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Industria y Comercio
SUPERINTENDENCIA

DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No 04-066836

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

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **545** DE

FECHA **29** DE **OCTUBRE DE 2004** EL TERMINO HABIL EÑALADO POR LA

LEY EXPIRA EL **27** DE **ENERO** DEL **2005**

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** _ _____

United States Patent Office 3,472,859 Patented Oct. 14, 1969

3,472,859

1-ALKYL-1,4-DIHYDRO-4-OXO-3 QUINOLINE-CARBOXYLIC ACIDS AND ESTERS

George Y. Lesher, Schodack, N.Y., assignor to Sterling Drug Inc., New York, N.Y., a corporation of Delaware

No Drawing. Filed Nov. 1, 1966, Ser. No. 591,095
Int. Cl. C07d 33/48; A01n 9/22; A61k 25/00
U.S. Cl. 260—287 8 Claims

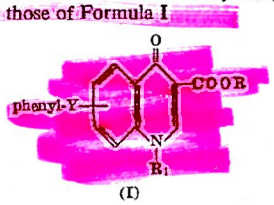
ABSTRACT OF THE DISCLOSURE

A 1,4-dihydro-1-(lower-alkyl)-4-oxo-7(or 6)-phenyl-Y-3-quinolinecarboxylic acid or its lower-alkyl ester, where Y is CH_2, O, S, CH_2S or is a direct linkage, is prepared by reacting the corresponding 3-(COOR)-4-hydroxy-7(or 6)-phenyl-Y-quinoline, where R is lower alkyl, with an alkylating agent, e.g., lower-alkyl halide, sulfate or sulfonate. The compounds have stimulatory, antibacterial and antifungal properties.

This invention relates to compositions of matter classified in the art of chemistry as 1,3-disubstituted-1,4-dihydro-4-oxoquinolines and to their preparation.

The invention sought to be patented, in its composition aspect, resides in the class of compounds which I designate 1,4-dihydro-1-(lower-alkyl)-4-oxo-7(or 6)-phenyl-Y-3-quinolinecarboxylic acids and lower-alkyl esters thereof where Y is a bivalent radical of the group CH_2, O, S, CH_2O and CH_2S or is a direct linkage between phenyl and the 7(or 6)-position of the quinoline ring. Accordingly, I depict these compounds as having phenyl attached to the 7(or 6)-position of a 1,4-dihydro-1-(lower-alkyl)-4-oxo-3-quinolinecarboxylic acid or lower-alkyl esters thereof either directly or through CH_2, O, S, CH_2O or CH_2S. The tangible embodiments of this composition aspect of the invention possess the inherent applied use characteristics of having stimulant properties, as determined by standard pharmacological evaluation procedures, and, further, of having chemotherapeutic properties, e.g., antibacterial activity and antifungal activity, as determined by standard chemotherapeutic evaluation procedures.

Without limiting the generality of the foregoing, illustrative and preferred embodiments of my composition embodiments are those of Formula I



(I)

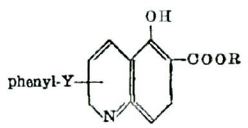
where Y is CH_2, O, S, CH_2O, CH_2S or a direct linkage and is connected to the quinoline ring at position 6 or 7, R is hydrogen or lower-alkyl, and R_1 is lower-alkyl.

The benzene ring of "phenyl" can bear any number and kind of substituents such as would occur to those skilled in the art. The presence of such substituents on the benzene ring does not adversely affect the pharmacological or chemotherapeutic activity of the compositions of this invention. Among such substituted-benzene rings are, without limiting the generality of the foregoing: lower-alkylphenyl, e.g., methylphenyl, ethylphenyl, isopropylphenyl, or any other analogous lower-alkylphenyl group; halophenyl, e.g., fluorophenyl, chlorophenyl, bromophenyl, iodophenyl, or any other analogous halophenyl group; lower-alkoxyphenyl, e.g., methoxyphenyl, ethoxyphenyl, butoxyphenyl, or any other analogous lower-alkoxyphenyl group; trifluoromethylphenyl; lower-alkylthiophenyl, e.g., methylthiophenyl, butylthiophenyl, or any

other analogous lower-alkylthiophenyl groups; N,N-di-lower-alkylaminophenyl, e.g., N,N-dimethylaminophenyl, N-methyl-N-ethylaminophenyl, or any other analogous N,N-di-lower-alkylaminophenyl groups; lower-alkylsulfonylphenyl, e.g., methylsulfonylphenyl, ethylsulfonylphenyl, or any other analogous lower-alkylsulfonylphenyl groups; loweralkylaminophenyl, e.g., propylaminophenyl, butylaminophenyl, or any other analogous lower-alkylaminophenyl groups; lower-alkanoylaminophenyl, e.g., acetylaminophenyl, propionylaminophenyl, or any other analogous lower-alkanoylaminophenyl groups; lower-alkanoyloxyphenyl, e.g., acetoxyphenyl, propionoxyphenyl, or any other analogous lower-alkanoyloxyphenyl groups; hydroxyphenyl; aminophenyl; or any other equivalent substituted phenyl group. Also, phenyl can be replaced by one of the groups: 2- or 3-furyl, 2- or 3-thienyl, or cycloalkyl having three to six ring carbon atoms, e.g., cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

Each of the terms "lower-alkyl," "lower-alkoxy" and "lower-alkanoyl," as used above and throughout the specification and claims, e.g., as used in the definition of R or R_1 of Formula I or as substituents of the benzene ring of phenyl, means alkyl, alkoxy or alkanoyl radicals having from one to six carbon atoms which can be arranged as straight or branched chains, among which are, for purposes of illustration but without limiting the generality of the foregoing, methyl, ethyl, n-propyl, isopropyl, sec-butyl and n-hexyl for lower-alkyl; by methoxy, ethoxy, n-propoxy, isopropoxy, isobutoxy, n-amoxy and n-hexoxy for lower-alkoxy; and, by formyl, acetyl, propionyl (n-propanoyl), isobutyryl (2-methyl-n-propanoyl) and caproyl (n-hexanoyl) for lower-alkanoyl.

The invention sought to be patented, in its process aspect, is described as residing in the process for the preparation of the composition aspect of the invention, illustrated by Formula I above, by reacting the corresponding 3-(COOR)-4-hydroxy-7(or 6)-phenyl-Y-quinoline, illustrated by Formula II



(II)

where Y and R have the meaning given above for Formula I, R preferably being lower-alkyl, with a lower-alkyl ester of a strong acid, i.e., an acid which is practically completely dissociated in aqueous solution. Illustrative and preferred esters are lower-alkyl esters of a strong inorganic acid or an organic sulfonic acid, said ester having the Formula R_1—An, where An is an anion of a strong inorganic acid or an organic sulfonic acid, e.g., chloride, bromide, iodide, sulfate, methanesulfonate, benzenesulfonate, and para-toluenesulfonate. R_1 has the meaning given above for Formula I. The chloride, bromide or iodide is preferred because of the ready availability of the requisite lower-alkyl halides; and the reaction is carried out preferably in the presence of an acid-acceptor. The acid-acceptor is a basic substance which preferably forms freely water-soluble by-products easily separable from the product of the reaction, including for example, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium alkoxides, potassium alkoxides, sodium amide, and the like. The purpose of the acid-acceptor is to take up the hydrogen halide (or HAn) which is split out during the course of the reaction. The reaction can be carried out in either the presence or absence of a suitable solvent, but preferably in a solvent such as a lower-alkanol, acetone, dioxane, dimethylform-

EXAMPLE 8

(a) Ethyl 6 - benzyl - 1 - ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylate, M.P. 203–205° C. was obtained following the procedure described in Example 1*a* using 15.36 g. of ethyl 6-benzyl-4-hydroxy-3-quinolinecarboxylate, 13.8 g. of anhydrous potassium carbonate, 100 cc. of dimethylformamide, 12 cc. of ethyl iodide and a heating period of seven hours. There was thus obtained 12.7 g. of the ester.

(b) 6 - benzyl - 1-ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, M.P. 185.0–187.0° C. (corr.) was obtained following the procedure described in Example 1*d* using 12.6 g. of ethyl 6-benzyl-1-ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylate, 41 cc. of 10% aqueous potassium hydroxide solution and 40 cc. of ethanol. There was thus obtained 7.2 g. of the product after recrystallization from dimethylformamide.

Analysis.—Calcd. for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.29; H, 5.62; N, 4.20.

6 - benzyl - 1 - ethyl - 1,4 - dihydro-4-oxo-3-quinolinecarboxylic acid was found to have central nervous stimulatory activity at 10 mg./kg. when tested by the above-described procedure designated as PST.

(c) The intermediate ethyl 6 - benzyl - 4 - hydroxy-3-quinolinecarboxylate used in Example 8*a* was prepared following the procedure described in Example 1*c* using 87 g. of diethyl 4-benzylanilinomethylenemalonate and 1300 cc. of diethyl phthalate. There was thus obtained 26.0 g. of the compound, M.P. 281.0–282.0° C. (corr.).

Analysis.—Calcd. for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.15; H, 5.49; N, 4.49.

(d) Diethyl 4 - benzylanilinomethylenemalonate, used as an intermediate in Example 8*c* was prepared following the procedure described in Example 1*d* using 72 g. of 4-benzylaniline and 86 g. of diethyl ethoxymethylenemalonate. There was thus obtained 105.8 g. of this intermediate, M.P. 63.8–65.0° C. (corr.).

Analysis.—Calcd. for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.19; H. 6.54; N, 3.85.

EXAMPLE 9

(a) Ethyl 1 - ethyl - 1,4 - dihydro - 4-oxo-6-phenoxy-3-quinolinecarboxylate was prepared following the procedure described in Example 4*a* using 21.5 g. of ethyl 4-hydroxy-6-phenoxy-3-equiolinecarboxylate, 19.3 g. of anhydrous potassium carbonate, 100 cc. of dimethylformamide, 20 cc. of ethyl iodide and a heating period of four and one-half hours. There was thus obtained 20.0 g. of the product, M.P. 140–143° C.

(b) 1 - ethyl-1,4-dihydro-4-oxo-6-phenoxy-3-quinolinecarboxylic acid, M.P. 182.0°–182.4° C. (corr.), was obtained following the procedure described in Example 4*b* using 20.0 g. of ethyl 1-ethyl-1,4-dihydro-4-oxo-6-phenoxy-3-quinolinecarboxylate, 70 cc. of 10% aqueous potassium hydroxide solution, 70 cc. of ethanol and a heating period of two hours. There was thus obtained 17.0 g. of the product.

Analysis.—Calcd. for $C_{18}H_{15}NO_4$: C, 69.89; H, 4.89; N, 4.53. Found: C, 70.13; H, 5.26; N, 4.50.

1 - ethyl - 1,4 - dihydro - 4 - oxo - 6 - phenoxy - 3-quinolinecarboxylic acid was found to have central nervous stimulatory activity when tested by the above-described procedures designated as PST, RPPT and RPRT at respective doses of 1.0, 50 and 50 mg./kg. This compound also was found to have in vitro bacteriostatic activity against *Staphylococcus aureus*, *Clostridium welchii* and *Pseudomonas aeruginosa* at 0.05, 0.075 and 0.10 mg./cc. respectively.

EXAMPLE 10

(a) 7 - benzyloxy - 1 - ethyl - 1,4 - dihydro - 4 - oxo - 3-quinolinecarboxylic acid.—A mixture containing 14.8 g. of 7 - benzyloxy - 4 - hydroxy - 3 - quinolinecarboxylic acid, 250 cc. of 1 N sodium hydroxide solution and 23.1 g. of diethyl sulfate was stirred for eighteen hours at room temperature. The reaction mixture was then refluxed with stirring for five minutes and concentrated hydrochloric acid was added to the hot stirred mixture until acidic. The mixture was allowed to cool and the precipitate was collected, dried in vacuo at 55° C. for three days to yield 13.5 g. of 7-benzyloxy-1-ethyl-1,4-dihydro-4-oxo - 3 - quinolinecarboxylic acid, M.P. 227–228.5° C. For analysis, a 3 g. portion was recrystallized from 10 cc. of dimethylformamide, washed with small portions of dimethylformamide and dried in vacuo at 55° C. for about sixteen hours to yield 2.5 g. of product, M.P. 230.0–233.0° C. (corr.).

Analysis.—Calcd. for $C_{19}H_{17}NO_4$: C, 70.57; H, 5.30; N, 4.33. Found: C, 70.61; H, 5.33; N, 4.48.

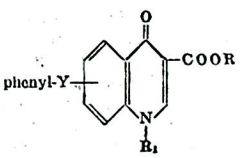
7 - benzyloxy - 1 - ethyl - 1,4 - dihydro - 4 - oxo - 3-quinolinecarboxylic acid was found to have central nervous stimulatory activity when tested by the above-described procedures designated as PST and RPRT at 1.0 and 50 mg./kg. respectively.

(b) The above intermediate 7 - benzyloxy-4-hydroxy-3-quinolinecarboxylic acid was prepared in three steps starting with 3-benzyloxyaniline as follows: A mixture containing 138.2 g. of 3-benzyloxyaniline and 165.2 g. of diethyl ethoxymethylenemalonate was heated on a steam bath for one hour and then allowed to cool to form diethyl 3 - benzyloxyanilinomethylenemalonate which was then added to 700 cc. of Dowtherm A and the mixture heated with stirring at 250° C. for about fifteen minutes while distilling off 51 cc. of ethanol. The mixture was allowed to cool and stand at room temperature overnight. The solid that separated was collected, washed with n-hexane, triturated with about 800 cc. of hot methanol, the mixture filtered and the solid dried in vacuo at 55° C. for about sixteen hours to yield 75.1 g. of ethyl 7-benzyloxy-4-hydroxy-3-quinolinecarboxylate, M.P. 281° C. A mixture containing 50.1 g. of ethyl 7-benzyloxy - 4 - hydroxy - 3 - quinolinecarboxylate and 430 cc. of 10% aqueous sodium hydroxide solution was refluxed with stirring for two hours; the hot reaction mixture was diluted with about 300 cc. of hot water; treated with decolorizing charcoal and filtered through infusorial earth; and the filtrate as allowed to cool and stand at room temperature overnight. The filtrate was acidified with about 130 cc. of concentrated hydrochloric acid and cooled. The resulting precipitate was collected and triturated with about 500 cc. of water. The solid was then collected by filtering the aqueous mixture and was air-dried to yield 48.4 g. of 7 - benzyloxy-4-hydroxy-3-quinolinecarboxylic acid, M.P. 268–269.5° C.

(c) Following the three-step procedure of Example 10b but using 4-benzylthioaniline, a known compound, in place of 3-benzyloxyaniline, there is obtained, after the third step, 6-benzylthio-4-hydroxy-3-quinolinecarboxylic acid, which when used in the procedure of Example 10a in place of 7-benzyloxy-4-hydroxy-3-quinolinecarboxylic acid yields 6-benzylthio-1-ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid.

I claim:

1. A compound of the formula



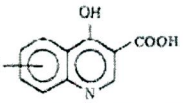
where Y is CH_2, O, S, CH_2O or CH_2S and is connected to the quinoline ring at position 6 or 7, R is hydrogen or lower-alkyl, and R_1 is lower-alkyl.

2. A compound according to claim 1 where Y is CH_2, R is hydrogen and R_1 is lower-alkyl.

3. A compound according to claim 1 where Y is O, R is hydrogen and R_1 is lower-alkyl.

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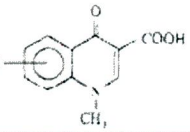
Table V. Physical Properties of R



No.	R[a]	Solvent[b]	Mp, °C	Yield, %	Formula[c]
3	6-C_4H_9-n	A	235–236 dec	89	$C_{14}H_{15}NO_3$
4	6-C_6H_5	B	288–289 dec	78	$C_{16}H_{11}NO_3$
5	6-$C_6H_5CH_2$	B	262–263 dec	42	$C_{17}H_{13}NO_3$
7	6-$C_6H_5CH_2O$	C	264–265 dec	66	$C_{17}H_{13}NO_4$
8	6-$C_6H_5(CH_2)_2O$	C	247–249 dec	63	$C_{18}H_{15}NO_4$
9	6-$C_6H_5(CH_2)_3O$	D	247–248 dec	72	$C_{19}H_{17}NO_4$
10	6-$C_6H_5O(CH_2)_2O$	D	235–237 dec	54	$C_{18}H_{15}NO_5$
11	6-$C_6H_5O(CH_2)_3O$	A	202–205	98	$C_{19}H_{17}NO_5$
12	6-$C_6H_5O(CH_2)_4O$	A	237–239	58	$C_{20}H_{19}NO_5$
13	6-$C_6H_5O(CH_2)_5O$	A	215–217	45	$C_{21}H_{21}NO_5$
14	7-C_6H_5	D	279–280 dec	10	$C_{16}H_{11}NO_3 \cdot 0.25H_2O$
15	7-$C_6H_5CH_2$	A	268 dec	37	$C_{17}H_{13}NO_3$
16	7-$C_6H_5O(CH_2)_3O$	A	218–221	63	$C_{19}H_{17}NO_5$
17	8-C_6H_5	A	247–248	58	$C_{16}H_{11}NO_3$
18	8-$C_6H_5CH_2$	C	258–259	33	$C_{17}H_{13}NO_3$
19	8-$C_6H_5O(CH_2)_3O$	C	247–248	56	$C_{19}H_{17}NO_5$

[a] Compds in Table IV saponified by previously described procedure.[3] [b] Recrystn solvents: A, EtOH; B, HOAc; C, 2-methoxyethanol; D, 2-methoxyethanol-H_2O. [c] *Anal.* C, H, N.

Table VI. Physical Properties of R



No.	R[a]	Solvent[b]	Mp, °C	Yield, %	Formula[c]
24	6-C_6H_5	A	251–252	82	$C_{17}H_{13}NO_3$
25	6-$C_6H_5CH_2$	B	238–240	40	$C_{18}H_{15}NO_3$
26	6-$C_6H_5CH_2O$	B	253–255	58	$C_{18}H_{15}NO_4$
27	6-$C_6H_5O(CH_2)_3O$	B	194–195	59	$C_{20}H_{19}NO_5$
28	7-$C_6H_5CH_2$	B	235–237	66	$C_{18}H_{15}NO_3$
29	7-$C_6H_5O(CH_2)_3O$	A	177–179	16	$C_{20}H_{19}NO_5$
30	8-C_6H_5	B	278–280	63	$C_{17}H_{13}NO_3$
31	8-$C_6H_5CH_2$	A	191–215[d]	40	$C_{18}H_{15}NO_3$
32	8-$C_6H_5O(CH_2)_3O$	A	172–175	46	$C_{20}H_{19}NO_5$

[a] By alkylation and saponification of compds in Table IV according to the previously described procedure.[3] [b] Recrystn solvents: A, EtOH; B, 2-methoxyethanol. [c] *Anal.* C, H, N. [d] Retains this mp after addl recrystns.

give 2.75 g (56%), mp 196–197°. *Anal.* ($C_{16}H_{17}NO \cdot HCl$). See Table II for other compounds prepared in this manner.

The free amine was liberated by partitioning the HCl salt between 2 *N* NaOH and CH_2Cl_2. The org phase was dried ($MgSO_4$), spin-evapd and used in the next step.[5]

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Irreversible Enzyme Inhibitors. 192.[†,1] Hydrophobic Bonding to Some Dehydrogenases with 5-Substituted-4-hydroxyquinoline-3-carboxylic Acids

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Received August 13, 1971

Fifteen derivatives of 4-hydroxyquinoline-3-carboxylic acid bearing aryl, aralkyl, aralkoxy, or aroxyalkoxy substituents at the 5 position and Cl, Me, or H at the 8 position were synthesized and evaluated as inhibitors of glutamate, lactate, malate, and glyceraldehyde phosphate dehydrogenases: good to excellent hydrophobic interaction was observed with the first three enzymes, the 8-Cl-5-$C_6H_5(CH_2)_6$ substituent (12) giving the best interaction. 12 was complexed to malate dehydrogenase 1100-fold more effectively than the parent 4-hydroxyquinoline-3-carboxylic acid (1) and 4300-fold more effective than L-malate; 12 complexed to glutamate dehydrogenase 250-fold better than the parent 1 and 500-fold better than L-glutamate. Furthermore, 12 was complexed to lactate dehydrogenase 65-fold better than the parent 1 and 300-fold better than the substrate, pyruvate.

The possible utility of inhibitors or glutamate, glyceraldehyde phosphate, lactate, and malate dehydrogenases for treatment of cancer cells in the resting phase (G_0) was discussed in a previous paper.[2] 4-Hydroxyquinoline-3-carboxylic acid (1) was selected[2] for further study to determine if potency could be increased by hydrophobic bonding with

†This work was generously supported by Grant CA-08695 from the National Cancer Institute, U. S. Public Health Service.

D3 S60 S60

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
17 January 2002 (17.01.2002)

PCT

(10) International Publication Number
WO 02/04444 A2

(51) International Patent Classification[7]: C07D 471/00

(21) International Application Number: PCT/US01/16495

(22) International Filing Date: 25 June 2001 (25.06.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/217,558	12 July 2000 (12.07.2000)	US
60/272,142	28 February 2001 (28.02.2001)	US

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/04444 A2

(54) Title: HETEROCYCLE CARBOXAMIDES AS ANTIVIRAL AGENTS

(57) Abstract: The present invention provides a compound of formula I which is useful as antiviral agents, in particular, as agents against viruses of the herpes family.

HETEROCYCLE CARBOXAMIDES AS ANTIVIRAL AGENTS

Background of the Invention

1. Field of the Invention

The present invention provides heterocycle carboxamide derivatives. These compounds are useful as antiviral agents, in particular, as agents against viruses of the herpes family.

2. Technology Description

The herpesviruses comprise a large family of double stranded DNA viruses. They are also a source of the most common viral illnesses in man. Eight of the herpes viruses, herpes simplex virus types 1 and 2 (HSV-1 and HSV-2), varicella zoster virus (VZV), human cytomegalovirus (HCMV), Epstein-Barr virus (EBV), and human herpes viruses 6, 7, and 8 (HHV-6, HHV-7, and HHV-8), have been shown to infect humans.

HSV-1 and HSV-2 cause herpetic lesions on the lips and genitals, respectively. They also occasionally cause infections of the eye and encephalitis. HCMV causes birth defects in infants and a variety of diseases in immunocompromised patients such as retinitis, pneumonia, and gastrointestinal disease. VZV is the causative agent of chicken pox and shingles. EBV causes infectious mononucleosis. It can also cause lymphomas in immunocompromised patients and has been associated with Burkitt's lymphoma, nasopharyngeal carcinoma, and Hodgkin's disease. HHV-6 is the causative agent of roseola and may be associated with multiple sclerosis and chronic fatigue syndrome. HHV-7 disease association is unclear, but it may be involved in some cases of roseola. HHV-8 has been associated with Karposi's sarcoma, body cavity based lymphomas, and multiple myeloma.

U.S. Patent Nos. 5,753,666 and 5,891,878 and WO 97/04775 disclose specific 1-alkyl-substituted-quinolone-3-carboxamides that are alleged to have therapeutic utility via inhibition of Phosphodiesterase IV esterase and/or Tumor Necrosis factor activity.

degassed by alternately bubbling in nitrogen then subjecting to high vacuum. The mixture is heated rapidly to reflux and after 30 minutes cooled to room temperature. Diphenyl ether is distilled away under high vacuum and the residue taken up in CH_2Cl_2 (40 mL). The solid is collected by filtration and washed with CH_2Cl_2 with a second crop obtained by reducing the solvent volume of CH_2Cl_2 filtrate and collecting more solid. The title compound is obtained as a pale green powder, 0.24 g (47%). Physical characteristics: MS (ESI+) *m/z* 267 (M+H).

Preparation 44

Ethyl 8-Chloro-1,6-dimethyl-4-oxo-1,4-dihydro[1,7]naphthyridine-3-carboxylate [BT.4]

Ethyl 8-chloro-6-methyl-4-oxo-1,4-dihydro[1,7]naphthyridine-3-carboxylate (Preparation 43, 1.86 g) is dissolved in DMF (20 mL) and K_2CO_3 (2.4 g) is added followed by iodomethane (1.28 g) at room temperature. The mixture is stirred for 5 hours and then added to water (120 mL). The solid is washed with additional water, collected and dried under high vacuum to obtain 0.72 g (37%) of the title compound as a pale green powder. Physical characteristics: MS (ESI+) *m/z* 281 (M+H).

Preparation 45

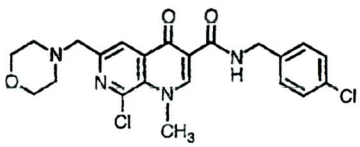
Ethyl 8-Chloro-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro[1,7]-naphthyridine-3-carboxylate [BT.6]

Ethyl 8-chloro-1,6-dimethyl-4-oxo-1,4-dihydro[1,7]naphthyridine-3-carboxylate (Preparation 44, 0.62 g) and *N*-bromosuccinimide (0.45 g) are dissolved in dichloroethane (100 mL). The solution is subjected to light by shining a 650W sunlamp with stirring for 25 minutes. Solvent is evaporated and the crude solid obtained is dissolved in DMF (15 mL). Morpholine (0.86 g) is added and the mixture stirred for 18 hours. The mixture is poured into CH_2Cl_2 (200 mL) and then washed with water (3 x 200 mL). The organics are dried with Na_2SO_4, filtered and the solvent evaporated. The crude solid is chromatographed with MeOH/CH_2Cl_2 (0-5%) to

obtain 0.32 g (40%) of the title compound as a light orange solid. Physical characteristics: MS (ESI+) *m/z* 366 (M+H).

Example 12

8-Chloro-*N*-(4-chlorobenzyl)-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-1,7]naphthyridine-3-carboxamide [BT.7]



Ethyl 8-chloro-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro[1,7]-naphthyridine-3-carboxylate (Preparation 45, 0.11 g) is dissolved in CH_2Cl_2 (5 mL) and 4-chlorobenzylamine (0.073 mL) added followed by 0.20 mL of a 2.0M solution of $AlCl_3$ in toluene at room temperature. After 3 hours the mixture is partitioned between CH_2Cl_2 (30 mL) and water (30 mL). The organics are dried with Na_2SO_4, filtered and solvent evaporated. The remaining solid is chromatographed with MeOH/CH_2Cl_2 (1-4%) to obtain 0.110 g (79%) of the title compound as a yellow solid. Physical characteristics: MS (ESI+) *m/z* 461 (M+H).

Preparation 46

Ethyl-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro[1,7]naphthyridine-3-carboxylate [BU.1]

A mixture of ethyl-8-chloro-1-methyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-[1,7]naphthyridine-3-carboxylate (Preparation 45, 0.090 g), potassium acetate (0.015 g) and 10% Pd/C (20 mg) in isopropyl alcohol is hydrogenated (balloon) for 18 hours. The mixture is filtered through celite and the filter cake washed with MeOH. The solvent is evaporated and the crude solid chromatographed with CH_2Cl_2\CH_3OH\TEA (90\9\1) to obtain 0.58 g (70%) of the title compound as an off-white solid. Physical characteristics: MS (ESI+) *m/z* 332 (M+H).

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
C07D 215/16, 215/18, 215/22, 215/36, 215/38, 215/58, 215/233, A61K 31/47, A61P 31/12

A1

(11) International Publication Number: **WO 00/40561**

(43) International Publication Date: 13 July 2000 (13.07.00)

(21) International Application Number: PCT/US99/27960

(22) International Filing Date: 22 December 1999 (22.12.99)

(30) Priority Data:

60/115,301	8 January 1999 (08.01.99)	US
60/140,610	23 June 1999 (23.06.99)	US

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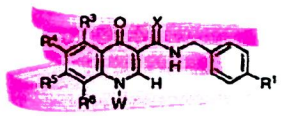
(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: QUINOLINECARBOXAMIDES AS ANTIVIRAL AGENTS



(I)

(57) Abstract

The present invention provides a compound of formula (I) which is useful as antiviral agents, in particular, as agents against viruses of the herpes family.

^{1}H NMR (300 MHz, $CDCl_3$) 7.1, 6.8, 3.7, 3.4, 2.4, 0.7, 0.5; MS (ESI) *m/z* 233 ($M+H^+$).

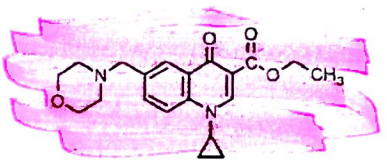
PREPARATION 24. Diethyl 2-{[cyclopropyl-4-(4-morpholinylmethyl)-anilino]methylene}malonate

To a flask containing *N*-cyclopropyl-4-(4-morpholinylmethyl)aniline (0.55 g) from Preparation No. 23 is added diethyl ethoxymethylenemalonate (0.45 mL) and pyridine (0.33 mL). The flask is tightly capped and heated to 145 °C for 2 hours. The reaction is cooled to room temperature and azeotroped under reduced pressure with toluene (3x). The residue is dissolved in dichloromethane and washed with brine, dried and concentrated under reduced pressure. The residue is chromatographed on silica eluting with 2% to 6% methanol in dichloromethane. The product-containing fractions are evaporated to give 0.77 g of the title compound as an oil.

Physical characteristics are as follows:

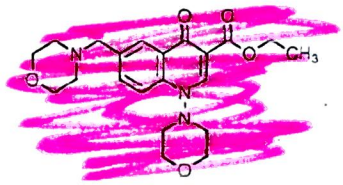
^{1}H NMR (300 MHz, $CDCl_3$) 7.8, 7.3, 7.1, 4.2, 4.1, 3.8, 3.1, 2.4, 1.3, 0.8, 0.7; MS (ESI) *m/z* 403 ($M+H^+$).

PREPARATION 25. Ethyl 1-cyclopropyl-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-quinolinecarboxylate



To a flask containing diethyl 2-{[cyclopropyl-4-(4-morpholinylmethyl)anilino]-methylene}malonate from Preparation No. 24 (0.77 g) is added polyphosphoric acid (4.4 g). The reaction mixture is tightly capped and heated to 120 °C. After 1 hour the reaction is cooled to room temperature. The reaction mixture is carefully added to a vigorously stirred mixture of dichloromethane and saturated aqueous bicarbonate. The layers are separated and the basic aqueous layer is extracted with two additional portions of dichloromethane. The combined organic layers are washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The residue is chromatographed on silica eluting with

PREPARATION 56. Ethyl 1-(4-Morpholinyl)-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-quinolinecarboxylate.



Ethyl 3-[2-fluoro-5-(4-morpholinylmethyl)phenyl]-3-oxopropanoate (10.0 g) of Preparation No. 55, triethylorthoformate (10.8 mL) and acetic anhydride (10.7 mL) are combined in a flask equipped with a Dean-Stark trap and condenser. The reaction is heated to 150 °C for 3.5 hours. The excess acetic anhydride and triethylorthoformate are distilled off at 100 °C and 0.2 torr leaving a burgundy oil containing a mixture of E- and Z- isomers of ethyl-3-ethoxy-2-[2-fluoro-5-(4-morpholinylmethyl)benzoyl]-2-propenoate.

This crude mixture is dissolved in ethanol (50 mL), and 4-aminomorpholine (4.7 mL) is added. The reaction mixture is stirred at room temperature for 2.5 hours and concentrated in vacuo. The resulting burgundy oil is purified in two batches by column chromatography ($MeOH/CH_2Cl_2$: 1%, 2%; 5%) to give ethyl (E)- and (Z)-2-[2-fluoro-5-(4-morpholinylmethyl)benzoyl]-3-(4-morpholinylamino)-2-propenoate as a yellow oil.

The crude enamine is dissolved in THF, and sodium hydride is slowly added to the solution. After heating the mixture to 70 °C for 2 hours, the reaction is quenched with water (5 mL) and concentrated in vacuo to a burgundy slurry. More water (100 mL) is added, and the remaining THF removed in vacuo. The resulting yellow precipitate suspended in an aqueous solution is filtered on a fritted funnel and washed twice with water and once with ether to afford 5.9 g (55%) of the title compound as a powdery, yellow solid.

Physical characteristics are as follows:

Mp 209-211 °C; ^1H NMR (DMSO-d_6) δ 8.87, 8.20, 8.11, 7.74, 4.23, 3.97, 3.78, 3.59, 3.57, 3.03, 2.37, 1.30; MS (ESI+) *m/z* 402 $(M+H)^+$; Anal. Found for $C_{21}H_{27}N_3O_5$: C, 62.83; H, 6.75; N, 10.44.

567
DS 567

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
27 December 2001 (27.12.2001)

PCT

(10) International Publication Number
WO 01/98275 A2

(51) International Patent Classification[7]: C07D 215/00

(21) International Application Number: PCT/US01/16481

(22) International Filing Date: 5 June 2001 (05.06.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/212,202 16 June 2000 (16.06.2000) US
60/272,136 28 February 2001 (28.02.2001) US

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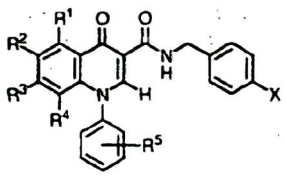
(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

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WO 01/98275 A2

(54) Title: 1-ARYL-4-OXO-1,4-DIHYDRO-3-QUINOLINECARBOXAMIDES AS ANTIVIRAL AGENTS



(I)

(57) Abstract: The present invention provides compounds of formula (I) which are useful as antiviral agents, in particular, as agent against viruses of the herpes family.

g (61%) of the title compound as a beige solid. Physical characteristics: M.p. 125-128 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.1, 10.21, 8.51-8.24, 7.87-7.68, 7.56-7.28, 7.15, 3.95, 3.57, 3.48, 2.35, 0.99-0.77; IR (diffuse reflectance) 1694, 1665, 1637, 1632, 1613 (s), 1574 (s), 1523 (s), 1430, 1295 (s), 1276, 1256 (s), 1231, 1217, 1209 (s), 1109 (s) cm^{-1}; MS (ESI) *m/z* 449 $(M+H)^+$; Anal. Calcd for $C_{23}H_{23}F_3N_2O_4$: C, 61.60; H, 5.17; N, 6.25; F, 12.71. Found: C, 61.54; H, 5.27; N, 6.21; F, 13.10.

General Preparation A.4. Method A. Sodium hydride (60% dispersion, 1.2 equiv) is added to a solution of the corresponding intermediate A.3 (General Preparation A.3) in THF (0.5 M). The mixture is heated to 70 °C for 3 h. The reaction mixture is quenched with water (5 mL) and concentrated in vacuo. The crude product is purified by either filtration or column chromatography to afford the desired intermediate A.4. **Method B.** Potassium *t*-butoxide (1.1 equiv) is added to a solution of the corresponding intermediate A.3 (General Preparation A.3) in *t*-butanol and the mixture is stirred at 60°C for 18 - 20 h. The reaction mixture is concentrated in vacuo to a slurry which is filtered and washed with water and diethyl ether. The crude product is purified by either recrystallization or column chromatography to afford the desired intermediate A.4. **Method C.** A mixture of potassium carbonate (1.5 equiv) and the corresponding intermediate A.3 (General Preparation A.3) in DMF (0.2 M) is heated at 85°C for 0.5- 8 h. The mixture is allowed to cool to room temperature and is poured into water. The crude product is purified as described below to afford the desired intermediate A.4.

The following compounds (Preparations 6a – 6p) are prepared according to one of these procedures.

Preparation 6a

Ethyl 6-(4-Morpholinylmethyl)-4-oxo-1-phenyl-1,4-dihydro-3-quinolinecarboxylate [A.4, W = morpholinylmethyl, aryl = phenyl]

According to general method A, ethyl 3-anilino-2-(2-fluoro-5-(4-morpholinylmethyl)-benzoyl)-2-propenoate (Preparation 5a, 1.0 g) affords upon filtration and drying 0.46 g

(48%) of the title compound as an orange solid. Physical characteristics: M.p. 159-161 °C; ^{1}HNMR (300 MHz, DMSO-d_6) δ 8.43, 8.20, 7.67, 7.60, 6.94, 4.21, 3.58-3.55, 2.36-2.32, 1.25; IR (drift) 1683, 1644, 1609, 1490, 1348, 1320, 1257, 1244, 1166, 1111, 865, 803 cm^{-1}; MS (ESI+) *m/z* 393 $(M+H)^+$; Anal. Calcd for $C_{23}H_{24}N_2O_4$: C, 70.39; H, 6.16; N, 7.14. Found: C, 70.28; H, 6.33; N, 6.97.

Preparation 6b

Ethyl 1-(2-Methylphenyl)-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-quinoline-carboxylate [A.4, W = morpholinylmethyl, aryl = 2-methylphenyl]

According to general method A, ethyl 2-(2-fluoro-5-(4-morpholinylmethyl)benzoyl)-3-(2-toluidino)-2-propenoate (Preparation 5b, 1.0 g) affords after purification by column chromatography (CH_2Cl_2/MeOH, 99/1, 97/3, 96/4) to afford 1.05 g (91%) of the title compound as a yellow oil. Physical characteristics: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.40, 8.21, 7.62-7.45, 6.73, 4.20, 3.58, 2.36, 2.01, 1.26; MS (ESI+) *m/z* 407 $(M+H)^+$; HRMS (FAB) calcd for $C_{24}H_{26}N_2O_4$+H *m/z* 407.1971, found 407.1969.

Preparation 6c

Ethyl 1-(3-iodophenyl)-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-quinoline-carboxylate [A.4, W = morpholinylmethyl, aryl = 3-iodophenyl].

According to general method B, ethyl 2-[2-fluoro-5-(4-morpholinylmethyl)benzoyl]-3-(3-iodoanilino)-2-propenoate (Preparation 5c, 3.65 g) affords after recrystallization from acetonitrile 1.417 g (40%) of the title compound as a light yellow powder. Physical characteristics: M.p. 209-212 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.44, 8.14, 8.02, 7.70, 7.6, 7.44, 6.94, 4.21, 3.65-3.53, 2.41-2.31, 1.26; ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.2, 189.3, 168.9, 151.9, 151.3, 140.5, 135.2, 132.9, 131.7, 130.7, 127.1, 126.6, 117.7, 117.0, 115.5, 115.3, 106.0, 95.4, 67.3, 62.8, 60.7, 60.423, 53.9, 14.3, 13.9; IR (drift) 1693, 1663, 1615, 1583, 1560, 1295, 1278, 1271, 1261, 1255, 1241, 1232, 1214, 1110, 769 cm^{-1}; MS (ESI+) *m/z* 539 $(M+H)^+$; Anal. Calcd for $C_{23}H_{24}FIN_2O_4$: C, 51.31; H, 4.49; N, 5.20; Found: C, 51.30; H, 4.52; N, 5.14.

570 570

Preparation 6d

Ethyl 1-(4-chlorophenyl)-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-quinoline-carboxylate [A.4, W = morpholinylmethyl, aryl = 4-chlorophenyl].

According to general method B, ethyl 3-(4-chloroanilino)-2-(2-fluoro-5-(4-morpholinylmethyl)benzoyl)-2-propenoate (Preparation 5d, 2.5 g) affords after recrystallization from ethanol 1.51 g (63%) of the title compound as an off-white crystalline powder. Physical characteristics: M.p. 178-181°C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.45, 8.19, 7.77-7.69, 7.60, 6.96, 4.21, 3.61-3.52, 2.39-2.32, 1.26; ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.7, 165.9, 148.6, 140.0, 139.5, 136.6, 136.1, 133.8, 131.1, 129.2, 128.5, 128.1, 117.9, 112.1, 67.4, 62.9, 61.4, 53.9, 14.8; IR (diffuse reflectance) 1718, 1608, 1489, 1365, 1347, 1333, 1324, 1255, 1246, 1212, 1165, 1117, 1087, 844, 822 cm^{-1}. HRMS (FAB) calcd for $C_{23}H_{23}ClN_2O_4$+H *m/z* 427.1424, found 427.1419. Anal. Calcd for $C_{23}H_{23}ClN_2O_4$: C, 64.71; H, 5.43; N, 6.56; Cl, 8.31. Found: C, 64.35; H, 5.47; N, 6.47; Cl, 8.23.

Preparation 6e

Ethyl 1-(4-isopropylphenyl)-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-quinoline-carboxylate [A.4, W = morpholinylmethyl, aryl = 4-isopropylphenyl].

According to general method B, ethyl-2-(2-fluoro-5-(4-morpholinylmethyl)benzoyl)-3-(4-isopropylanilino)-2-propenoate (Preparation 5e, 3.00 g) affords after recrystallization from isopropanol 1.294 g (45%) of the title compound as a yellow powder. Physical characteristics: M.p. 181-184 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.42, 8.19, 7.61, 7.57-7.51, 6.95, 4.21, 3.57, 3.05, 2.36, 1.31-1.22; ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.8, 166.1, 151.5, 149.0, 140.3, 138.7, 135.7, 133.6, 128.7, 128.5, 127.9, 127.5, 118.4, 111.7, 67.4, 62.9, 61.3, 53.9, 34.4, 25.8, 24.3, 14.8; IR (drift) 1726, 1605, 1510, 1486, 1384, 1359, 1334, 1317, 1244, 1217, 1164, 1114, 1084, 862, 828 cm^{-1}; HRMS (FAB) calcd for $C_{26}H_{30}N_2O_4$+H *m/z* 435.2284, found 435.2278.

Preparation 6f

Ethyl 1-(4-methoxyphenyl)-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-quinolinecarboxylate [A.4, W = morpholinylmethyl, aryl = 4-mothoxyphenyl].

According to general method B, ethyl 2-[2-fluoro-5-(4-morpholinylmethyl)benzoyl]-3-(4-methoxyanilino)-2-propenoate (Preparation 5f, 2.00 g) affords after recrystallization from isopropanol 0.946 g (50%) of the title compound as a yellow powder. Physical characteristics: M.p. 177-179°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.4, 8.18, 7.61, 7.59-7.56, 7.22-7.16, 6.95, 4.20, 3.87, 3.57, 2.38-2.33, 1.26; ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 164.1, 158.8, 147.2, 138.5, 133.6, 131.7, 131.6, 126.8, 126.4, 125.8, 116.3, 113.7, 109.6, 65.3, 60.9, 59.2, 54.1, 51.8, 12.8; IR (drift) 1721, 1608, 1512, 1486, 1365, 1346, 1330, 1300, 1248, 1172, 1163, 1115, 1086, 1029, 808 cm^{-1}; HRMS (FAB) calcd for $C_{24}H_{26}N_2O_5$+H *m/z* 423.1920, found 423.1925.

Preparation 6g

Ethyl 1-(2-(Hydroxymethyl)phenyl)-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-quinolinecarboxylate [A.4, W = morpholinylmethyl, aryl = 2-hydroxymethylphenyl].

Ethyl 2-(2-fluoro-5-(4-morpholinylmethyl)benzoyl)-3-(2-(hydroxymethyl)anilino)-2-propenoate (Procedure 5g, 2.79 g) is reacted according to general method C for 1 h. The resulting mixture is extracted with EtOAc (3 x 50 mL). The combined organic layers are washed with brine (5 mL), dried (Na_2SO_4), and concentrated. The crude product is crystallized from ethanol to afford 1.54 g (58%) of the title compound as a light yellow solid. Physical characteristics: M.p. 164-166 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.41, 8.20, 7.74, 7.68, 7.60-7.56, 6.71, 5.26, 4.25-4.15, 3.58, 2.37, 1.26; ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.4, 164.5, 148.9, 139.7, 139.6, 138.3, 135.4, 134.0, 130.7, 129.7, 129.4, 128.6, 127.5, 126.4, 118.1, 110.8, 66.5, 62.0, 60.2, 59.2, 56.4, 53.5, 14.6; IR (diffuse reflectance) 1691 (s), 1634, 1609 (s), 1601 (s), 1549, 1489 (s), 1322, 1276, 1244 (s), 1224, 1181, 1142, 1113, 806, 783 cm^{-1}; MS (ESI+) *m/z* 423 (100, $(M+H)^+$), 424 (23); HRMS calcd for $C_{24}H_{26}N_2O_5$+H *m/z* 423.1920,

found 423.1902. Anal. Calcd for $C_{24}H_{26}N_2O_5$: C, 68.23; H, 6.20; N, 6.63. Found: C, 68.24; H, 6.31; N, 6.58.

Preparation 6h

Ethyl 1-(2,3-Dihydro-1*H*-inden-5-yl)-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-quinolinecarboxylate [A.4, W = morpholinylmethyl, aryl = indan].

Ethyl 3-(2,3-dihydro-1*H*-inden-5-ylamino)-2-(2-fluoro-5-(4-morpholinylmethyl)-benzoyl)-2-propenoate (Procedure 5h, 2.0 g) is reacted according to general method C for 8 h. The resulting mixture is extracted with EtOAc (3 x 50 mL). The combined organic layers are washed with brine (5 mL), dried (Na_2SO_4), and concentrated. The crude product is triturated with diethyl ether and recrystallized from EtOAc/hexane to afford 1.55 g (81%) of the title compound as a light yellow solid. Physical characteristics: M.p. 133-135 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.41, 8.19, 7.60, 7.50, 7.49, 7.37, 6.98, 4.21, 3.58, 2.98, 2.36, 2.13, 1.26; ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.3, 164.5, 148.7, 146.6, 146.1, 140.1, 139.0, 135.5, 133.8, 127.6, 126.4, 126.0, 125.6, 123.7, 118.6, 110.6, 66.5, 62.0, 60.2, 53.4, 32.7, 32.5, 25.6, 14.6; IR (diffuse reflectance) 2953, 2813, 1686 (s), 1641 (s), 1608 (s), 1550, 1489 (s), 1321, 1264, 1249 (s), 1220, 1174, 1115, 862, 802 cm^{-1}; MS (ESI+) *m/z* 433 (100, $(M+H)^+$), 434 (28). Anal. Calcd for $C_{26}H_{28}N_2O_4$: C, 72.20; H, 6.53; N, 6.48. Found: C, 72.30; H, 6.57; N, 6.46.

Preparation 6i

Ethyl 1-(1,3-Benzodioxol-5-yl)-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-quinolinecarboxylate [A.4, W = morpholinylmethyl, aryl = 3,4-methylenedioxy-phenyl].

Ethyl 3-(1,3-benzodioxol-5-ylamino)-2-(2-fluoro-5-(4-morpholinylmethyl)benzoyl)-2-propenoate (Procedure 5i, 2.53 g) is reacted according to general method C for 8 h. The resulting precipitate is filtered and recrystallized from ethanol to afford 1.55 g (64%) of the title compound as a gray solid. Physical characteristics: M.p. 173-174

°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.41, 8.18, 7.61, 7.33, 7.16, 7.13, 7.03, 6.20, 4.21, 3.58, 2.36, 1.26; ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.4, 164.5, 148.9, 148.7, 148.6, 140.3, 135.3, 134.5, 133.8, 127.6, 126.3, 121.7, 118.6, 110.6, 109.3, 109.0, 102.7, 66.5, 62.0, 60.2, 56.4, 53.4, 18.9, 14.6; IR (diffuse reflectance) 3046 (w), 2804, 1691, 1644, 1608, 1489 (s), 1452 (w), 1349 (w), 1321, 1277 (w), 1250, 1225 (s), 1117, 1031, 866 (w) cm^{-1}; MS (ESI+) *m/z* 437 (100, $(M+H)^+$), 438 (23); HRMS calcd for $C_{24}H_{24}N_2O_6$+H *m/z* 437.1712, found 437.1714. Anal. Calcd for $C_{24}H_{24}N_2O_6$: C, 66.04; H, 5.54; N, 6.42. Found: C, 65.80; H, 5.67; N, 6.33.

Preparation 6j

Ethyl 1-(1*H*-Indol-5-yl)-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-quinoline-carboxylate [A.4, W = morpholinylmethyl, aryl = 5-indole].

Ethyl 2-(2-fluoro-5-(4-morpholinylmethyl)benzoyl)-3-(1*H*-indol-5-ylamino)-2-propenoate (Procedure 5j, 2.94 g) is reacted according to general method C for 2 h. The resulting mixture is extracted with EtOAc (3 x 50 mL). The combined organic layers are washed with brine (5 mL), dried (Na_2SO_4), and concentrated. The crude product is purified by column chromatography (CH_2Cl_2/methanol, 50/1; 33/1; 25/1; 13/1) to afford 1.98 g (71%) of the title compound as a white solid. Physical characteristics: M.p. 207-210 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.55, 8.49, 8.20, 7.82, 7.63, 7.58, 7.56, 7.26, 6.97, 6.58, 4.21, 3.57, 2.36, 1.25; ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.4, 164.6, 149.3, 140.7, 136.1, 135.2, 133.7, 132.8, 128.4, 127.6, 126.3, 120.2, 119.3, 119.0, 113.1, 110.3, 102.3, 66.5, 62.1, 60.1, 56.4, 53.4, 14.6; IR (diffuse reflectance) 3313, 1721 (s), 1683, 1628, 1605 (s), 1485 (s), 1349, 1319, 1291, 1250, 1234, 1181, 1119, 821, 732 cm^{-1}; MS (ESI+) *m/z* 432 (100, $(M+H)^+$), 433 (26). Anal. Calcd for $C_{25}H_{25}N_3O_4$: C, 69.59; H, 5.84; N, 9.74. Found: C, 69.36; H, 5.95; N, 9.61.

Preparation 6k

Ethyl 1-(3-Hydroxyphenyl)-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-quinoline-carboxylate [A.4, W = morpholinylmethyl, aryl = 3-hydroxyphenyl].

Ethyl-2-(2-fluoro-5-(4-morpholinylmethyl)benzoyl)-3-(3-hydroxyanilino)-2-propenoate (Procedure 5k, 2.78 g, 6.5 mmol) is reacted according to general method C for 2 h. The resulting mixture is extracted with EtOAc (3 x 50 mL). The combined organic layers are washed with brine (5 mL), dried (Na_2SO_4), and concentrated. The aqueous layer is neutralized with saturated aqueous ammonium chloride and the resulting precipitate is filtered and combined with the preceding concentrate. The crude product is purified by column chromatography (CH_2Cl_2/methanol, 50/1; 33/1; 20/1; 13/1) to afford 1.33 g (50%) of the title compound as a white solid. Physical characteristics: M.p. 245-246 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.14, 8.41, 8.18, 7.62, 7.46, 7.05-7.02, 6.97, 4.21, 3.57, 2.36, 1.26; IR (diffuse reflectance) 1719 (s), 1608 (s), 1549, 1488 (s), 1467, 1449, 1366, 1350, 1327, 1226 (s), 1173, 1116, 1089, 866, 811 cm^{-1}; MS (ESI+) *m/z* 409 (100, $(M+H)^+$), 410 (24), 431 (66, $(M+Na)^+$). Anal. Calcd for $C_{23}H_{24}N_2O_5$: C, 67.63; H, 5.92; N, 6.86. Found: C, 67.54; H, 5.98; N, 6.84.

Preparation 6l

Ethyl 1-(3-(2-Hydroxyethyl)phenyl)-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-quinolinecarboxylate [A.4, W = morpholinylmethyl, aryl =3-(2-hydroxyethyl)-phenyl].

Ethyl 2-(2-fluoro-5-(4-morpholinylmethyl)benzoyl)-3-(3-(2-hydroxyethyl)anilino)-2-propenoate (Procedure 5l, 2.73 g) is reacted according to general method C for 2 h. The resulting mixture is extracted with EtOAc (3 x 50 mL). The combined organic layers are washed with brine (5 mL), dried (Na_2SO_4), and concentrated. The crude product is purified by recrystallization from EtOAc/hexane to afford 1.85 g (71%) of the title compound as a light yellow solid. Physical characteristics: M.p. 161-162 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.43, 8.20, 7.61, 7.57 (d, J = 7.5 Hz, 1 H), 7.52-7.46, 6.98, 4.70, 4.22, 3.68, 3.58, 2.84, 2.37, 1.26; ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.3, 164.6, 148.5, 142.8, 140.6, 139.9, 135.4, 133.9, 130.8, 130.3, 128.2, 127.6, 126.4, 125.3, 118.5, 110.7, 66.5, 62.0, 61.9, 60.2, 53.4, 14.6; IR (diffuse reflectance) 3418, 2951, 2932, 1680 (s), 1634, 1607 (s), 1548, 1487 (s), 1360, 1322 (s), 1275,

1251 (s), 1133, 1114, 808 cm^{-1}; MS (ESI+) *m/z* 437 (100, $(M+H)^+$), 438 (15). Anal. Calcd for $C_{25}H_{28}N_2O_5$: C, 68.79; H, 6.47; N, 6.42. Found: C, 68.68; H, 6.51; N, 6.36.

Preparation 6m

Ethyl 1-(3-methoxyphenyl)-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-quinolinecarboxylate [A.4, W = morpholinylmethyl, aryl = 3-methoxyphenyl].

According to general method C, ethyl 2-(2-fluoro-5-(4-morpholinylmethyl)benzoyl)-3-(3-methoxyanilino)-2-propenoate (Preparation 5m, 0.44 g) affords after recrystallization from ethanol 295 mg (70%) of the title compound as a light yellow solid. Physical characteristics: M.p. 199-202 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 8.43, 8.19, 7.63-7.55, 7.30, 7.21, 7.00, 4.21, 3.8, 3.60-3.55, 2.38-2.36, 1.27; IR (diffuse reflectance) 1724 (s), 1602 (s), 1489, 1403, 1361, 1317, 1269, 1229, 1219, 1161, 1156, 1132, 1113, 1085, 1033 cm^{-1}; MS (ESI) *m/z* 423 $(M+H)^+$. Anal. Calcd for $C_{24}H_{26}N_2O_5$: C, 68.23; H, 6.20; N, 6.63. Found: C, 68.29; H, 6.25; N, 6.54.

Preparation 6n

Ethyl 1-[3-(hydroxymethyl)phenyl]-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-quinolinecarboxylate [A.4, W = morpholinylmethyl, aryl = 3-(hydroxymethyl)phenyl].

According to general method C, ethyl-2-(2-fluoro-5-(4-morpholinylmethyl)benzoyl)-3-(2-(hydroxymethyl)anilino)-2-propenoate (Preparation 5n, 1.2 g) affords after recrystallization from ethanol 257 mg (23%) of the title compound as a light yellow solid. Physical characteristics: M.p. 193-196 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 8.42, 8.20, 7.66-7.50, 6.95, 5.41, 4.62, 4.21, 3.60-3.53, 2.36, 1.26; IR (diffuse reflectance) 3389, 1715 (s), 1605 (s), 1552, 1487 (s), 1360, 1348, 1320, 1247, 1217, 1167, 1118, 1087, 864, 808 cm^{-1}; MS (ESI) *m/z* 423 $(M+H)^+$. Anal. Calcd for $C_{24}H_{26}N_2O_5$: C, 68.23; H, 6.20; N, 6.63. Found: C, 68.08; H, 6.18; N, 6.59.

576

Preparation 6o

Ethyl 6-(4-morpholinylmethyl)-1-[4-(4-morpholinyl)phenyl]-4-oxo-1,4-dihydro-3-quinolinecarboxylate [A.4, W = morpholinylmethyl, aryl = 4-morpholinylphenyl].

According to general method C, ethyl 2-(2-fluoro-5-(4-morpholinylmethyl)benzoyl)-3-(4-(4-morpholinyl)anilino)-2-propenoate (Procedure 5o, 1.8 g) affords 1.27 g (75%) of the title compound. Physical characteristics: M.p. 214-217 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38, 8.18, 7.60, 7.46, 7.15, 7.00, 4.21, 3.78, 3.58, 3.25, 2.36, 1.26; IR (diffuse reflectance) 1732 (s), 1630, 1609 (s), 1516 (s), 1485, 1361, 1332, 1320, 1261, 1246 (s), 1217, 1119 (s), 1086, 925, 833 cm^{-1}; HRMS (FAB) calcd for $C_{27}H_{31}N_3O_5$+H *m/z* 478.2342, found 478.2358.

Preparation 6p

Ethyl 1-(3,4-difluorophenyl)-6-(4-morpholinylmethyl)-4-oxo-1,4-dihydro-3-quinolinecarboxylate [A.4, W = morpholinylmethyl, aryl = 3,4-difluorophenyl].

According to general method C, ethyl 3-(3,4-difluoroanilino)-2-(2-fluoro-5-(4-morpholinylmethyl)benzoyl)-2-propenoate (Preparation 5p, 1.0 g) affords after recrystallization from ethanol 520 mg (37%) of the title compound as a yellow solid. Physical characteristics: M.p. 214-217 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.48, 8.18, 8.03-7.97, 8.00, 7.63-7.58, 7.01, 4.21, 3.60-3.54, 2.36, 1.27; IR (diffuse reflectance) 1695, 1639, 1608, 1517 (s), 1488, 1289, 1267, 1232, 1178, 1118, 1113, 865, 826, 803, 779 cm^{-1}; MS (ESI) *m/z* 429 $(M+H)^+$. Anal. Calcd for $C_{23}H_{22}F_2N_2O_4$: C, 64.48; H, 5.18; N, 6.54; F, 8.87. Found: C, 64.36; H, 5.22; N, 6.50; F, 8.99.

General Preparation A.5. A mixture of quinoline ester obtained according to General Preparation A.4 and a substituted benzylamine (5 equiv) is heated to 180 °C for a period of 1 - 24 h. The reaction mixture is allowed to cool to rt. The crude product may be either purified by column chromatography or precipitated by trituration with an appropriate solvent followed by recrystallization. The following compounds (Examples 1 - 18) are prepared according to these procedures.

D6 577 577



US005688791A

United States Patent [19]

Kimura et al.

[11] Patent Number: 5,688,791

[45] Date of Patent: Nov. 18, 1997

[54] **ARYL GROUP-OR AROMATIC HETEROCYCLIC GROUP-SUBSTITUTED AMINOQUINOLONE DERIVATIVES AND ANTI-HIV AGENT**

[75] Inventors: **Tomio Kimura**; **Tetsushi Katsube**, both of Ube, Japan

[73] Assignee: **UBE Industries, LTD.**, Ube, Japan

[21] Appl. No.: **526,225**

[22] Filed: **Sep. 11, 1995**

Related U.S. Application Data

[62] Division of Ser. No. 341,295, Nov. 15, 1994, Pat. No. 5,519,016, which is a continuation of Ser. No. 066,985, May 25, 1993, abandoned.

[30] **Foreign Application Priority Data**

May 27, 1992 [JP] Japan 4-158912

[51] **Int. Cl.**[6] **A61K 31/54**; A61K 31/535; C07D 401/02; C07D 403/02

[52] **U.S. Cl.** **514/224.5**; 514/230.2; 514/250; 514/253; 514/294; 514/934; 546/80; 546/81; 546/82; 546/83; 546/84; 544/32; 544/101; 544/344; 544/361

[58] **Field of Search** 544/32, 101, 344, 544/361; 546/80–84, 94; 514/934, 224.5, 230.2, 250, 253, 294

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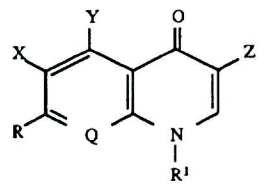
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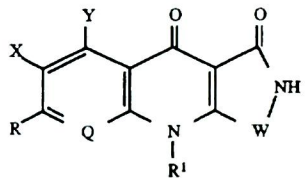
Attorney, Agent, or Firm—Frishauf, Holtz, Goodman, Langer & Chick, P.C.

[57] **ABSTRACT**

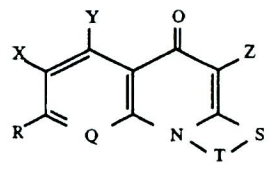
Disclosed are an aryl group- or heterocyclic group-substituted aminoquinolone compound represented by the formula (Ia), (Ib) or (Ic):



(Ia)



(Ib)



(Ic)

wherein each of the substitutents are defined in the specification,

or a salt of the compound, and an AIDS curing agent containing the same as an effective ingredient.

21 Claims, No Drawings

ARYL GROUP-OR AROMATIC HETEROCYCLIC GROUP-SUBSTITUTED AMINOQUINOLONE DERIVATIVES AND ANTI-HIV AGENT

This is a continuation division of application Ser. No. 08/341,295 filed Nov. 15, 1994, now U.S. Pat. No. 5,519,016 which is a continuation of application Ser. No. 08/066,985 filed May 25, 1993 now abandoned.

BACKGROUND OF THE INVENTION

The present invention relates to derivatives of aminoquinolone, and uses therefor.

AIDS (Acquired Immuno-deficiency Syndrome) is now generally accepted as being caused by the Human Immunodeficiency Virus (HIV).

The aetiology of AIDS is not yet precisely known, but it is known that HIV mainly infects CD_4 lymphocytes, generally of the class of helper/inducer cells. Lymphocyte numbers gradually decrease, and this eventually leads to severe cellular immunodeficiency.

Very considerable research has been put into finding a cure for AIDS, but the development of a vaccine has proven extremely difficult. Accordingly, other avenues have also been pursued. One such avenue is the development of antiviral agents.

An antiviral agent currently on the market for the treatment of AIDS is AZT (Azidothymidine). The method of action of AZT is to inhibit the inherent reverse transcriptase of HIV, thus retarding or stopping reproduction of the virus. However, such a treatment can, at the best, only prolong life expectancy, and cannot cure AIDS completely. Other antiviral agents which have been developed act in a similar fashion.

Such inhibitory agents are also associated with side effects, such as disorders of the bone marrow and digestive system, and it has also been found that tolerance, or even total resistance, can be induced in the virus with a high frequency. Such resistant viruses can be generated even in patients receiving long-term therapy.

In order to overcome the above problems, it would be highly desirable to develop new antiviral agents which could be used either alone, or in combination therapy with known agents.

Anti-HIV activity has recently been reported for the compound DR-3355, which is an optical isomer (S-isomer) of Ofloxacin, a synthetic anti-bacterial agent. Ofloxacin has a quinolone skeleton [J. Nozaki, Renard et al., AIDS (1990), 4, p. 1283]. Attempts by the present inventors to reproduce the antiviral activity of DR-3355, using the method of R. Pauwel, et al., (infra), have failed.

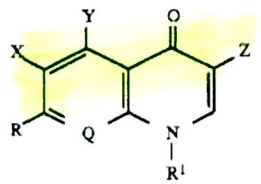
WO-A-90-13542 discloses the anti-HIV activity of Norfloxacin, Enoxacin, Ciprofloxacin, Lomefloxacin, Difloxacin and Tosufloxacin but, again, these compounds demonstrate little or no anti-HIV activity when tested by the Pauwel method. These compounds also possess a quinolone skeleton.

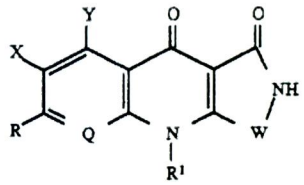
SUMMARY OF THE INVENTION

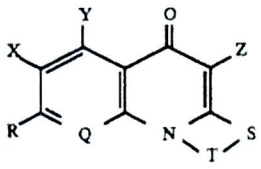
We have now discovered a series of new quinolone derivatives which, whilst exhibiting considerably weaker antibacterial activity than those quinolone derivatives described above, exhibit very considerably enhanced anti-HIV activity. The new compounds disclosed herein have increased lipophilicity, and possess a diamine substituent

which is, itself, further substituted by an aromatic group, such as an aryl group or an aromatic heterocyclic group. The compounds of the invention are both capable of inhibiting HIV replication and inhibiting the cytopathic effect (CPE) of HIV, and so are useful as agents to inhibit HIV replication and as anti-AIDS agents.

In a first aspect, the present invention provides a compound of the general formula (Ia), (Ib) or (Ic):


(Ia)


(Ib)


(Ic)

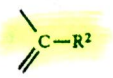
in which

X represents a hydrogen atom or a halogen atom;

Y represents a hydrogen atom, a halogen atom, a lower alkyl group, an amino group, or an amino group substituted by one or two groups selected from lower alkyl and aralkyl groups;

Z represents a carboxyl group or a 5-tetrazolyl group;

Q represents a nitrogen atom or a group of formula (d):


(d)

where R^2 represents a hydrogen atom, a halogen atom, a lower alkoxy group, a lower alkoxy group substituted by one or more halogen atoms, a lower alkyl group, a lower alkyl group substituted by one or more halogen atoms;

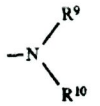
W represents an oxygen atom or a sulfur atom;

T represents a C_{1-4} alkylene group or a C_{2-4} alkenylene group, said groups optionally being substituted by a lower alkyl group;

R^1 represents: a hydrogen atom; a lower alkenyl group which may optionally be substituted by one or more halogen atoms; a lower alkynyl group; an amino group which may optionally be substituted by one or more lower alkyl groups; a cycloalkyl group which may optionally be substituted by at least one halogen atom; a lower alkoxy group; an aryl group which may optionally be substituted by at least one substituent R^o as defined below; a 5- or 6-membered aromatic heteromonocyclic group having one or two heteroatoms selected from N, O and S, said ring optionally being substituted by at least one substituent R^o as defined below; a fused aromatic group consisting of a benzene ring fused with a 5- or 6-membered aromatic heteromonocyclic group as defined above, said fused group

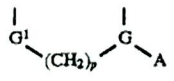
optionally being substituted by at least one substituent R^0 as defined below; a lower alkyl group; or a lower alkyl group substituted by at least one substituent selected from

halogen atoms, hydroxyl groups, carboxyl groups, alkanoyloxy groups, cycloalkyl groups, aryl groups which may optionally be substituted by at least one substituent R^0 as defined below, 5- or 6-membered aromatic heteromonocyclic groups having one or two heteroatoms selected from N, O and S, said ring optionally being substituted by at least one substituent R^0 as defined below, fused aromatic groups as defined above, said fused group optionally being substituted by at least one substituent R^0 as defined below, or an amino group represented by the formula (e):



(e)

wherein R^9 and R^{10} separately represent a hydrogen atom or a lower alkyl group, or R^9 and R^{10}, together with the nitrogen atom to which they are attached, form a 3- to 7-membered saturated monocyclic group comprising at least one further heteroatom selected from N, O and S, or when Q is a group of formula (d), then R^1 and R^2 may together represent a group of formula (f):



(f)

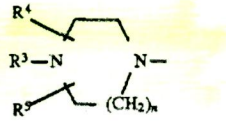
wherein A represents a hydrogen atom, or a lower alkyl group which may optionally be substituted by at least one substituent selected from halogen atoms, hydroxy and lower alkoxy groups; G represents a nitrogen atom or a group of formula (g):



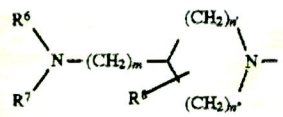
(g)

G^1 represents a methylene group, a carbonyl group, an oxygen atom, a sulfur atom or a group of formula $—N(R^{11})—$, where R^{11} represents a hydrogen atom or a lower alkyl group; and p=0 or 1;

R represents a group of formula (h) or (i):



(h)



(i)

where R^3 and R^6 each represents an aryl group which may optionally be substituted by at least one substituent R^0 as defined below; a 5- or 6-membered aromatic heteromonocyclic group having one or two heteroatoms selected from N, O and S, said ring optionally being substituted by at least one substituent R^0 as defined below; a fused aromatic group consisting of a benzene ring fused with a 5- or 6-membered aromatic heteromonocyclic group as defined above, said fused group optionally being substituted by at least one substituent R^0 as defined below;

R^4, R^5 and R^7 may be the same or different, and each represents a hydrogen atom or a lower alkyl group;

R^8 represents a hydrogen atom, a lower alkyl group, a hydroxy group or a lower alkoxy group;

n=1 or 2;

m=0 or 1;

n'=1 or 2; and

n"=1, 2, 3 or 4; and

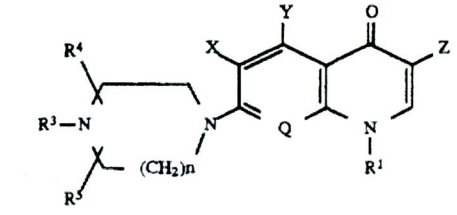
substituent R^0 are selected from halogen atoms, nitro groups, hydroxy groups, lower alkyl groups which may optionally be substituted with at least one halogen atom, lower alkoxy groups, and amino groups which may optionally be substituted with one or two lower alkyl groups, and when there are two or more substituents R^0, each may be the same or different,

or a pharmaceutically acceptable salt or ester thereof and an AIDS curing agent containing the compound represented by the above formula (Ia), (Ib) or (Ic) or an ester thereof as an active ingredient.

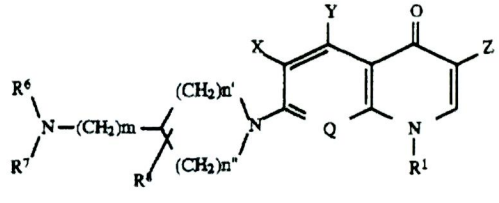
DESCRIPTION OF THE PREFERRED EMBODIMENTS

In the following, the present invention is explained in detail.

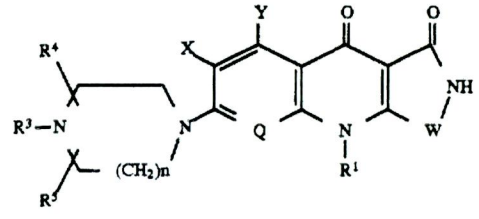
The compounds represented by the formula (Ia), (Ib) and (Ic) include compounds represented by the formulae (Ia-1), (Ib-1) and (Ic-1) and the formulae (Ia-2), (Ib-2) and (Ic-2) shown below.



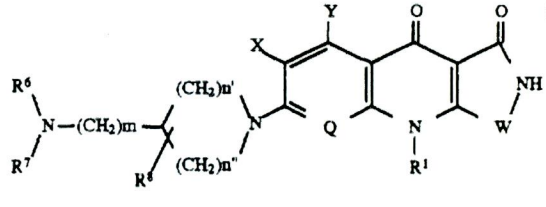
(Ia-1)



(Ia-2)



(Ib-1)



(Ib-2)

blue formazan produced by the reduction of MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide] which was added to the preparations.

CPE inhibitory activity was defined as 100% in non-infected cells to which no test compounds had been added, while CPE inhibitory activity was defined as 0% in infected cells to which test compounds had not been added. The effective concentration (EC_{50}) of the compound at which 50% CPE inhibition was observed in HIV infected cells was then determined. A second index was then generated, concerning cellular cytotoxic activity of the compounds, by calculating the concentration (CC_{50}) at which the test compounds caused 50% growth inhibition of non-infected cells.

Finally, a selective index (S.I.) was generated by calculating the value of CC_{50}/EC_{50}, to give an index of anti-HIV activity. The results are shown in Table 28.

Analysis of the preparations, at various stages, indicated that the cells and preparations consistently remained mycoplasma-free.

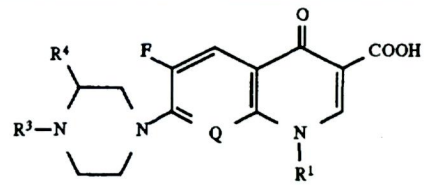
TABLE 28

Compound of Example	EC_{50} μg/ml	S.I.
1	0.015	400
2	0.03	100
6	0.02	34
7	0.22	113
8	0.1	500
17	0.5	250
18	0.07	121
19	0.07	57
21	0.037	16
23	0.021	309
24	0.07	257
29	0.05	22
37	0.23	>109
38	0.07	79
46	0.06	155
53	0.3	>83
63	0.01	1000
67	0.08	>500
(96)		
70	0.5	20
85	1.0	17
87	0.074	>512
92	0.8	31
94	0.5	21
95	0.4	>62
99	1.0	>25
100	0.4	9

As can be seen from the above Table, the compounds of the present invention are effective in very small doses, and also exhibit an extremely high selective index.

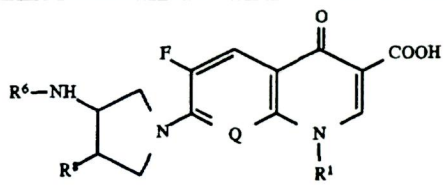
By contrast, the prior art compounds (shown in Tables 29 and 30 below), and which are known as antibacterials, all had an EC_{50} in excess of 100 μg/ml, when tested as above. Thus, the known compounds are at least 100 times less effective than the compounds of the present invention as anti-HIV agents.

TABLE 29



General name	Q	R^1	R^3	R^4
Enoxacin	=N−	Ethyl	H	H
Ciprofloxacin	=CH−	Cyclopropyl	H	H
Norfloxacin	=CH−	Ethyl	H	H
Ofloxacin	=C−O−CH_2−$CH(CH_3)$−		Methyl	H
DR-3355	=C−O−CH_2−$CH(CH_3)$-(s)		Methyl	H
Lomefloxacin	=CF−	Ethyl	H	Methyl
Fleroxacin	=CF−	2-Fluoroethyl	Methyl	H
Difloxacin	=CH−	4-Fluorophenyl	Methyl	H

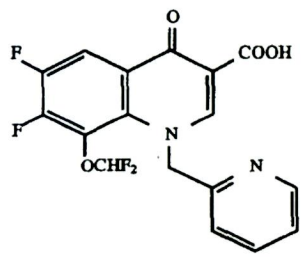
TABLE 30



General name	R^1	Q	R^6	R^8
Tosufloxacin	2,4-Difluorophenyl	=N−	H	H

Reference Example 1

Synthesis of 6,7-difluoro-8-difluoromethoxy-1-(2-pyridylmethyl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid



In 37 ml of toluene was dissolved 30 g (0.124 mole) of 2,4,5-trifluoro-3-difluoromethoxybenzoic acid, and 35 ml of thionyl chloride and 0.5 ml of N,N-dimethylformamide were added thereto. The mixture was refluxed by heating for 4 hours. After the reaction, toluene and excess thionyl chloride were removed under reduced pressure to obtain 2,4,5-trifluoro-3-difluoromethoxybenzoyl chloride.

Separately, 15.5 g (0.135 mole) of magnesium ethoxide and 20.9 g (0.130 mole) of diethyl malonate were refluxed by heating in 100 ml of anhydrous tetrahydrofuran for 2.5 hours under stirring to obtain a tetrahydrofuran suspension of diethyl ethoxy magnesium malonate. To the suspension was added dropwise a solution of the above acid chloride dissolved in 20 ml of tetrahydrofuran at room temperature under stirring, and the mixture was further stirred at room temperature for 2 hours. To the reaction mixture was added

581

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

202075
Bogotá, D.C., (23 de Noviembre de 2007).

Abogado
MARGARITA CASTELLANOS A.

ASUNTO		
	Radicación	04066836
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	15938
	Folios	035

Patente de Invención ■ Patente de Modelo de Utilidad □

Vía Nacional □

Vía PCT (fase nacional) □ Cap.I □ Cap. II ■

No. Sol. Internacional PCT/JP03/14773
Fecha de Presentación Internal. 22 de Noviembre de 2003.

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: 284 a 509 (como se radicó inicialmente)

1.2. Reivindicaciones: Folios: 510 a 547 (como se radicó inicialmente)

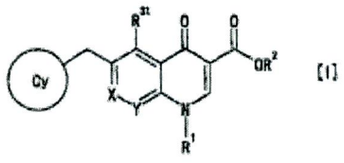
1.3. Prioridad: Folio 1 (20 de Noviembre de 2002, JP336843/2002).
(11 de Marzo de 2003, JP65807/2003).
(16 de Mayo de 2003, JP139616/2003).

2. Objeto de la invención

- Título de la solicitud: Compuesto de 4- oxoquinolina y aplicación del mismo como inhibidor de integrasa de VIH.

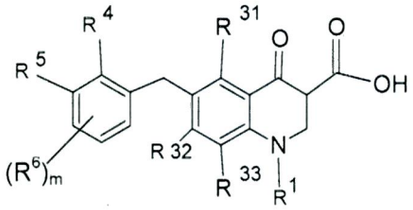
El objeto de la presente solicitud de patente de invención consiste en:
Compuesto de 4- oxoquinolina

Reivindicaciones 1-4 ,28 : Un agente antiVH caracterizado por un compuesto de fórmula I.



[I]

Reivindicaciones 5-22 : Un compuesto de fórmula (II).



Reivindicaciones 23,37 : Composición farmacéutica del compuesto de Fórmula II.
Reivindicación 24 :Un inhibidor de integrasa según reivindicaciones 1-22.
Reivindicación 25 : Un agente antiviral según reivindicaciones 5-22.
Reivindicación 26 : Un agente antiVH según reivindicaciones 5-22.
Reivindicación 27 : Una composición antiVH según reivindicaciones 1-22.
Reivindicaciones 29-31 : De uso.
Reivindicaciones 32-35 : Método terapéutico.
Reivindicación 36 : Una composición antiVH según reivindicaciones 5-22.
Reivindicación 38 :Una composición antiviral según reivindicaciones 5-22.
Reivindicaciones 39-41 : Un paquete comercial.

El problema planteado en esta solicitud es la necesidad de compuestos que posean una acción inhibitoria de la integrasa como agentes anti-VIH eficaz.

Para solucionar este problema técnico la solicitud en estudio proporciona compuestos de fórmula (I) procedimientos para su preparación y composiciones farmacéuticas que los contienen.

El objeto de la invención definido anteriormente se clasificó de acuerdo con la Clasificación Internacional de Patentes (IPC) : C07D215/56, C07D401/06, C07D409/06, C07D417/04, A61K31/4709, A61K31/5377, A61K31/4375, A61P31/12, A61P31/18.

3. De la solicitud de Patente

3.1. Descripción *(artículo 28 D. 486)*

- El término "pro-droga" del folio 352 debe ser eliminado , ya que los grupos estructurales que lo conforman no pueden ser claramente identificados. Se solicita realizar la corrección respectiva.

- Teniendo en cuenta la definición de los compuestos de fórmula I y II de los folios (510 a 547) , esta Dependencia se permite señalar que lo único que se encuentra dentro del aparte descriptivo son unos ejemplos de síntesis, (folios 359-433),combinaciones con otras sustancias activas (Folio 355-359) pero estas combinaciones no muestran ninguna ventaja técnica o inesperada ya que no se encuentran datos que las respalden (Folio 436-437) y formulaciones farmacéuticas de los compuestos de fórmula 1y 2 (folio 353).
- Se encuentran algunos ejemplos experimentales para los compuestos de fórmula I y II (folios 461-465) con su metodología . No todos los compuestos que se reivindican se encuentran sustentados y adicionalmente para los compuestos de los ejemplos 1-57 y 1-58 (que se encuentran afectados por novedad) no hay datos que revelen el efecto inesperado de la presente solicitud , por lo que tampoco se ve la ventaja cuando se hace la restricción especifica para los compuestos de fórmula II en los cuales el fenilo se encuentra sustituido . A pesar de que estos datos demuestran que los compuestos ejemplificados tienen una actividad inhibitoria (medición de VIH IC_{50}), no se muestra una ventaja sobre los del estado del arte más cercano , ya que no hay datos que permitan comparar un efecto superior o inesperado sobre estos ,ya que como es conocido con anterioridad los compuestos de 4-oxoquinolina, 3 carboxílicos tienen propiedades como agentes antiVIH,

En consecuencia, las reivindicaciones 1-28, 36-38 no encuentran sustento dentro del aparte descriptivo de la solicitud

Se requiere al solicitante ajustar su capítulo descriptivo y reivindicatorio de acuerdo a aquellas modalidades que son objeto de la invención y a las observaciones realizadas, teniendo cuidado de no ampliar la materia más allá de cómo se estableció originalmente.

3.2. Reivindicaciones *(artículo 30 D 486)*

- La reivindicación 1 y en consecuencia sus dependientes, no son claras ni concisas ya que resultan amplias y especulativas en el sentido que existen múltiples posibilidades de sustitución a nivel del compuesto de fórmula I para los radicales R^1,C y, R^{31}, R^{32} y R^{33} especificados de acuerdo con los parámetros de sustitución señalados . Por este motivo la característica esencial de las moléculas que corresponden a la estructura de la fórmula (I) no es representativa. Se le requiere al interesado definir o especificar las sustituciones que son relevantes para la invención.

- Para las reivindicaciones1,5, 8, 9,13,20y 21,se encuentran términos como : Anillo de carbono de C_3- C_{10} , grupo heterocíclico los cuales no son claros ni concisos ya que no se especifica el número de carbonos , tamaño de los anillos , si son mono o biciclicos etc. Se le requiere al interesado definir o especificar las sustituciones (si es por ejemplo pirrol, pirrolidina, fenilo etc) y los números de carbono a los que hace referencia y que son relevantes para la intención.

- Para la reivindicación 23, como se trata de una composición farmacéutica se recomienda incorporar el término " en una cantidad terapéutica eficaz.

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- Para la reivindicación 27, si se trata de una composición farmacéutica se recomienda incorporar el término " en una cantidad terapéutica eficaz.

- La reivindicación 27 no es clara ni concisa cuando se refiere a " y a otro o mas tipos de sustancia activa anti-VIH", no se entiende si se trata de una combinación farmacéutica o una composición farmacéutica. Además es amplia y especulativa en el sentido que existen múltiples posibilidades de combinaciones obtenidas con "y a otro o mas tipos de sustancia activa anti-VIH". Por este motivo la característica esencial de la combinación o composición no es representativa. Se le requiere al interesado definir o especificar las combinaciones o composiciones que son relevantes para la invención.

- La reivindicación 28 no es clara cuando enuncia " para terapia de combinación de múltiples droga con otro(s) agente(s) anti-VIH". Además es amplia y especulativa en el sentido que existen múltiples posibilidades de terapia de combinación obtenidas con "múltiples droga con otro(s) agente(s) anti-VIH". Por este motivo la característica esencial de la combinación no es representativa. Se le requiere al interesado definir o especificar las combinaciones que son relevantes para la invención.

- Para la reivindicaciones 36 - 38 como se trata de una composición farmacéutica se recomienda incorporar el término " en una cantidad terapéutica eficaz".

4. Unidad de invención *(artículo 25 D 486)*

Se aclara que, de acuerdo al Art 25 , el paquete comercial descrito en las reivindicaciones : 39-41. , **NO** presentan un concepto único inventivo , ya que los elementos que conforman el "paquete comercial " se caracterizan por estar dentro de un mismo paquete, más no por ser **un conjunto** de elementos necesarios para efectuar una función única . Por lo tanto carecen de unidad de invención.

5. Excepción a la patentabilidad *(artículo 20 D486 literal a)-d))*

Se aclara que, de acuerdo al Art 20 literal d) el método terapéutico de las reivindicaciones : 32-35, no es patentable.

6. Reivindicaciones relativas a un uso o a un uso distinto *(artículos 14 y 21 D 486)*

Se aclara que, de acuerdo con el Art 14, no se puede otorgar patente al uso de las reivindicaciones 29-31, porque no es un producto ni un procedimiento tecnológico.

7. Determinación del Estado de la Técnica

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es 20 de Noviembre de 2002, se consultaron las bases de datos y los archivos con que cuenta la entidad con fecha de publicación anterior y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud :

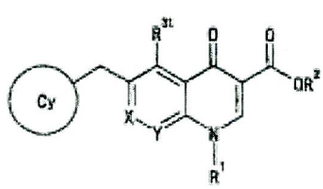
N°	Documento	Título	Fecha de Publicación*
D1	US3472859	1-ALKYL-1,4-DIHYDRO-4-OXO-3-QUINOLINE-CARBOXYLIC ACIDS AND ESTERS	14 de Octubre de 1969.
D2	JOURNAL OF MEDICINAL CHEMISTRY Tabla VI , VOL 15, No 3 pag 237.	IRREVERSIBLE ENZYME INHIBITORS 191.+,1 HYDROPHOBIC BONDING TO SOME DEHYDROGENASES BY 6-,7-,OR 8- SUBSTITUTED 4-QUINOLONE-3 CARBOXILIC ACIDS.	1972
D3	WO0204444	HETEROCYCLE CARBOXAMIDES AS ANTIVIRAL AGENTS.	17 de Enero de 2002.
D4	WO0040561	QUINOLINECARBOXAMIDES AS ANTIVIRAL AGENTS	13 de Julio de 2000.
D5	WO0198275	1-ARYL-4-OXO-1,4-DIHYDRO-3-QUINOLINE CARBOXAMIDES AS ANTIVIRAL AGENTS.	27 de Diciembre de 2001.
D6	US5688971	ARYL GROUP-OR AROMATIC HETEROCYCLIC GROUP SUBSTITUTED AMINOQUINOLONE DERIVATES AND ANTI-HIV AGENT.	18 de Noviembre de 1997.

8. Análisis de patentabilidad (artículo 14 D486)

8.1 Novedad (artículo 16 D486)

Comparando elemento por elemento el objeto de esta solicitud con lo mencionado en las anterioridades, tenemos que:

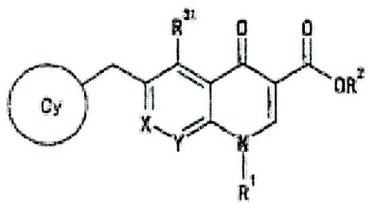
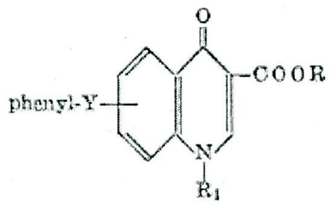
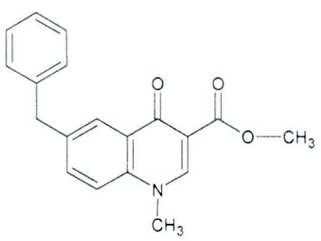
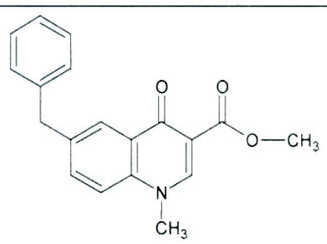
La presente Solicitud de Patente Colombiana No. 04066836, se refiere a:
Reivindicaciones 1-22 : Compuestos de la fórmula (I) :



[I]

D1(folios 557-558) enseña 4-oxoquinolinas caracterizadas por ser tener propiedades antibacteriales y antifùngicas.

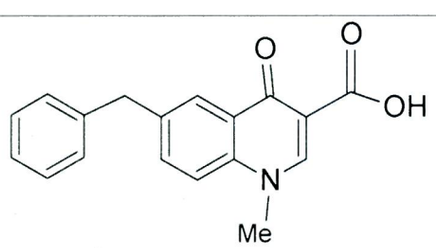
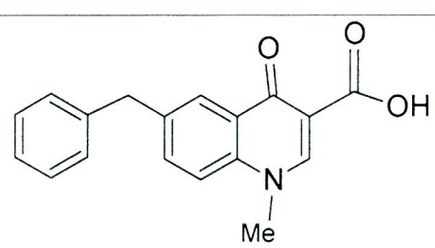
586

SOLICITUD	DOCUMENTO D1
 [I]	 (I)
	
En donde Cy es un anillo de carbono C_3-C_{10} (fenilo). R^1 es alquilo de C_1-C_{10}, R^2 es alquilo de C_1-C_4 R^{31} es hidrógeno. X es CR^{32} y Y es CR^{33} y , en donde R^{32} y R^{33} son hidrógeno.	En donde: R y R_1 son alquilo bajo . Y = CH_2 .

Este compuesto específico de la anterioridad D1 (Folio 557 columna 1 líneas 46-57 y columna 11 , ejemplo 8 líneas1-2 y 10-11) es igual al compuesto de la presente solicitud, tras hacer los reemplazos respectivos de sustituyentes.

Como se observa, el elemento característico del compuesto reivindicado en 1-4,28 : era conocido en D1 y está comprendido en el estado de la técnica, con lo cual se considera que NO cumple con el requisito de Novedad.

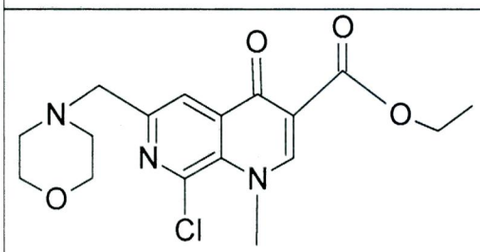
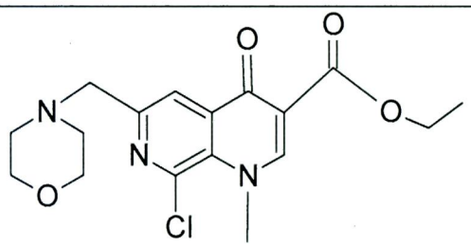
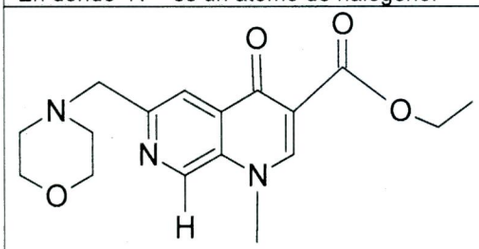
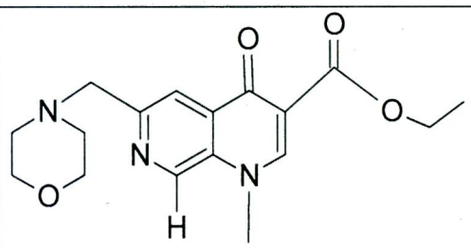
D2 (Folios 559) enseña compuestos derivados de 4-quinolona caracterizados por ser inhibidores de deshidrogenasa.

SOLICITUD	D2
	
En donde Cy es un anillo de carbono C_3-C_{10} (fenilo). R^1 es alquilo de C_1-C_{10}, R^2 y R^{31} son hidrógeno. X es CR^{32} y Y es CR^{33} y , en donde R^{32} y R^{33} son hidrógeno.	Tabla VI, compuesto25 en el que R es igual a 6-$C_6H_5CH_2$

Este compuesto específico de la anterioridad D2 (Folio 559) igual al compuesto de la presente solicitud, tras hacer los reemplazos respectivos de sustituyentes.

Como se observa, el elemento característico del compuesto reivindicado en 1-4,28 : era conocido en D2 y está comprendido en el estado de la técnica, con lo cual se considera que NO cumple con el requisito de Novedad.

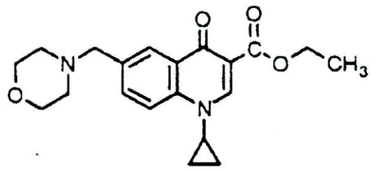
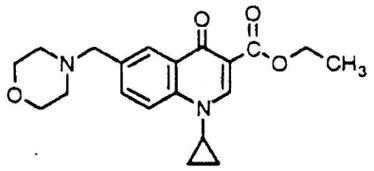
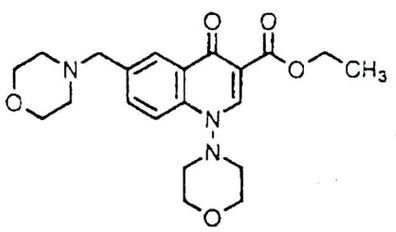
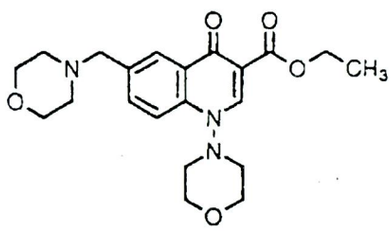
D3 (Folios 560-563) enseña carboxamidas heterocíclicas caracterizados por ser agentes antivirales principalmente para el virus del herpes.

SOLICITUD	D3
 En donde Cy es un anillo heterocíclico saturado con un átomo de Nitrógeno y otro de oxígeno. R^1 es alquilo de C_1-C_{10}, R^2 es alquilo de C_1-C_4 , R^{31} es hidrógeno. X es nitrógeno y Y es CR^{33} , En donde R^{33} es un átomo de halógeno.	 Compuesto de la preparación 45. Etil 8-Cloro-1-metil-6-(4-morfolinilmetil)-4-oxo-1,4 dihidro[1,7]-naftiridine-3 carboxilato.
 En donde Cy es un anillo heterocíclico saturado con un átomo de Nitrógeno y otro de oxígeno. R^1 es alquilo de C_1-C_{10}, R^2 es alquilo de C_1-C_4 , R^{31} es hidrógeno. X es nitrógeno y Y es CR^{33} , En donde R^{33} es hidrógeno.	 Compuesto de la preparación 46. Etil -1-metil-6-(4-morfolinilmetil)-4-oxo-1,4 dihidro[1,7]-naftiridine-3 carboxilato.

Estos compuestos específicos de la anterioridad D3 (Folio 562 y 563, líneas 21-24) igual a los compuestos de la presente solicitud, tras hacer los reemplazos respectivos de sustituyentes.

Como se observa, el elemento característico del compuesto reivindicado en 1-4,28 : era conocido en D3 y está comprendido en el estado de la técnica, con lo cual se considera que NO cumple con el requisito de Novedad.

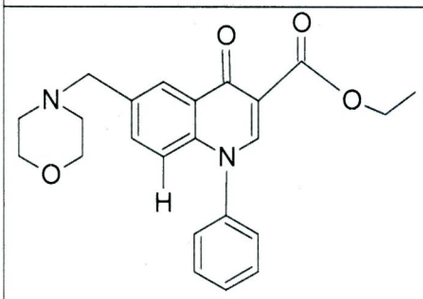
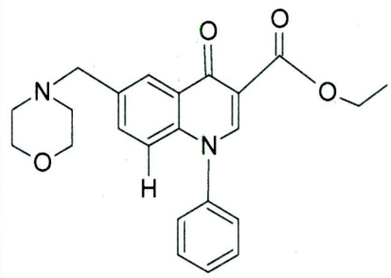
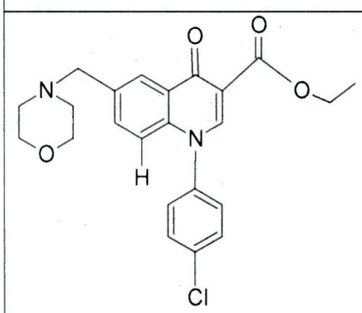
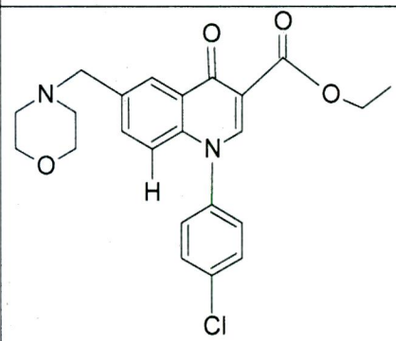
D4 (Folios 564-566) enseña carboxamidas de quinolinas caracterizadas por ser agentes antivirales principalmente para el virus del herpes.

SOLICITUD	D4
 En donde Cy es un anillo heterocíclico saturado con un átomo de Nitrógeno y otro de oxígeno. R^1 es un anillo de carbono de C_3-C_{10}, R^2 es alquilo de C_1-C_4 , R^{31} es hidrógeno. X y Y son , CR^{32} y CR^{33} respectivamente , En donde R^{32} y R^{33} son hidrógeno.	 Compuesto de la preparación 25. Etil -1-ciclopropil-6-(4-morfolinilmetil)-4-oxo-1,4-dihidro-3 quinolinacarboxilato.
 En donde Cy es un anillo heterocíclico saturado con un átomo de Nitrógeno y otro de oxígeno. R^1 es un grupo heterocíclico, saturado con un átomo de Nitrógeno y otro de oxígeno. R^2 es alquilo de C_1-C_4 , R^{31} es hidrógeno. X y Y son , CR^{32} y CR^{33} respectivamente , En donde R^{32} y R^{33} son hidrógeno.	 Compuesto de la preparación 56. Etil -1-(4-morfolinil)-6-(4-morfolinilmetil)-4-oxo-1,4-dihidro-3 quinolinacarboxilato.

Estos compuestos específicos de la anterioridad D4 (Folio 565 líneas18-24 y 566 líneas 1-6) son iguales a los compuestos de la presente solicitud, tras hacer los reemplazos respectivos de sustituyentes.

Como se observa, el elemento característico del compuesto reivindicado en 1-4,28 : era conocido en D4 y está comprendido en el estado de la técnica, con lo cual se considera que NO cumple con el requisito de Novedad.

D5 (Folios 567-576) enseña carboxamidas de quinolinas caracterizadas por ser agentes antivirales principalmente para el virus del herpes.

SOLICITUD	D5
 En donde Cy es un anillo heterocíclico saturado con un átomo de Nitrógeno y otro de oxígeno. R^1 es un anillo de carbono de C_3-C_{10}, R^2 es alquilo de C_1-C_4 , R^{31} es hidrógeno. X y Y son , CR^{32} y CR^{33} respectivamente , En donde R^{32} y R^{33} son hidrógeno.	 Compuesto de la preparación 6a.. Etil -6-(4-morfolinilmetil)-4-oxo-1-fenil-1,4-dihidro-3 quinolinacarboxilato.
 En donde Cy es un anillo heterocíclico saturado con un átomo de Nitrógeno y otro de oxígeno. R^1 es un un anillo de carbono de C_3-C_{10} sustituido por un átomo de halógeno. R^2 es alquilo de C_1-C_4 , R^{31} es hidrógeno. X y Y son , CR^{32} y CR^{33} respectivamente , En donde R^{32} y R^{33} son hidrógeno.	 Compuesto de la preparación 6d Etil -6-(4-morfolinilmetil)-4-oxo-1-(4-clorofenil)-1,4-dihidro-3 quinolinacarboxilato

Estos compuestos específicos de la anterioridad D5 (Folio 568 líneas 27-30 y 570 líneas 4-5) son iguales a los compuestos de la presente solicitud, tras hacer los reemplazos respectivos de sustituyentes. Si se mira las preparaciones de la (6a a 6p) de dicha anterioridad, se puede apreciar que puede haber más compuestos idénticos a compuestos de la actual solicitud, al hacer los correspondientes reemplazos de grupos sustituyentes.

Como se observa, el elemento característico del compuesto reivindicado en 1-4,28 : era conocido en D5 y está comprendido en el estado de la técnica, con lo cual se considera que NO cumple con el requisito de Novedad.

El inhibidor de integrasa de la (reivindicación 24) y la composición antiVH (reivindicación 27) no son nuevos porque el componente que lo caracteriza no es nuevo.

590

8.2. Nivel inventivo.

Se procede sobre las reivindicaciones 5-22 que no son afectadas por novedad realizar el análisis de nivel inventivo.

El documento del estado de la técnica más cercano es D6 (Folios 577-580) que enseña **Derivados de aminoquinolona con grupos arilo o heterociclos aromàticos sustituidos caracterizados por inhibir la replicación del virus del VIH**

La diferencia con D6 es que en esta solicitud los **Compuestos son derivados 4 – oxoquinolona sustituidos en la posición 6 por un grupo fenilo sustituido** y en la anterioridad son **Compuestos son derivados 4 – oxoquinolona insustituidos o sustituidos en la posición 6 por un àtomo de halògeno (Folio 578 columna 2, líneas 10-15 y líneas 33-64).**

Esta diferencia no parece conceder un efecto técnico inesperado ò una ventaja a los compuestos reivindicados en comparación con los compuestos del Estado de la Técnica más cercano; porque estos compuestos no tienen **efecto superior como inhibidores de la replicación del virus del VIH. (Ver folios 461-465)**

Así que el Problema Técnico planteado en esta solicitud que consiste en la necesidad de compuestos que posean una acción anti-VIH eficaz, se había solucionado previamente mediante compuestos muy similares de derivados de 4-oxoquinolona , sin tener un grupo fenilo sustituido en la posición 6. De manera que los nuevos compuestos **son una alternativa a los compuestos conocidos** porque **no presentan un efecto superior como inhibidores de la replicación del virus del VIH.**

El experto en la materia, en vista del Estado de la Técnica en su totalidad, es decir en vista de D6, hubiera sugerido sin mucho esfuerzo de su parte, modificar los grupos de D6(de la 4-oxoquinolona, 3 àcidos carboxílicos) **mediante la sustitución en la posición 6 por un grupo fenilo sustituido** , y así lograr los compuestos de 4-oxoquinolona reivindicados que no parecen tener un efecto superior como inhibidores de la replicación del virus del VIH.

Por lo cual se consideran obvios para el experto en la materia. En consecuencia, carecen de nivel inventivo.

La composición farmacéutica que contienen el compuesto reivindicado (reivindicaciones 23,37), el agente antiviral de la reivindicación 25 , el agente antiVH de la reivindicación 26 y la composición antiVH y antiviral de las reivindicaciones 36 y 38, carecen de nivel inventivo porque el componente que los caracteriza no es inventivo .

9. Conclusión:

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

591

591

N°	Documento N°	Reivindicaciones afectadas	Requisito que afecta
D1	US3472859	1-4, 24,27-28	Novedad
D2	JOURNAL OF MEDICINAL CHEMISTRY Tabla VI , VOL 15, No 3 pag 237.	1-4, 24,27-28	Novedad
D3	WO0204444	1-4, 24,27-28	Novedad
D4	WO0040561	1-4, 24,27-28	Novedad
D5	WO0198275	1-4, 24,27-28	Novedad
D6	US5688971	5-23, 25-26, 36-38	Nivel inventivo.

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 numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha 07 DIC. 2007

CONCEPTO TÉCNICO No. 2335	**EXAMINADOR TÉCNICO** Código No. 202075

J. ORG

04-66836

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

Señora

Jefe de la División de Nuevas Creaciones

Superintendencia de Industria y Comercio

Ministerio de Comercio, Desarrollo, Industria y Turismo

E. S. D.

RIA Y COMERCIO
03-0000
2020 NUECREACIONE
FASENACIONALI
Hos: 2

Re.: Expediente No. **04.066.836**
Solicitud de Patente de Invención para: **COMPUESTO 4-OXOQUINOLINA Y AOLICACION DEL MISMO COMO INHIBIDOR DE INTEGRASA DE VIH**
Solicitante: **JAPAN TOBACCO INC**

SOLICITUD DE PRORROGA DE TERMINO

Yo, Margarita Castellanos Abondano, identificada como aparece al pie de mi firma, obrando en mi calidad de apoderada de la sociedad solicitante de la solicitud de Patente de Invención citada en la referencia, atentamente solicito a Ud., que conforme al Artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se sirva conceder un plazo adicional de treinta (30) días, para cumplir con lo dispuesto en su Oficio No. 15938 Notificado por Fijación en Lista el 7 de Diciembre de 2007.

Adjunto el comprobante correspondiente a esta solicitud de prórroga.

Señora Jefe,

Margarita Castellanos Abondano
C.C. No. 39.779.654 de Usaquén
T.P.A. No.70819 del C. Sup. de la Judicatura
Calle 94 A No. 7 A - 09
Teléfonos: 610 74 20

Bogotá, D.C., 03 MAR. 2008

593

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 18,771
FECHA : MARZO 3 DE 2008

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
ALVARO CASTELLANOS	CONSIGNACION	BANCO DE BOGOTA	062754387	1483210	03/03/2008	1,763,000.00

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

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-08 PRORROGA DE TERMINOS	31	PRORROGA DE TERMINOS	75,000.00
			TOTAL : $	75,000.00

SON: SETENTA Y CINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

04-66836 594

S94

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

Señora
Jefe de la División de Nuevas Creaciones
Superintendencia de Industria y Comercio
Ministerio de Desarrollo Económico
E. S. D.

-00004-0000

Ref.: Expediente No. **04.066.836**
Solicitud de Patente de Invención para: **COMPUESTO 4-OXOQUINOLINA Y APLIICACION DEL MISMO COMO INHIBIDOR DE INTEGRASA DE VIH**
Solicitante: **JAPAN TOBACCO, INC**

RESPUESTA AL EXAMEN DE FONDO

MARGARITA CASTELLANOS ABONDANO, mayor de edad, identificada y domiciliada como aparece al pié de mi firma, atentamente me permito presentar respuesta al oficio No. 15338 notificado por fijación en lista el 7 de diciembre de 2007 correspondiente al examen de fondo, estando dentro del término legal en los siguientes términos:

En primer lugar, presento nuevo capítulo reivindicatorio sobre el cual solicito se realice el examen de patentabilidad y en cual se han realizado las modificaciones que enuncio a continuación:

Reivindicaciones

Las reivindicaciones 1-4 dirigida al compuesto de fórmula (I) han sido eliminadas del capítulo reivindicatorio. El nuevo capítulo reivindicatorio basado en las anteriores reivindicaciones 5 a 21 esta dirigido a los compuestos revelados en los ejemplos por lo que el nuevo capítulo reivindicatorio se encuentra debidamente sustentado en la descripción.

Los sustituyentes a lo largo del capítulo reivindicatorio han sido claramente definidos, por ejemplo los grupos heterociclos. Así mismo el término anillos de carbono de C_3-C_{10} ha sido eliminado del capítulo reivindicatorio.

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Bogotá, D.C., COLOMBIA

En cuanto a las composiciones farmacéuticas, se ha incluido el término una cantidad terapéuticamente eficaz siguiendo así la sugerencia del señor examinador.

Las reivindicaciones 27 y 28 objetadas han sido eliminadas del capítulo reivindicatorio.

Unidad de Invención

Con el fin de superar esta objeción, las reivindicaciones 39-41 han sido eliminadas del capítulo reivindicatorio.

Por otra parte, el solicitante ha decidido presentar una solicitud divisional de la presente invención la cual anexo al presente memorial.

Excepciones de Patentabilidad y usos

Las reivindicaciones 29-35 que reivindican métodos de tratamiento y usos han sido eliminadas del capítulo reivindicatorio por lo que las objeciones sobre dichas reivindicaciones deben tenerse como superadas.

Novedad

En cuanto a la novedad, su Despacho objetó la las reivindicaciones 1-4, 24, 27 y 28 por encontrase reveladas en estado de la técnica.

Teniendo en cuenta que las reivindicaciones 1-4, y 27 a 28 han sido eliminadas del capítulo reivindicatorio, la objeción por novedad debe tenerse como superada.

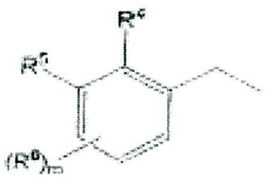
Nivel inventivo

El documento D6 en la columna 43, líneas 61-65 revela que los nueve compuestos mostrados en las tablas 29-30 conocidos por tener actividad antibacterial presentan actividad anti-VIH extremadamente baja y por lo tanto no son útiles para el tratamiento de VIH.

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Bogotá, D.C., COLOMBIA

Por otra parte, los compuestos de D6 y los nueve compuestos revelados en las tablas 29-30 comparten una estructura química común en la cual presentan un grupo carboxilo en la posición 3 y un átomo de flúor en la posición 6 del anillo de quinolina o naftiridina. Sin embargo, los compuestos de las tablas 29-30 demostraron tener baja actividad como agentes anti-VIH. Lo anterior claramente demuestra que **NO** todos los compuestos con estructura 4-oxoquinolina que presentan un grupo carboxilo en la posición 3 y un átomo de flúor en la posición 6 presentan actividad anti-VIH.

Es más, el compuesto de la presente invención presenta una diferencia aún mayor en cuanto a su estructura química en relación a D6 ya que presenta el siguiente sustituyente:



en la posición 6 del anillo de quinolina. Por lo tanto, una persona versada en la materia no llegaría a los compuestos de la presente invención con elevada actividad anti-VIH en vista de las enseñanzas del documento D6 y teniendo en cuenta que no todos los compuestos con el núcleo 4-oxoquinolina sustituidos en la posición 3 y 6 presentan actividad anti-VIH..

Ahora bien, los compuesto revelados en las reivindicaciones 19-21 presentan una actividad inhibitoria de la integrasa del VIH (IC50) no mayor a 1 μm, no mayor a 0.1μm y no mayor a 0.01 μm respectivamente (ver tablas 5-7). Según estos resultados, queda claro que los compuestos de la presente invención presentan actividad inhibitoria de la integrasa de VIH bastante elevada.

Por otra parte, si bien es cierto que los compuestos de la presente invención y los revelados en D1 son similares diferenciándose únicamente por la sustitución en la posición 6 del anillo de quinolona los compuestos de la presente invención muestran una mejora sustancial en cuanto a la actividad anti-VIH según los resultados expuestos anteriormente.

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En consecuencia, teniendo en cuenta que todas las objeciones de su Despacho han sido superadas con la modificación del capítulo reivindicatorio y los resultados experimentales de los compuestos reivindicados, solicito conceder el privilegio de patente a la presente invención.

Anexos

- Nuevo capítulo reivindicatorio
- Formato de Modificaciones
- Formulario de conversión, división y fusión
- Solicitud divisional
- Recibos de Pago

De la Señora Jefe,

Margarita Castellanos Abondano
C.C. No. **39.779.654** de Usaquén
T.P.A. No.**70819** del C. Sup. de la Judicatura
Calle 94 A No. 7 A - 09
Teléfonos: 610 74 20

Bogotá, D.C., 17 ABR. 2008

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Industria y Comercio
SUPERINTENDENCIA

Espacio reservado para el adhesivo de radicación

FORMULARIO ÚNICO DE CORRECCIONES Y MODIFICACIONES

1 SOLICITUD DE:

☐ **Corrección de Errror Material** ☒ **Modificación a una solicitud**

2 SOLICITANTE

Nombre: JAPAN TOBACCO INC.

Dirección: 2-1, Toranomon 2-chome,
Minato-ku,
Tokyo 105-8422
JAPON

Domicilio: Tokyo 105-8422
JAPON

Lugar de Constitución: JAPON

Teléfono: Fax:
E-mail:

IDENTIFICACIÓN

C.C. ☐ NIT ☐

C.E. ☐ Otro ☐

Cual _____

Número _____

3 REPRESENTANTE O APODERADO

Nombre: MARGARITA CASTELLANOS A.

Dirección: Calle 94 A No. 7 A-09

Teléfono: 610 7420 Fax: 610 0706

E-mail: mail@alvarocastellanos.com

IDENTIFICACIÓN

C.C. ☒ NIT ☐

C.E. ☐ Otro ☐

Cual

Número 39'779.654 TPA 70.819

4 Número de Expediente: 04.066.836

5 Descripción de la corrección o modificación solicitada:

Presento nuevo capítulo reivindicatorio sobre el cual solicito que se realice el examen de patentabilidad.

6 Comprobante de pago No. 08-31,184 **Fecha** 16 de abril de 2008

7 Anexos:

☒ Comprobante de pago de la tasa.
☒ Poderes si fuere el caso, junto con la sustitución de los mismos a mi favor.
☐ Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas
☒ Nuevo capítulo reivindicatorio

8

NOMBRE MARGARITA CASTELLANOS A. **FIRMA** Margarita Castellanos

17 ABR. 2008

CC 39'779.654 Usaquén - TPA 70.819 CSJ

Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página - P1087

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

...RIA Y COMERCIO
...00004-0000
...Sep 2020 NUECREACIONE
...de 378 FASENACIONALI
...Folios: 679

RECIBO OFICIAL DE CAJA : 08 - 31,184
FECHA : ABRIL 16 DE 2008

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
ALVARO CASTELLANOS	CONSIGNACION	BANCO DE BOGOTA	062754387	316186	16/04/2008	7,723,000.00

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

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-03 CAMBIO DE MODALIDAD Y MODIFICA	12	MARCAS Y LEMAS COMERCIALES	103,000.00
			TOTAL : $	103,000.00

SON: CIENTO TRES MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

6