI)Het being optionally substituted with R150;
15 or is OR or N(R124)2 wherein R’23 and each R124 is independently H,
(CaIkyl), (C37)cycloa1kyl, or (C1)alkyl-(C7)cycloa1kyl, aryl, Het, (C
6alkyt)aryl or (C1alkyl)Het, or R12’ is OH or O(C1ackyl) or both R124 are
covalently bonded together to form a 5, 6 or 7-membered saturated
heterocycle, said alkyl, cycloalkyl, alkyt-cycloalkyl, aryl, Het, (C1alkyl)ary!
20 or (C1alkyl)Het and heterocycle being optionally substituted with R°;
I) COR’27 wherein R’27 is H, (C14)alkyl, (C37)cycloalkyl or (C1)alkyl-(C3
7)cycloalkyl, aryl, Het, (Calkyl)aryl or (C1alkyJ)Het, said alkyt, cycloalkyl,
aryl. Het, (01alkyl)aryl or (C1alkyl)Het being optionally substituted with

25 j) GOOR128 wherein R128 is H, (C1)alkyl, (C7)cycloalkyl, or(C1)alkyl-(C
7)cycloalkyi, aryl, Het, (C8alkyl)ary1 or (CaikyI)Het, said (C1)alky1, (C3
4cycloalkyl, or(C16)alky1-(C7)cycJoakyl. aryl, Het, (C1alkyl)ary1 and (C1
6alkyl)Hel being optionally substituted with R"’°,
k) CONR1R1 wherein R’29 and R1° are independently H, (Cl)alkyl,
30 (C7)cycloalkyI, (C1)alkyl-(C)cycloalkyl, aryl, Het, (Cal.kyl)aryf or(C1
6aikyl)l-let, or both R and R1 are covaiently bonded together and to the
nitrogen to which they are attached to form a 5, 6 or 7-niernbored
saturated heterocycle, said alkyl, cycloalkyl, alkyl-cycloalkyl, aryl, Het, (Ci.
 alkyl)aryl, (C16alkyl)Het and heterocycle being optionally substituted with

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HI50;

I) aryl, Wet, (C1-6a)kyl)ary! or (Cl -6alkyl)Het, all of which being optionally
substituted with H185-
wherein R is preferably:
- 1 to 3 substituents selected from: halogen, NO2, cyano or azido;

or

1 to 3 substituents selected from:

a) (C1$ alkyl or haloalkyl, (C)cycloalkyl, (C2)alkenyJ, (C
8)alkyrryl, (C) alkyl-(C7)cycloalkyl, all of which optionally
10 substituted with H180;
b) OR104 wherein R1 is F-I, (C1aIkyl) or (C7)cycloalkyl, said alkyl
or cycloalkyl optionally substituted with R°;
SR108. SO2N(R1°)2 or SO2N(R°)C(0)R180 wherein each R108 is
independently H, (C10)alkyl, (C7)cycloalkyl or (CI)aikyl-(C
15 7)cycloalkyl, aryl, Het, or both H108 are cova(ently bonded together
and to the nitrogen to which they are attached to form a5, 6 or 7-
membered saturated heterocycle, said alkyl, cycloalkyl, aryl, Wet
and heterocycle being optionally substituted with R108;
e) NR811R112 wherein R1 is H, (C1,6)alkyl, or (C27)cycloalkyl, and
20 R2 is H, (C1)alkyl or (C7)cycloalkyl, C00R115 or SO2R1
wherein H115 is (C)alkyl or (C7)cycloalkyl, or both R111 and R112
are covalently bonded together and to the nitrogen to which they
are attached to form a 5, 6 or 7-membered saturated heterocycle,
said alkyl, cycloalkyl and heterocycle being optionally substituted
25 with R;
I) NR116C0R117 wherein A116 and H117 is each H, (C1)alkyl or (C3-
7)cycloalkyl said (C1)alkyl and (C37)cycloalkyl being optionally
substituted with R°;
g) NR11000MR1R120, wherein 11110, R119 and FI° is each H, (C1
30 6)alkyl or (C37)cycloalkyl, or H118 is covalently bonded to R119 and to
the nitrogen to which they are attached to form a 5, 6 or 7-
membered saturated heterocycle;
or R119 and R’2° are covalently bonded together and to the nitrogen
to which they are attached to form a 5, 6 or 7-membered saturated

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heterocycle;

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said a!kyl, cycloalkyl, and heterocycle being optionally substituted
with R1°;

h) NIR121 COCOR’22 wherein R’ is I-i, (C)alkyl or (C17)cycloalkyl, said alkyl and cycloalkyl being optionally substituted with 1111;
or R122 is OR’23 or N(R)2 wherein R and each R124 is
independently H, (GaIkyl) or (C37)cycloalkyl, or both R124 are
covalently bonded together to form a 5, 6 or 7-membered
saturated heterocycle, said alkyl, cycloalkyl and heterocycle being
optionally substituted with fl160;
i) COR27 wherein R127 is H, (C1)alkyl or (C17)cycloalkyl, said alkyl and cycloalkyl being optionally substituted with R10;
j) C00R2 wherein R128 is I-i, (C1)alkyl or (C37)cycloalkyl, said
(C1)alkyl and (C7)cycloalkyl being optionally substituted with R60; and

k) CONR’R wherein R1 and R1° are independently H, (C1
)alkyl or (C37)cycloalkyl, or both R1 and A130 are covalently
bonded together and to the nitrogen to which they are attached to
toim a 5, 6 or 7-membered saturated heterocycle, said alkyl,
cycloalkyl and heterocycle being optionally substituted with R150;
wherein R’6° is defined as 1 or 2 subsfltuents selected
from:
halogen, CN, C1a]kyl, baloalkyl, COOR, OR’, N(R1)2,
S02NR1)2, NR1COR162 or CON(R1)2, wherein R161 and
25 each R162 is independently H, (C16)alkyl, (C)cycloalkyl or (C1)alkyl-(C37)cycloalkyl; or both R’62 are covalently
bonded together and to the nitrogen to which they are
attached to form a 5, 6 or 7-membered saturated
heterocycle.
30

More preferably, A2 is selected from: aryl or Het, each optionally rnonosubstituted
or disubstitLrted with subsiltuents selected from the group consisting of: halogen, haloalkyl, N1 or
a) {C16alkyI optionally substituted with OH, O(Ci)alkyl or S02(C

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alkyl);
b) (C1)alkoxy;
e) NR1R’12 wherein both A111 and R1 are independently H, (C1.
6)alkyl, (C3-7)cycloalkyl, or H112 is 6- or 10-membered aryl, Het, (C1
)alkyi-aryl or(C16)alkyl-Het; or both R111and A112 are covalently
bonded together and to the nitrogen to which they are attached to
tori-n a nitrogen-containing heterocycle, each of said alkyl,
cycloalkyl, aryl, Het, alkyl-aryl or alkyl-Het beng optionally
substituted with halogen or:
- OR1 or N(R12), wherein flhGl and each R162 is
independently H, (C)alkyl, or both R162 are covalently
bonded together and to the nitrogen to which they are
attached to form a nitrogen-containing heterocycle;
1) NHGOR117 wherein H117 is (C alkyl, O(C16)alkyl or 0(C3
7)cycloalkyl;
i) CO-aryl; and
k) CONH2, CONH(Calkyl), C0N(Calkyl)2, CONH-aryl, or
CONHC16alkyl-aryl.

20 Still, more preferably, R2 is aryl or Het, each optionally monosubstituted or disubstituted with substituents selected from the group consisting of: halogen, haloa]kyl, or
a) (C1)alkyi optionally substituted with OH, 0(C1)alkyl or S02(C1
6alkyl);
25 b) (C1)alkoxy; and
e) NR11R112 wherein both R111 and R112are independently H, (C1
)alkyl, (C37)cycloalkyl, or H112 is 6- or 10-membered aryl, Het, (C1
6)alkyl-aryl or (C1)alkyl-Het; or both H111 and R1’ are covalently
bonded together and to the nitrogen to which they are attached to
30 form a nitrogen-containing heterocycle, each of said alkyl,
cycloalkyl, aryl, Het, alkyl-aryl or alkyl-Het; or being Optionally
substituted with halogen or.
- OR’ or N(H)2,wherein H’61 and each R’52 is
independently H, (C,4alkyl, or both R1’52 are covalently
35 bonded together and to the nitrogen to which they are

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F
F

HH

F,G_O
F -r0

cooea fl° Pdcl)PPh __ coor +/hit

1(i) A eat

PdP/KCO H2I Pd ash.

R2_IIIiEIIII

, 0TIA, 1
7H,

/ ea

A’ coupling

COOMe

R i) NaOH" Compound of formula I
H,N-Fl° coupflng

In carrying out the route illustrated in Scheme 1, a suitably protected form of 3-trifluoroaeetamido-4-iodoberizoic acid 1(i) is reacted with an alkyne 1(u) in the
5 presence of a metal catalyst (e.g. a palladium metal complex such as
PdCl2(PPh3)2, Pd7dba3, Pd(PPh),I and the like), a base (EI3N, DIEA and the like
or an inorganic basic salt including metal carbonates, fluorides and phosphates), and optionally in the presence of an additional pliosphine ligand (triaryl or heferoarylphosphine, dppe, dppf, dppp and the like). Suitable solvents for this
10 reaction include DMF, dioxane, THF, DME, toluene, MeCN, DMA and the like at
temperatures ranging from 20 °C to 170 "C, or alternatively without solvent by heating the components together. Alternatively, the cross-coupling reaction can
be carried out on a suitably protected form of 3-amino-4-iodobenzoate and the
amino group can be trifluoroacetylated in the subsequent step as described by
15 J.W. Ellingboe et al (TeL Lett. 1997, 387963).

Reaction of the above diarylalkynes 1(111) with an enol inflate under cross-coupling conditions similar to those described above gives after hydrogenation of the
douple bond, indole derivatives I(iv). Enol tnflates are known and can be
20 prepared from the corresponding ketones by following known literature methods
(for example, cyclohexene Inflate can be prepared from cyclohexanone, triflic anhydride and a hindered organic base such as 2,6-di-fert-butyl-4-methylpynidine). The hydrogenation of the double bond originally present in R1 can be carried out

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0
H
, NcoOH

CoOhl , 2(U)

NaOMe - or H

29)

thee H, 1 Pdcat. 2(iii)

I. MeOH/S00

rK

2 .N._-,COOMe

2. NaH I R°X

aF?2ue__

(for R°t H.) A’ 2(v)

1OuiJ1-75’C I 2. H SrrU or

or R°-Sr,Fh’,,
catalyst I base

\ 000Me

M R3Sn or Cen

eaatI base

M

A1

2(vi)

In carrying the route illustrated in Scheme 2, commercially available 6-indolecarboxylic acid 2(i), which can also be prepared according to the method of
5 S. Kamiya et al. (Chem. Pharm. Bull. 1995, 43,1692) is used as the starting
material. The indole 2(1) is reacted with a ketone 2(u) under basic or acidic aEdol-
type conditions. Suitable conditions to affect this condensation include strong
bases such as alkali metal hydroxides, alkoxides and hydrides In solvents such as lower alkyl alcohols (MeOH, EtOH, terLBuOH etc.), THF, dioxane, DMF, DM50,
10 DMA and the like at reaction temperature ranging from 20°C to 120 "C.
Alternatively, the condensation can be carried out under acid conditions using
organic or mineral acids or both. Appropriate conditions include mixtures of
AcOH and aqueous phosphoric acid at temperatures ranging from 15°C to 120

’C.

15 Following protection of the carboxylic acid group in the form of an ester (usually
lower alkyl) using known methods, the indole nitrogen can be alkylated with W if desired. Reaction conditions to alkylate the nitrogen of an indole derivative are
well known to those skilled In the art and include the use of strong bases such as alkali metal hydrides, hydroxides, amides, alkoxides and alkylmetals, in the
20 appropriate solvent (such as TI-IF, dioxane, DM E, DMF, MeCN, DM50. alcohols

ly

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27

attached to form a nitrogen-containing heterocycle.

Even more preferably, R2 is phenyl or a heterocycle selected from:

NJ NN

7 7 7 7 7 7

\> aN CCN

5 ,

>

all of which optionally H, arid
substituted as defined above.

Even more preferably, R2 is selected from the group consisting of:
H, Sr, CH=CH2,

HN’O HN’O

10 6
_S

L o

N NZN N
N N N

ç i

I 7

N 1

00I

/ OH ro HN

S::

HN H, N

H

HN
15

fe

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obtained.

EXAMPLE 2:

K\I +

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1. NaOMe
MeOH I reflux
2. MeOH I SOd2

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e

COOMe COOMe

1. lI2 (1 atm) pyridine tribromide B
20% Pd(OH)2 - C

Jf(
THF-CHCI3/O°C
THF- MeOH
2. MeOHISOCl2
5

3-Cyclohexenyl-6-indole carboxylic acid:
A 12 L round-bottomed flask was equipped with a reflux condenser and a
mechanical stirrer, and the system was purged with nitrogen gas. 6-I ndole
carboxylic acid (300.00g, 1.86 mole, 3 equivalents) was charged into the flask,
10 followed by MeOH (5.5 L). After stirring for 10 min at room temperature,
cyclohexanone (579 mL, 5.58 mole) was added, Methanolic sodium methoxide
(25% w/w, 2.6 L, 11.37 mole, 6.1 equivalents) was added in portions over 10
The mixture was then refluxed for 48 h. After cooling to room temperature, water
(4 L) was added and methanol removed under reduced pressure. The residual
15 aqueous phase was acidified to pH 1 with concentrated HCI (-1.2 L). The
resulting yellowish precipitate was collected by filtration, washed with water and
dried under vacuum at 50 °C. The desired cyclohexane derivative was obtained
as a beige solid (451.0g, 100% yield).

3-Cyclohexyl-6-indole carboxylic acid:
20 The unsaturated derivative from above was hydrogenated for 20 h under 55 psi
hydrogen gas pressure over 20% Pd(OH)2/0 (10.25 g) using 1:1 THF - MeOH
(2.5 L) as solvent. After filtration of the catalyst, volatiles were removed under reduced pressure and the residue was triturated with hexane. The beige solid was collected by filtration, washed with hexane and dried under vacuum (356.4 g,
25 78% yield).

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(54) FUSED-RING COMPOUNDS AND USE
THEREOF AS DRUGS

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548/304.4

(57) ABSTRACT

The present invention provides a fused ring compound of the following formula [I]

[’1

G2

b R6
wherein each symbol is as defined in the specification, a pharmaceutically acceptable salt thereof, and a therapeutic agent for hepatitis C, which contains this compound. The compound of the present invention shows an anti-hapalitis C virus (HCV) action based on the HCV polymerase inhibitory activity, and is useful as a therapeutic agent or prophylactic agent for hepatitis C.

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[0237] (7) The therapeutic agent of (6) above, which
comprises a fused ring compound of the following
formula [1-1]

RI

RI

[0238] wherein each symbol is as defined in (1),

[0239] or a pharmaceutically acceptable salt thereof as an
active ingredient.

[0240] (8) The therapeutic agent of (6) above, which
comprises a fused ring compound of the following formula [1-2]

[0246] (10) The therapeutic agent of (6) above, which
comprises a fused ring compound of the following formula [1.4]

[0247] wherein each symbol is as defined in (1),

[0248] or a pharmaceutically acceptable salt thereof as an
active ingredient.

[0249] (11) The therapeutic agent of any of (1) to (10)
above, wherein at least one of gi, R°, R and R is
carboxyl, COOR1, CONR°R3, SO,R7
(wherein pai, R2, W3 and R are as defined in (1)),

a [1-2)
or

NN \N
H II H

II

[0241.] wherein each symbol is as defined in (1),

[0242] or a pharmaceutically acceptable salt thereof as an
active ingredient.

[0243 (9) The therapeutic agent of (6) above, which
comprises a fused ring compound of the following formula [1-3]

[1-3]

R3XR6X

[0244] wherein each symbol is as defined in (1),

[0245] or a pharmaceutically acceptable salt thereof as an
active ingredient.

[0250] (12) The therapeutic agent of (11) above
wherein at least one of R1, R, R3 and R4 is carboxyl,

 COOR, __C0NRa2Ra3 or SO2R7 wherein R, ga2 R and ga7 are as defined in (1).
[0251.] (13) The therapeutic agent of any of (1) to (10)
above, wherein at least one of R1, R2, R and R4 is --- COOR wherein R is glucuronic acid residue.

[0252] (14) The therapeutic agent of any of (1) to (10)
above, wherein at least one of Rr, R°, g3 and i4 is heterocyclic group having Ito 4 heteroatotn(s) selected from an oxygen atom, a nitrogen atom and a sulfur
atom.

[0253] (15) The therapeutic agent of any of (1) to (J 4)
above, wherein the ring Cy is cyclopentyl, cyclohcxyl, cycloheptyl, tetrahydrothiopyranyl or piperidino.

[0254] (16) The therapeutic agent of any of (1) to (14)
above, wherein the ring Cy is

[0255] wherein each symbol is as defined in (1).

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[0256] (17) The therapeutic agent of any of (1) to (16)
above, wherein the ring A is aryl.

[0257] (18) The therapeutic agent of any of (1) to (17)
above, wherein at least one substituent optionally sub-stituted by group A is a substituent substituted by C1 alkoxy C alkoxy.

[0258] (19) The therapeutic agent of any of (1) to (17)
above, wherein the Y is _CH2)rn_CRal5RalC_ (Cu2)11 wherein each symbol is as defined in (1).

[0259] (20) The therapeutic agent of any of (1) to (19)
above, wherein at least one group represented by Z is heterocycle C5 alkyl optionally substituted by 1 to 5 substituent(s) selected from the group D.

[0260] (21) The therapeutic agent of any of (1) to (19)
above, wherein at least one group represented by Z is a heterocyclic group optionally substituted by I to 5 substituent(s) selected from the group I), wherein said heterocyclic group is selected from the following groups:

0,

j1a35

1.

0 N 0

0L0

Q

T 35
E2
: bo NO2

, 0. S 0, >7 Vb!

and

W35N

V,

- - </ I

I
N SC

N

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-continued

R’35

"fR-35

R’5

[0261] wherein E1 is an oxygen atom, a sulfur atom or
N(R35) E2 is an oxygen atom, CH, or N(_RaSS), E5 is an oxygen atom or a sulfur atom, wherein each R5 is inde-pendently hydrogen atom or CIE alkyl, f is an integer of 1 to 3, and h and h are the same or different and each is an integer of 1 to 3.

[0262] (22) The therapeutic agent of (2.1) above,
wherein at least one group represented by Z is hetero-cyclic group optionally substituted by 1 to 5 substitu-ent(s) selected from the group D wherein said hetero-cyclic group is selected from the following groups:

0 0 0 0

 N N N

)fand

[0263] wherein each symbol is as defined in (21).

[0264] (23) The therapeutic agent of any of (1) to (19)
above, wherein at least one group represented by group
B is _ CH2)1_CONRaZ7R wherein each symbol is
as defined in (1), and at least one of R27 and R2a is
C1 alkoxy.

[0265] (24) The therapeutic agent of any of (1) to (19)
above, wherein at least one group represented by group D is _(CH2)_C=NRaSS)M{2 wherein each symbol is as defined in (1), and RSS is hydroxyl group or C alkoxy.

[0266] (25) The therapeutic agent of any of (1) to (19)
above, wherein at least one group represented by group D is - wherein each

symbol is as defined in (1), and RZi is amino.

[0267] (26) The therapeutic agent of any of (1) to (19)
above, wherein at least one group represented by group
D is _ (CH2)1_NRCO_Ra2l wherein each symbol
is as defined in (1), and R24 is amino or C1 alky-
lamino.

[0268] (27) The therapeutic agent of any of (1) to (19)
above, wherein at least one group represented by group
B is (CH2),_NRa22R wherein each symbol is as
defined in (1), and at lease one of R22 and R23 is heterocyclic group optionally substituted by 1 to S substituent(s) selected from the group B.

[0269] (28) The therapeutic agent of any of (1) to (19)
above, wherein at least one group represented by group D is heterocyclic group having 1. to 4 heteroatom(s) selected from an oxygen atom, a nitrogen atom and a sulfur atom.

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[0270] (29) The therapeutic agent of (1) above, which [0291] (S) CONW2R3

comprises a fused ring compound of the following [0292] wherein R2 and R3 are each independently formula [I] or a pharmaceutically acceptable salt hydrogen atom, C1 alkoxy or optionally substi- thereof as an active ingredient: tuted C alkyl (as defined above),

[0293] (9) C (=NR)NB2
Ui
Gi 7

[0294] wherein R4 is hydrogen atom or hydroxyl
2

(t -. [0295] (10 NHR5
R6 [0296] wherein R is hydrogen atom, C
alkanoyl or C alkylsulfonyl,
Cy

[02971 (11) OR’

[0298] wherein R"’ is hydrogen atom or optionally
substituted atkyl(as defined above),
[0271] wherein
[0299] (12) SO2R7
[0272] a broken line is a single bond or a double bond,
[0300] wherein R7 is hydroxyl group, amino, C
[0273] G1 is C(R) or a nitrogen atom, alkyl or C alkylamino

[0274] G2 is CR2) or a nitrogen atom, [0301] or

[0275] (’? is C(R3) or a nitrogen atom, [0302] (13) P(=O) (oR1),

[0276] G4 is C(.-R4) or a nitrogen atom, [0303] wherein R1 is hydrogen atom, optionally

[0277] G, GO, G5 and G’ are each independently a substituted C1 alkyl (as defined above)oraryl carbon atom or a nitrogen atom, C alkyl optionally substituted by 1 to 5

substituent(s) selected from the above group B,
[0278] is C(.R7), an oxygen atom, a sulfur atom, or and

a nitrogen atom optionally substituted by R5, [0304] R7 and R8 are each hydrogen atom or option -
[0279] wherein R1, R2, R3 and R4 are each indepcn- ally substituted alkyl(as defined above),

deutly, [0305] ring
[0280] (1) hydrogen atom,

[0281] (2) C alkanoyl,

[0282] (3) carboxyl,

[0283] (4) cyano,

[0284] (5) nitro,

[0285] (6) C_,-6 alkyl optionally substituted by 1 to 3
substitu ent(s)selected from the following group A,

[0286] group A; halogen atom, hydroxyl group,
carboxyl, amino, C1 alkoxy, C1, alkoxycarbonyl and (C15 alkylaniinc,

[0287] (7) COOR

[0288] wherein R1 is optionally substituted C
alkyl (as defined above) or C4 aryl C alkyl optionally substituted by 1 to 5 substituent(s) selected tram the following group B,

[0289] group B; halogen atom, eyano, nitro, C1
alkyl, halogenated C alkyl, C1 alkanoyl,

 (CI],) Rb2, _.(Ct lz)T_-NR’1__C0R52,

 (CH,),--SRt’, (CH2)rSO7R and

[0290] wherein Rbl and R6’2 are each indepen-
dently hydrogen atom or C1 alkyl and r is 0 or an integer of 1to 6,

[0306] (1) C3 cycloalkyl optionally substituted by 1
to 5 substituent(s) selected from the following group C, group C; hydroxyl group, halogen atom, C,
alkyl and C alkoxy,

[0307] (2) C cycloalkenyl optionally substituted by
1t5 substituent(s) selected from the above group C,

[0308] wherein u and v are each independently an
integer of 1 to 3,

[0309] ring A is

[0310] (1) -6-14 aryl,

[0311] (2) Ca cycloalkyl,

[0312] (3) C3 eycloalkenyl or

[0313] (4) heterocyclic group having I to 4 heteroa-
torn(s) selected from an oxygen atom, a nitrogen atom and a sulfur atom,

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[0314] R5 and R6 are each independently
[0315] (1) hydrogen atom,
[0316] (2) halogen atom,
[0317] (3) optionally substituted alkyl (as
defined above)
[031$] or
03191 (4) OR
[0320] wherein R is hydrogen atom, C alkyl or
C aryl C alkyl, and
[0321] X is
[0322] (1) hydrogen atom,
[0323] (2) halogen atom,
[0324] (3) cyano,
[0325] (4) nitro,
[03261 (5) amino, C,., alkartoylamino,
[0327] (6) C alkylsulfonyl,
[0328] (7) optionally substituted C1.6alkyl (as defined above),
[0329] (8) C alkenyl optionally substituted by 1 to
3 substituent(s) selected from the above group A,
[0330] (9) COOR
[0331] wherein R’ is hydrogen atom or C alkyl,
[0332] (10) CON1-I.
[0333] wherein RIO is optionally substituted C16
alkyl (as defined above), C1 alkoxycarbonyl or C, alkanoylamino and 1 is 0 or an integer of 1 to

[0334] (1I) -0W1’
[0335] wherein R1’ hydrogen atom or option-
substituted C1.6alkyl (as defined above)
[0336] or

[0337] wherein
[0338] ring 13 is
[0339] (1’) C61,1 aryl,
[0340] (2) C cycloalkyl or
[0341] (3’) heterocyclic group (as defined above),
[0342] each Z is independently
[0343] (1’) a group selected from the following
group 0,
[0344] (2) C33 aryl optionally substituted by 1
to 5 substituent(s) selected from the following group 0,

[0345] (3’) C38 cycloalkyl optionally substi-
tuted by I to 5 substituent(s) selected from the following group 0,
[0346] (4’) C14 aryl C16 alkyl optionally sub-
stituted by 1 to 5 substituent(s) selected from the following group 13 or
[0347] (5’) heterocyclic group optionally substi-
tuted by 1 to 5 substituent(s) selected from the following group 13
[0348] wherein the heterocyclic group has I to
4; heteroatom(s) selected from an oxygen atom, a nitrogen atom and a sulfur atom, group D:
[0349] (a) hydrogen atom,
[0350] h) halogen atom,
[0351] (c) cyano,
[0352] (d) nitro,
[0353] (e) optionally substituted C1,3 alkyl (as
defined above),
[0354] (f) (CH,,),COR8,
[0355] (hereinafter each t means independently
0 or an integer of 1 to 6),
[0356] wherein R is
[0357] (1") optionally substituted C1 alkyl
(as defined above),
[0358] (2") C14 aryl optionally substituted
by I to 5 substituent(s) selected from the above group 13 or
[0359] (3") heterocyclic group optionally substituted by I to 5 substituent(s) selected from the above group B wherein the hetero-cyclic group has I to 4 heteroatorn(s) selected from an oxygen atom, a nitrogen atom and a sulfur atom,
[0360] (g)
[0361] wherein R’ is hydrogen atom,
optionally substituted C1 alkyl (as defined above) or C614 aryl C16 alkyl optionally substituted by 1 to 5 substituent(s) selected from the above group B,
[0362] (h)
[0363] wherein R17 and R"28 are each mdc-
penclently,
[0364] (1") hydrogen atom,
[0365] (7) optionally substituted C alkyl
(as defined above),
[0366] (3") C14 aryl optionally substituted
by I to 5 substituent(s) selected from the above group B,
[0367] (4")6-14 aryl C16 alkyl optionally
substituted by 1 to 5 substituent(s) selected from the above group 13,

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[0368] (5’) heterocyclic group optionally substituted by 1 to 5 substituent(s) selected from the above group B,

[0369] (6") heterocycle C alkyl optionally
substituted by 1 to 5 substituent(s) selected from the above group B,

[0370] wherein the heterocycle Cj_6 alkyl
is C alkyl substituted by heterocyclic
group optionally substituted by I to 5 sub-stituent(s) selected from the above group B, as defined above,

[0371] (7") cycloalkyl optionally substi-
tuted by 1 to 5 substituent(s) selected from the above group B, or

[0372] (8’) C38 cycloalkyl C alkyl option-
ally substituted by 1 to 5 substituent(s) selected from the above group B,

[0373] (1) (CH2)----C(NW33)NH2

[0374] wherein R33 is hydrogen atom or C1
alkyl,

.

[0375] (j) Cl-l2)OR20

[0376] wherein R° is

[0377] (1’) hydrogen atom,

[0378] (2) optionally substituted CI-6 alkyl
(as defined above),

[0379] optionally substituted alk-enyl (as defined above),

[0380] (4’) C26 alkynyl optionally substi-
tuted by 1 to 3 substituent(s) selected from the above group A,

[0381] (5") C4 aryl optionally substituted
by 1 to 5 substituent(s) selected from the
above group B,

[0382] (61") C14 aryl alkyl optionally
substituted by I to 5 substituent(s) selected
from the above group B,

[0383] (7") heterocyclic group optionally
. substituted by 1 to 5 substitucnt(,,selected from the above group 13,

[0384] (8’) heterocycle C alkyl optionally
substituted by I to 5 substituent(s) selected
from the above group ft

[0385] (9 ") (: cycloalkyl optionally substi-
tuted by 1 to 5 substituent(s) selected from the above group B, or

[0386] (10") C cycloalkyl C alkyl
optionally substituted by 1 to 5 substituent(s) selected from the above group B,

[0387] (k) (CH2)-----O--(CH2)COR21

[0388] wherein RUal is C alkylamino or
heterocyclic group optionally substituted by
1 to 5 substituent(s) selected from the above group B, and p is 0 or an integer of 1 to 6,

[0389] (1) (CiI2)---NR22W23
[0390] wherein R and Ra23 are each inde-
pendently

[0391] (11") hydrogen atom,

[0392] (211) optionally substituted C alkyl
(as defined above),

[0393] (3") C14 aryl optionally substituted
by 1 to 5 substituent(s) selected from the above group B,

[0394] (4’) C4 aryl C alkyl optionally
substituted by 1 to 5 substituent(s) selected from the above group B or

[0395] (5") heterocycle C1 alkyl optionally
substituted by I to 5 substituent(s) selected from the above group B,

[0396] (m) __(CIi)__NRa2CCO__R4

[0397] wherein R’29 is hydrogen atom, C
alkyl or C1 alkanoyl, R24 is optionally substituted C1 alkyl (as defined above), C
aryl optionally substituted by I to 5 substitu-ent(s) selected from the above group B or heterocyclic group optionally substituted by
1 to 5 substituent(s) selected from the above group B,

[0398] (n) (CH2)---NHS0---R2

[0399] wherein R2S is hydrogen atom, optionally substituted C1 alkyl (as defined above), C,14 aryl optionally substituted by 1
to 5 substituent(s) selected from the above group B or heterocyclic group optionally substituted by 1 to 5 substituent(s) selected from the above group B,

[0400] (a)

[0401] wherein R25 is as defined above, and
q is 0, 1 or 2,

[0402] and

[0403] (p) (CIT2)L-.. SO2NHW25
[0404] wherein R26 is hydrogen atom, optionally substituted C1 alkyl (as defined above), C4 aryl optionally substituted by(1
to 5 substituent(s) selected from the above group B or heterocyclic group optionally substituted by I to 5 substituent(s) selected
from the above group B,

[0405] w is an integer of 1 to 3, and

[0406] Y is

[0407] (1’) a single bond,

[0408] (2’) C alkylene,

[0409] (3’) C.,1 alkenylene,

[0410] (4’) (CH),11-0--(CH2)--,

[0411] (hereinafter m and ii are each indepen-
dently 0

[0412] or an integer of 1 to 6),

[0413] (5’) --CO--,

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[0414] (6) 00--(ClI),,
[0415] (7’) CON1 I(CH2)11_-NlI.,
[0416] (8) 1TCO2--,
[0417] (9’) NH(ONH--,
[0418] (10’) O---(CH2),,---CO--,
[0419] (11’) o--(CI-12),1--O,
[0420] (12’) SO2---,
[0421] (13’) _(CH2),NRal2_(CH2
[0422] wherein RlZ is
[0423] (1") hydrogen atom,
[0424] (2’) optionally substituted C alkyl
(as defined above),
[0425] (3") C4 aryl C alkyl optionally
substituted by 1 to 5 substituent(s) selected Iroru the above group B,
[0426] (4") C4 aryl optionally substituted
by I to 5 substituent(s) selected from the above group B,
[0427] (5") COR"5
[0428] wherein Rb5 is hydrogen atom, optionally substituted C1(, alkyl (as defined above), C14 aryl optionally substituted by 1 to 5 substituent(s) selected from the above
group B or C514 aryl C1 alkyl optionally
substituted by I to S substituent(s) selected from the above group B,
[0429] (6") 000R55 (Rb-5 is as defined
above) or
[0430] (7) ---S02R1’5 (R’s is as defined
above),
[0431] (11’) _NRa12CO_ (R’12 is as defined
above),
[0432] (15)
[0433] wherein R’3 is hydrogen atom,
optionally substituted C1 alkyl (as defined
above) or C4 aryl C1 alkyl optionally
substituted by 1 to 5 substituent(s) selected from the above group B,
[0434] (16’) C0NH__CHR*_
[0435] wherein RI4 is C14 aryl optionally
substituted by 1 to 5 substituent(s) selected from the above group B,
[0436] (17) .0 (Cl1)cR"5R----
(Cll2)

[0437] wherein R15 and R6 are each inde-
pendently
[0438] (1") hydrogen atom,
[0439] (2") carboxyl,
[0440] (3 ’d) C1 alkyl,
[0441] (4 ") OR’6

14

[0442] wherein R1 is C alkyl or C14 alkyl
C16 alkyl, or

[0443] (5 ") _NHRb7
[0444] wherein R1 is hydrogen atom, C1
alkyl, C1 alkanoyl or C aryl C5 alky-loxycarboisyl, or R’15 is optionally

(5")
(Z’)w

[0445] wherein n’, ring B’, Z’ and w’ are the
same as the above-mentioned n, ring B, Z and
w, respectively, and may he the same as or different from the respective counterparts,
[0446j (18’) (CH2)NR’1 CHR15--
(R and R5 are each as defined above),
[0447] (19’) NRa17SO2
[0448] wherein Rl7 is hydrogen atom or C1
alkyl
[0449] or

[0450] (20’)
(CH) (e is 0, 1 or 2, RUIS and RI6 are each
as defined above).
[0451] (30) The therapeutic agent of (29) above,
wherein ito 4 of the 61, 62" 63, G’, G5, G, U7, G and G° is (are) a nitrogen atom.
[0452] (31) The therapeutic agent of (30) above, wherein G2 is C(R) and G is a carbon atom.

[0453] (32) The therapeutic agent of (30) or (31) above, wherein G5 is a nitrogen atom.
[04541 (33) The therapeutic agent of (29) above, wherein, in formula [I], the moiety

[0455] is a fused ring selected from

R

R

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I

Eli

-continued

R2

R8

R2 N /

Rl

R1

R2X
R3 N

RI

R2XJ\.
R N N

Ry:

Rl
R2N

R’

15

-continued

R3:1

and

R2

(34) The therapeutic agent of (33) above, wherein, in formula [I], the moiety

Ci 7 02 G8"

Tr5

[0457] is a fused ring selected from

and

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[0619] (15)
[0620] wherein Rl3 is hydrogen atom, optionally
substituted C1.6 alkyl (as defined above) or
aryl C alkyl optionally substituted by I to 5
substituent(s) selected from the above group B,

[0621] (16) -. CONH-CI1R4--
[0622] wherein R’° is C4 aryl optionally sub-
stituted by 1 to S substituent(s) selected from the above group B,

[0623] (17) 0(CH)mCR"15R(CFI2)n
[0624] wherein R"15 and R6 are each indepen-
dently
[0625] (1) hydrogen atom,

[0626] (2) carboxyl,

[0627] (3) C alkyl,
[0628] (41) ()R’
[0629] wherein Rhe is C alkyl or aryl C1
alkyl, or
[0630] (5’) __NIIRb7
[0631] wherein Rh7 is hydrogen atom, C alkyl,
C alkanoyl or aryl alkyloxycarbonyl,
[0632] or

[0633] R15 is optionally

(6’)

[0641] (43) The fused ring compound of (42) above,
which is represented by the following formula [IT-i]

R

[0642] wherein each symbol is as defined in (42),
[0643] or a pharmaceutically acceptable salt thereof,
[0644] (44) The fused ring compound of (42) above,
which is represented by the following formula [11-2]

[0645] wherein each symbol is as defined in (42),
[0646] or a pharmaceutically acceptable salt thereof.
[0647] (45) The fused ring compound of (42) above,
which is represented by the following formula [11-3]
[0634] wherein n’, ring 13’, 1 and w’ are the same
as the above-mentioned n, ring 13, Z and w,

respectively, and may be the same as or differ- {113j
ent from the respective counterparts, R1
[0635] (iS) and R
are each as defined above), aAY
[0636] (19) NR7SO2wherein ReIl is hydrogenN
atom or C alkyl,
[0637] (20) -. S(0)(CII,CR Ra1
(Cl--L)---- (e is 0, 1 or 2, gaI3 and R1 are each as
defined above),

[0638] or [0648] wherein each symbol is as defined in (42),
[0639] (21)

and R’°’ are each as defined above), [0649] or a pharmaceutically acceptable salt thereof.
[0650] (46) The fused ring compound of (42) above,
[06401 or a pharmaceutically acceptable salt thereof. which is represented by the following formula [114]

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I

rf

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aryl optionally substituted by Ito 5 sub-
stituent(s) selected from the above group B or
C6 aryl C1 alkyl optionally substituted by 1t
5 substitucnt(selected from the above group
B,
[0818] (6’) COOR (R’5 is as defined above) or

[0819] (7’) SO2Rb5 (R"5 is as defined above),
[0820] (14) NR CO (R is as defincd above),
[0821] (iS) --...CONR(CII2),1--
[0822] wherein RI3 is hydrogen atom, optionally
substituted C1 alkyl (as defined above) or
aryl C alkyl optionally substituted by 1 to 5 substituent(s) selected from the above group B,
[0823] (16)---CONHCHRai4
[0824] wherein RU is C1 aryl optionally sub-
stituted by i to 5 substituent(s) selected from the above group B,

[0825] (17) _O_(ClJ)CRaiSWi6__(CH2)__
[0826] wherein R5 and Ri are each indepen-
dently
[0827] (1 hydrogen atom,
[0828] (2) carboxyl,
[0829] (3’) C alkyl,
[0830] (4’) R
[0831] wherein R is C1alkyl or aryl C1
alkyl,
[0832] or
[0833] (5’) NHR"7
[0834] wherein Rb7 is hydrogen atom, C1
alkyl, (aikanoyl or Ca aryl C alkyloxy
cathonyl, or R- is optionally

(6)

18 [0835] wherein n’, ring 13’, Z and w’ are the same as the above -mentioned n, ring B, Z and
w, respectively, and may be the same as or
different from the respective counterparts,

[0836] (18) (CHNR’12CI-IR’15 (R’2 and
R5 each as defined above),
[0837] (19) NR7SO2---
[0838] wherein R17 is hydrogen atom or C1 alkyl
[0839] or
[0840] (20)
(Cll2)a (e is 0, 1 or 2, and Ralo are each as
defined above)

[0841] or a pharmaceutically acceptable salt thereof,
[9842] (75) The fused ring compound of (74) above,
which is represented by the following formula [11-1]

TZ
R7
R5
(7)w
N
R6’

Y-&

[0843] wherein each symbol is as defined in (74),
[0844] or a pharmaceutically acceptable salt thereof.
[0845] (76) The fused ring compound of (74) above,
which is r(presented by the following formula [11-2]

A’

Y_&(Z)w

#

R6’

A4

bcv,

[0846] wherein each symbol is as defined in (74),
[0847] or a pharmaceutically acceptable salt thereof.
[0848] (77) The fused ring compound of (74) above,
which is represented by the following formula [11-3]

í a a -a]

R2
Nr

R5’

)--?Y_&(Z)W
R3jc,,:,:,cN N

b

R6’

[0849] wherein each symbol is as defined in (74),
[0850] or a pharmaceutically acceptable salt thereof.

F’

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(54) ’Title: QUTNOIiI4ONE-CARBOXAMII)E COMPOUNDS AS 5-WI5 RECEPTOR AGONISTS

OR R5

-

if
aN? 0

C (0
salt or solvate or stercoisomer thereof.

(57) Abstract: The invention provides novel quinolinone-car-boxumide 5-1114 receptor agonist compounds of Formula (I). Tho invention also provides pharmaceutical compositions comprising such compounds, the use such compounds to treat diseases associated with 5-HT4 receptor activity, and processes and intermediates useful for preparing such compounds. Wherein; R1 is hydrogen, halo, hadroxy, C14 alkyl, or C4 alkoxy: R is (3,4 alkyl, or C3.5cycloakyl; R3 is hydrogen or Ci 3 alkyl: H4 is  S(0)2 R5 or----C(0)R7: R is hydrogen, Cj3aikyl, C alkyl subtituted with -011 or C1.3 alkoxy, orCl-12py:ydvl; H6 is C. alkyl; or R5 and R5 taken together from C3.4 alkylenyl; arid R is hydrogen, CaJky], or pyrydyl; or pharmaceutically-acceptable

A

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evaporation. To the crude product, toluene (400 mL) was added and removed by rotary evaporation. After three additional cycles ofthe toluene process, the title intermediate
was obtained (228.2 g) which was used without further purification in the next step.

d. Synthesis of 1-isopropyl-2-oxo-1.2-dihydroQuinolifle-3-carboxylic acid {(1S,3R,5R’)’8-
5 .2.1 loct-3-

In a 3 L flask, 1 -isopropyl-2-oxo- 1,2-dihydroquinoline-3-carboxylic acid (1S,3R,5R)-8-azabicyclo[3.2.1)oet-3-yl} amide trifluoroacetate (105.0 g, 0,232 mol) was suspended in absolute ethanol (400 mL). To this suspension, NaOH (50 % in water,
10 0.243 mol. 1.05 eq) dissolved in absolute ethanol (100 mL) was added at room
temperature. The beaker containing the NaOH was washed with ethanol (2 x 50 mL) and the washings were added to the reaction mixture. After 30 min ofstirring, a solution of Nmethy1-N-[(S-2-oxiran-2-y1methy1]methanesU1fOflafflide (62.0 g, 1.5 eq) in absolute ethanol (100 mL) was added. The mixture was refluxed for 2 h, cooled to room
15 temperature and seed crystals ofthe title compound were added. After about 5 nun of
stirring a white solid formed. The mixture was cooled to 3-5 °C and stirred for 2 h. The white solid was filtered and the wet cake was washed with cold absolute ethanol
(3 x 50 mL). The solid was dried under vacuum at 30 °C for 60 ii to provide the title compound (93.8 g, water content by Karl Fischer method 2.03 %). 1H NMR (CDC13)
20 3 ppm 10.52 (d, 1H), 8.83 (s, 1H), 7.75 (d, 2H), 7.64-7.60 (m, 2H), 7.28-7.26 m, 1H),
4.33-4.26 (m, 2H), 3.78-3.75 (m, lil), 3.27-3.20 (m, 4H), 3.01 (s, 3H), 2.88 (s, 3H), 2.58-2.53 (in, 1H), 2.30-1.81(m 1IH), 1.68 (d, 611).
The seed crystals were obtained from a previous preparation ofthe title compound
by the method ofthis example at smaller scale, in which crystallization occurred
25 spontaneously.

Example 25: Synthesis of 1-isopropyl-2-oxo-1,2-dihydroquinoline-3-
carboxylic acid {(1S,3R,5R)-8-[(R)-2-hydroxy-3-(methanesulfonyl-methyl-ainlno)propylj-8-aza-bicyelo[3.2.11 oct-3-yl} amide hydrochloride
In a 1 L flask, 1-isopropyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid

30

bieyclo[3.2. 1]oct-3-yl}amide (34.7 g, 0.069 mol) was suspended in absolute ethanol
(210 mL). Concentrated HC1 (1.1 eq) was added at room temperature with stirring. The mixture was stirred at rcflux for 30 min and cooled to room temperature and stirred for

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2 li. The solid was filtered and the wet cake was washed with cold absolute ethanol
(3 x 50 mL). The solid was dried under vacuum at 30 °C for 48 h to provide the title compound (34.5 g, 93.7 % yield, water content by Karl Fischer method 0.13 %).

Example 26: Synthesis of citric acid salt of 1-isopropyl-2oxo-1,2-dihydroquinoline-3-carboxylic acid {(1S,3R,5R)-8-[(R)-2-hydroxy-3-(methanesulfonyl-methyl-amino)propyl]-8-azabicyclo[3.2.1] oct-3-yI} amide
1 -Isopropyl-2-oxo- 1,2-di]aydroquinoline-3-carboxylic acid {(1 S,3R,5R)-8-{(R)-2-hydroxy-3-(methanesu1fonyl-methyl-amino)propylJ-8-azabicyclo[3.2.1]oct-3-yl} amide
(0.1 g, 0.2 nmiol) was suspended in ethanol (1 mL). To this suspension was added a IM
10 solution of citric acid in ethanol (0.072 mL, 0.072 nunol, 0.33 eq). The mixture was
briefly sonicated until clarity, capped, and then allowed to sit overnight. The cap was
then removed and the mixture was allowed to evaporate under ambient conditions until
solids were observed, The mixture was then recapped and allowed to sit for 72 h. The Sresultingsolid was filtered and washed with cold ethanol to give the title compound as a
15 solid (74,3mg),

Example 27: Synthesis of acid salts of 1-isopropyl-2-oxo-1,2-cl1hydroquinoLine-3-carboxylic acid {(1S,3R,5R)-S-[(1?)-2-hydroxy-3-(methänesulfonyl-methyl-amino)propyl] -8-aza-bicyclo[3.2.1] oct-3-yl} amide
Following the procedure of Example 26, the acid salts of l-isopropyl-2-oxo-1,2-
20 dihydroquinoline-3 -carboxylic acid {(1S,3R,5R)-8-{(R)-2-hydroxy-3 -(methanesulfonyl-
niethyl-amino)propylj-8-aza-bicyelo[3.2. 1]oet-3-yl} amide listed below in Table ifi were prepared in solid form using the indicated equivalents of acid.
Table 111: Acid Salts

Acid No. of equivalents of acid Product weight (mg)
adipic 0.5 48.5
phosphoric 0.5 86.6
sulfuric 0.5 27.0
tartar-ic 0.5 66.3
malic 0.5 _25.3
hydrobromic 1 62.9

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WHAT IS CLAIMED IS:

1. A compound of formula (I):
N’(-R
OR R

Rt - _5 NH

0

5 (J) wherein:

R1 is hydrogen, halo, hydroxy, C14a1ky1, or C14alkoxy;
R2 is C34alkyl, or C36cycloalkyl;
R3 is hydrogen or C13alkyl;
10 RisS(0)2R6orC(0)R7;

R5 is hydrogen, C13a1ky1, C23a1ky1 substituted with OH or C1.3alkoxy, or
 CH2---pyridyl;
R is C13a11y1;
or, R5 and R6 taken together form C3,alkyleny1; and
15 R1 is hydrogen, C1..3alkyl, orpyridyl;
or a pharmaceutically-acceptable salt or solvate or stereoisomer thereof.

2. The compound of Claim 1 wherein
R5 is hydrogen, C13alkyl, C23a1ky1 substituted with OH or C1alkoxy, or 20 CH2--pyridyl; aid
R6 is C1 -alkyl.

3 The compound of Claim 2 wherein R1 is hydrogen or halo.

25 4. The compound ofClaim 2 wherein R2 is C3.4alkyI.

5, The compound ofClaim 2 wherein R4 is S(0)2R6.

6. The compound ofClaim 5 wherein R4 is S(0)2CH3.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO DIRECCION DE NUEVAS CREACIONES

2020

Abogado
DILIA RODRIGUEZ D’ALEMAN

ASUNTO RadicaciOn 07 105 206
TrÆmite 002
Evento 001
Actuaciôn 430

Oficto 5
Folios 8

Patente de Invención .1. Patente de Modelo de Utilidad LJ
Via Nacional

Via PCT (Fase Nacional) F7 Cap.I Cap. II
No. Solicitud I nternacional PCT/US20060 12978
Fecha de Presentación Internacional 2 de Abril de 2006

Coma resultado del Examen de Fondo realizado, con fundamento en el ArtIculo 45 de la Decision 486 de la ComisiOn de la Comunidad Aridina, se comunica:

1. Documentos estudiados

DescripciÆn:

Reivindicaciones

Prioridad:

2. AnÆIisisde la. Prioridad

Folios 53 a 94 coma se radicó inicialrnente.

Folios 95 a 97 como se radicO inicialmente

US 60 668 780 de 06 de Abril 2005

Se acepta Ia reivindicaciOn de Prioridad porque:
Esta solicitud fue preseritada dentro del plazo establecido (Art. 9 D 486).
Y su contenido tØcnico corresponde con el de la prioridad reivindicada.

3. Objeto de la invención

TItulo de la solicitud: "Forma cristalina de un compuesto de quinolona Carboxamida"

El problema planteado en esta solicitud es la necesidad sintetizar sales cristalinas de compuestos de quinolona carboxamida, presentados como clorhidrato a coma solvato, que no sean higroscOpicos y que sean tØrmicamente estables.

Para resolver este problema tØcnico la solicitud en estudio proporciona compuestos de quinolona carboxamida en forma cristalina a solvatada, asI como los mØtodos de preparación y los usos de los compuestos reivindicados.

Expedente 07 105 206 1er Art 45

El objeto de la presente Solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): A 61 K 31/46, A 61 P 9/00

4. Reivindicaciones relativas a un uso o a un segundo uso (Art 14 y 21 0 486)

El uso de las reivindicaciones 14 - 22 no es patentable de acuerdo con los Art citados,

5. De la Solicitud de Patente

Reivindicaciones (Art 30 D 486, Art 22 PCT)

1- Las reivindicaciones 22 y 23 no son concisas ya que los reactivos adicionados se nombran de forma general, se sugiere restririgirlo a compuestos y condiciones de reacción especificas.

Se requiere al Solicitante hacer las aclaraciones necesarias.

6. Determinaciôn del Estado de la TØcnica

El Estado de la TØcnica se determinó con base en la

Fecha de Presentación Internacional: 10 de Abril de 2006

y se encontraron los sguientes documentos que anticipan el objeto de esta solicitud:

Item Documento Titulo Fecha de Publicación* Quinolinones carboxamides as
Dl W02005100350 compounds as 5hT4 receptor 27/Octubre/2005 antagonist

Dl divulga (ejemplo 25, pag 57) compuestos del tipo quinolinonas carboxamidas presentados como su sal clorhidrato y compuesto en forma de sal o solvato (Pag 69, pÆrrafo15)

6. AnÆlisis dePatentabilidad (Art 14 D486)

Novedad (Art 16 D486)

La reivindicación I consiste en un compuesto de formula I

ComoaracOn de las caracteristicas tØcnicas esenciales con las del estado de Ia TØcnica
. . . enciaIes Dl

Forma sauna cristalina como Sal de Clorhidrato de {(IS, 3R,
5R) 8 2-hidroxi-3- (metanosulfonhlo-metil-amino) propil] 8-
azabicyclo [3.2.1] oct-3-hl)amida de acido 1 -hsopropil-2- oxo-cido_2-dihydroguinolina-3-carboxHico
Solvato de {(IS, 3R, 5R) 8 2-hidroxi-3- (meta nosulfonilo-metil-amino) propil] 8-azabicyclo [3.2.1] oct-3-il)amida de acido 1-isopropil-2- oxo-, Æcido 2-dihydroquinolina-3-carboxilico

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Comparando las caracteristicas esenciales de la reivindicación 1 con Ia divulgado en el documento Dl se considera novedosa por cuanto la forma cristalina coma Sal Clorhidrato del activo reivindicado no se encuentra descrita con anterioridad, sin embargo los solvatos (PÆg.69, pÆrrafo15) se encuentran descritos con anterioridad en el documento Dl.

Las reivindicaciones dependientes 2 7 mencionan algunas caracterIstica que hacen nueva la forma cristalina coma clorhidrato de la reivindicación 1, coma la lectura de su patron de difracción de rayos X (R&vindicaciOn 3) y el escaneo de calorimetrIa diferencial (Reivindicación 6 y 7) par Ia cual se considera que la forma cristalina coma sal clorhidrato del activo es nueva.

Las reivindicaciones dependientes 8 12 mencionan algunas caracteristica que hacen nueva la forma cristalina coma solvato de la reivindicaciOn 1 coma la lectura de su patron de difracción de rayos X (Reivindicación 9) y el escaneo de calorimetria diferencial (Reivindicación 12) por lo cual se considera que la forma cristalina coma solvato del activo es nueva.

Nivel Inventivo (Art18 D486)

La reivindicaciôn I consiste en una forma sauna cristalina que es la sal clohidrato de {(1S, 3R, 5R) - 8 2-hidroxi-3- (metanosulfonilo-metil-amino) propil] 8-azabicyclo [3.2.1] oct-3-il)amida de acido 1-isoprapil-2- oxo-, Æcida 2-dihydroquinolina-3-carboxilico a un solvato del mismo.

El documento Dl considerado el estado de la tØcnica mÆscercano a la invenciôn definida en la reivindicación 1, divulga (ejemplo 25, pÆg. 57) compuestos del tipo quinolinonas carboxamidas presentados camo su sal clorhidrato y compuesto en
forma de sal a solvato (Pag 69, pÆrrafo15)

La diferencia entre la invención, definida en la reivindicaciOn 1, y el compuesto de Dl
consiste en la forma cristalina obtenida tanto para la sal clorhidrato coma para el
solvato.

No hay evidencia de que la forma cristalina reivindicada tanto para la sal clorhidrato
. como para el solvato sean menos higroscOpicas y tØrmicamente mas estables que los compuestos conocidos.

Par Ia tanto, el Problema TØcnico Objetivo que pretende resolver esta invenciOn no
parece haberse resuelto.

Conclusion

La reivindicaciOn I cumple el requisito de novedad (Art. 16), y
No cumple con el requisito de nivel inventivo (Art, 18).

7, Conclusion

La reivindicaciôn 1 cumple el requisito de novedad (Art. 16), y
No cumple con el requisito de nivel inventivo (Art. 18).

En cumplimiento del artIculo 45 de la Decision 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del tØrmino de sesenta (60) dias contados a partir de la fecha de notificaciOn de la presente comunicaciOn. En caso

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

NotifIquese el presente oficio conforme a to dispuesto en el numeral 52, literal e), del capItulo quinto del titulo primero de la Circular Unica No. 10 de 2001.

JOSE LUIS SALAZAR LOPEZ
Director de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha

0 / MR

CONCEPTO TECNICO EXAMINADOR TECNJCO
No. 1045 Código No.202099

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