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Señora Jefe de la
DIVISION DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-079188- -00004-0000

Fecha: 2009-02-27 16:43:57 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 538 PETICION Folios: 3

Trámite : 011
Evento : 378
Actuación : 538

Referencia : Expediente No. 07.079.188
Asunto : Solicitud de Patente para **1-H-PIRROL-2-CARBOXAMIDAS E IMIDAZOL-5-CARBOXAMIDAS Y SU USO COMO MODULADORES DE QUINASAS FAK, KDR Y TIE2 PARA EL TRATAMIENTO DEL CÁNCER**
Solicitante : **AVENTIS PHARMA S.A.**
Clase : A61K 031/040, A61K 31/4164, A61P 035/000,
Publicada en : La Gaceta No. **595** Del 29 de agosto de 2008
Fecha de Solicitud : 2 de agosto de 2007

1. Yo, Emilio FERRERO, identificado como aparece al pie de mi firma, actuando como apoderado en el asunto de la referencia, atentamente, solicito se efectúe el examen de patentabilidad de la solicitud en referencia presentada de acuerdo con el Capítulo I del PCT y según lo establecido en el artículo 44 de la Decisión 486 de la Comisión de la Comunidad Andina. Para tal efecto presento junto con este escrito el recibo por valor de \$452.000.00, que corresponde a la tasa fijada según lo dispuesto en la resolución No. 55819 de 26 de diciembre de 2008.

2. Ruego atentamente a la Señora Jefe se sirva ordenar que se anexe este recibo para que se efectúe dicho examen y se continúe con el trámite de la solicitud.

Señora Jefe,

EMILIO FERRERO
T.P.A. No. 31.929

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ASG\JGG\ID-145005\WPC12457
No. M-2009-145005\ASG

NIT 860.041.367-3

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 809176089-2

RECIBO OFICIAL DE CAJA : 09 - 3,019
FECHA : ENERO 14 DE 2009

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-079188- -00004-0000

Fecha: 2009-02-27 16:43:57 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 538 PETICION Folios: 3

CONSIGNACION

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	Nº. PAGO	FECHA PAGO	Vº. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO DE BOGOTÁ	042234387	102210922	13/01/2009	61,689,000.00

CONCEPTO

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50003-01-01	SOLICITUD	
		5	FRANQUES DE SOL. DE MODELO DE UTI
		TOTAL	317,000.00

SON: TRESCIENTOS DIEZ Y SIETE MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No.

Edo 12417-841024-1

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 806176089-2

RECIBO OFICIAL DE CAJA : 09 - 2,983
FECHA : ENERO 14 DE 2009

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-079188- -00004-0000

Fecha: 2009-02-27 16:43:57 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 538 PETICION Folios: 3

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	VAL. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	102210922	13/01/2009	61,400.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
		B3 INDICACION DE UNA PRIORIDAD EN SI	150,000.00
		TOTAL :	\$ 150,000.00

SON: CIENTO CINCUENTA Y UNO MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

810 12451-891029-1

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Industria y Comercio
SUPERINTENDENCIA

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 07-79188

EL EXTRACTO DE LA PRESENTE SOLICITUD DE PATENTE DE INVENCION

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No 595 DE

FECHA 29 DE AGOSTO DE 2008 EL TÉRMINO HÁBIL SEÑALADO POR LA

LEY EXPIRA EL 26 DE NOVIEMBRE DE 2008

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

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____

NO X



US 20040138269A1

(19) **United States**(12) **Patent Application Publication** (10) **Pub. No.: US 2004/0138269 A1****Sun et al.**(43) **Pub. Date: Jul. 15, 2004**(54) **SUBSTITUTED PYRROLES AS KINASE
INHIBITORS****Publication Classification**(75) **Inventors: Connie Li Sun, Foster City, CA (US);
Peng Cho Tang, Moraga, CA (US);
Denise Ockey, Oakland, CA (US)**(51) **Int. Cl.⁷ A61K 31/4439; A61K 31/4025;
A61K 31/401; C07D 43/02**
(52) **U.S. Cl. 514/343; 514/422; 514/423;
546/276.4; 548/517; 548/518;
548/530****Correspondence Address:
FOLEY AND LARDNER
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007 (US)**(57) **ABSTRACT**(73) **Assignee: Sugan, Inc.**(21) **Appl. No.: 10/679,693**(22) **Filed: Oct. 7, 2003****Related U.S. Application Data**(60) **Provisional application No. 60/417,555, filed on Oct.
11, 2002.**

The present invention relates to certain substituted pyrroles which modulate the activity of protein kinases ("PKs"). The compounds of this invention are therefore useful in treating disorders related to abnormal PK activity. Pharmaceutical compositions comprising these compounds, methods of treating diseases utilizing pharmaceutical compositions comprising these compounds and methods of preparing them are also disclosed.

SUBSTITUTED PYRROLES AS KINASE INHIBITORS

BACKGROUND OF THE INVENTION

[0001] 1. Field of Invention

[0002] The present invention relates to certain substituted pyrroles which modulate the activity of protein kinases ("PKs"). The compounds of this invention are therefore useful in treating disorders related to abnormal PK activity. Pharmaceutical compositions comprising these compounds, methods of treating diseases utilizing pharmaceutical compositions comprising these compounds and methods of preparing them are also disclosed.

[0003] 2. State of the Art

[0004] PKs are enzymes that catalyze the phosphorylation of hydroxy groups on tyrosine, serine and threonine residues of proteins. The consequences of this seemingly simple activity are staggering; cell growth, differentiation and proliferation, i.e., virtually all aspects of cell life in one way or another depend on PK activity. Furthermore, abnormal PK activity has been related to a host of disorders, ranging from relatively non life threatening diseases such as psoriasis to extremely virulent diseases such as glioblastoma (brain cancer).

[0005] The PKs can be conveniently broken down into two classes, the protein tyrosine kinases (PTKs) and the serine-threonine kinases (STKs).

[0006] One of the prime aspects of PTK activity is their involvement with growth factor receptors. Growth factor receptors are cell-surface proteins. When bound by a growth factor ligand, growth factor receptors are converted to an active form which interacts with proteins on the inner surface of a cell membrane. This leads to phosphorylation on tyrosine residues of the receptor and other proteins and to the formation inside the cell of complexes with a variety of cytoplasm signaling molecules that, in turn, effect numerous cellular responses such as cell division (proliferation), cell differentiation, cell growth, expression of metabolic effects to the extracellular microenvironment, etc. For a more complete discussion, see Schlessinger and Ullrich, *Neuron*, 9:303-391 (1992) which is incorporated by reference, including any drawings, as if fully set forth herein.

[0007] Growth factor receptors with PTK activity are known as receptor tyrosine kinases ("RTKs"). They comprise a large family of transmembrane receptors with diverse biological activity. At present, at least nineteen (19) distinct subfamilies of RTKs have been identified. An example of these is the subfamily designated the "HER" RTKs, which include EGFR (epithelial growth factor receptor), HER2, HER3 and HER4. These RTKs consist of an extracellular glycosylated ligand binding domain, a transmembrane domain and an intracellular cytoplasm catalytic domain that can phosphorylate tyrosine residues on proteins.

[0008] Another RTK subfamily consists of insulin receptor (IR), insulin-like growth factor I receptor (IGF-1R) and insulin receptor related receptor (IRR). IR and IGF-1R interact with insulin, IGF-I and IGF-II to form a heterotetramer of two entirely extracellular glycosylated subunits and two β subunits which cross the cell membrane and which contain the tyrosine kinase domain.

[0009] A third RTK subfamily is referred to as the platelet derived growth factor receptor ("PDGFR") group, which includes PDGFR α , PDGFR β , CSFIR, c-kit and c-fms. These receptors consist of glycosylated extracellular domains composed of variable numbers of immunoglobulin-like loops and an intracellular domain wherein the tyrosine kinase domain is interrupted by unrelated amino acid sequences.

[0010] Another group which, because of its similarity to the PDGFR subfamily, is sometimes subsumed into the later group is the fetus liver kinase ("flk") receptor subfamily. This group is believed to be made up of kinase insert domain-receptor fetal liver kinase-1 (KDR/FLK-1, VEGF-R₂), flk-1R, flk-4 and fms-like tyrosine kinase 1 (flt-1).

[0011] A further member of the tyrosine kinase growth factor receptor family is the fibroblast growth factor ("FGF") receptor subgroup. This group consists of four receptors, FGFR₁₋₄, and seven ligands, FGF1-7. While not yet well defined, it appears that the receptors consist of a glycosylated extracellular domain containing a variable number of immunoglobulin-like loops and an intracellular domain in which the tyrosine kinase sequence is interrupted by regions of unrelated amino acid sequences.

[0012] Still another member of the tyrosine kinase growth factor receptor family is the vascular endothelial growth factor (VEGFTM) receptor subgroup. VEGF is a dimeric glycoprotein similar to PDGF but has different biological functions and target cell specificity in vivo. In particular, VEGF is presently thought to play an essential role in vasculogenesis and angiogenesis.

[0013] A more complete listing of the known RTK subfamilies is described in Plowman et al., *DN&P*, 7(6):334-339 (1994) which is incorporated by reference, including any drawings, as if fully set forth herein.

[0014] In addition to the RTKs, there also exists a family of entirely intracellular PTKs called "non-receptor tyrosine kinases" or "cellular tyrosine kinases." This latter designation, abbreviated "CTK," will be used herein. CTKs do not contain extracellular and transmembrane domains. At present, over 24 CTKs in 11 subfamilies (Src, Frk, Btk, Csk, Abl, Zap70, Fes, Fps, Fak, Jak and Ack) have been identified. The Src subfamily appear so far to be the largest group of CTKs and includes Src, Yes, Fyn, Lyn, Lck, Blk, Hck, Fgr and Yrk. For a more detailed discussion of CTKs, see Bolen, *Oncogene*, 8:2025-2031 (1993), which is incorporated by reference, including any drawings, as if fully set forth herein.

[0015] The serine/threonine kinases, STKs, like the CTKs, are predominantly intracellular although there are a few receptor kinases of the STK type. STKs are the most common of the cytosolic kinases; i.e., kinases that perform their function in that part of the cytoplasm other than the cytoplasmic organelles and cytoskeleton. The cytosol is the region within the cell where much of the cell's intermediary metabolic and biosynthetic activity occurs; e.g., it is in the cytosol that proteins are synthesized on ribosomes.

[0016] RTKs, CTKs and STKs have all been implicated in a host of pathogenic conditions including, significantly, cancer. Other pathogenic conditions which have been associated with PTKs include, without limitation, psoriasis, hepatic cirrhosis, diabetes, angiogenesis, restenosis, ocular

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diseases, rheumatoid arthritis and other inflammatory disorders, immunological disorders such as autoimmune disease, cardiovascular disease such as atherosclerosis and a variety of renal disorders.

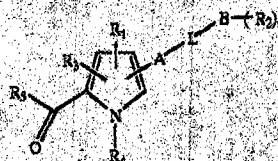
[0017] With regard to cancer, two of the major hypotheses advanced to explain the excessive cellular proliferation that drives tumor development relate to functions known to be PK regulated. That is, it has been suggested that malignant cell growth results from a breakdown in the mechanisms that control cell division and/or differentiation. It has been shown that the protein products of a number of proto-oncogenes are involved in the signal transduction pathways that regulate cell growth and differentiation. These protein products of proto-oncogenes include the extracellular growth factors, transmembrane growth factor PTK receptors (RTKs), cytoplasmic PTKs (CTKs) and cytosolic STKs, discussed above.

[0018] In view of the apparent link between PK-related cellular activities and wide variety of human disorders, it is no surprise that a great deal of effort is being expended in an attempt to identify ways to modulate PK activity. Some of this effort has involved biomimetic approaches using large molecules patterned on those involved in the actual cellular processes (e.g., mutant ligands (U.S. Pat. No. 4,966,849); soluble receptors and antibodies (App. No. WO 94/10202, Kendall and Thomas, *Proc. Nat'l Acad. Sci.*, 90:10705-09 (1994), Kim, et al., *Nature*, 362:841-844 (1993)); RNA ligands (Jelinek, et al., *Biochemistry*, 33:10450-56; Takano, et al., *Mol. Bio. Cell* 4:358A (1993); Kinsella, et al., *Exp. Cell Res.* 199:56-62 (1992); Wright, et al., *J. Cellular Phys.*, 152:448-57) and tyrosine kinase inhibitors (WO 94/03427; WO 92/21660; WO 91/15495; WO 94/14808; U.S. Pat. No. 5,330,992; Mariani, et al., *Proc. Am. Assoc. Cancer Res.*, 35:2268 (1994)).

[0019] In addition to the above, attempts have been made to identify small molecules which act as PK inhibitors. For example, bis-monocyclic, bicyclic and heterocyclic aryl compounds (PCT WO 92/20642), vinyleneazaindole derivatives (PCT WO 94/14808) and 1-cyclopropyl-4-pyridylquinolones (U.S. Pat. No. 5,330,992) have been described as tyrosine kinase inhibitors. Styryl compounds (U.S. Pat. No. 5,217,999), styryl-substituted pyridyl compounds (U.S. Pat. No. 5,302,606), quinazoline derivatives (EP App. No. 0 566 266 A1), selenaindoles and selenides (PCT WO 94/03427), tricyclic polyhydroxylic compounds (PCT WO 92/21660) and benzylphosphonic acid compounds (PCT WO 91/15495) have all been described as PTK inhibitors useful in the treatment of cancer.

SUMMARY OF THE INVENTION

[0020] In one aspect, the preferred embodiments of the present invention relate to a compound of the Formula I:



(I)

[0021] wherein

[0022] R_1 is H, alkyl, aryl or heteroaryl;

[0023] each R_2 is independently alkyl, cycloalkyl, aryl, heterocyclic, halo, hydroxy, cyano, nitro, $-N(R_3)_2$, trihaloalkyl, $-OR_6$, $-C(O)OR_6$ or $-C(O)NR_6R_7$;

[0024] R_3 or R_6 is independently selected from H and alkyl;

[0025] R_4 is selected from the group consisting of H, alkyl, cycloalkyl, aryl, heteroaryl, $-OR_6$ and $-SO_2R_6$;

[0026] R_5 is selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl, $-OR_6$ and $-NR_6R_7$;

[0027] R_6 and R_7 are each independently H, alkyl, cycloalkyl, aryl, arylalkyl, alkylaryl, heteroaryl, or heterocyclic, wherein said alkyl group can be substituted with heteroaryl or heterocyclic;

[0028] provided that when R_5 is $-NR_6R_7$, R_6 and R_7 , together with the nitrogen to which they are attached, may form a 5- or 6-membered heterocyclic ring;

[0029] L is a linker selected from the group consisting of $-(CH_2)_mC(O)NR_6(CH_2)_m-$, $-C(O)(CH_2)_mNR_6-$, $-NR_6-$, $-(CH_2)_mNR_6C(O)(CH_2)_m-$, $-NHC(O)NH-$ and $-O-$;

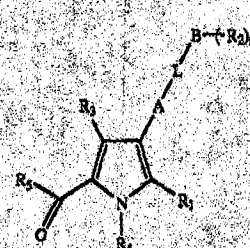
[0030] n is an integer from 0 to 5;

[0031] m is an integer from 0 to 3; and

[0032] A and B are each independently cycloalkyl, aryl or heteroaryl;

[0033] or a prodrug or pharmaceutically acceptable salt thereof.

[0034] In another aspect, the preferred embodiments of the present invention relate to a compound of the Formula II:



(II)

[0035] wherein:

[0036] R_1 , R_3 and R_6 are each independently H or alkyl;

[0037] each R_2 is independently alkyl, halo, trihaloalkyl or aryl;

[0038] R_4 is selected from the group consisting of H, alkyl, cycloalkyl, aryl, heteroaryl, $-OR_6$ and $-SO_2R_6$;

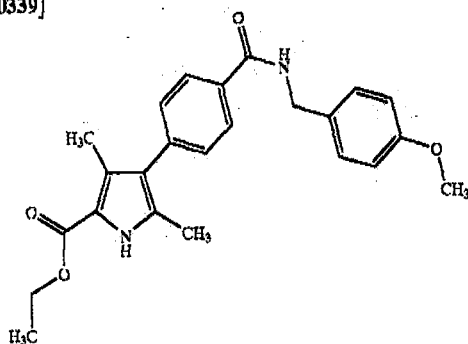
[0337] 4-(4-Carboxy-phenyl)-3,5-dimethyl-1H-pyrrole-2-carboxylic acid ethyl ester (110 mg, 0.4 mmol) was converted to acid chloride using oxalyl chloride (1.2 eq.) and DMF (1 drop) in DCM (20 mL). It was then coupled with 3-methoxy-benzylamine (137 mg, 1 mmol) in the presence of sodium bicarbonate (500 mg) to give 61 mg (30%) of the titled compound.

[0338] ¹HNMR (400 MHz, DMSO-d₆) δ 11.53 (br s, 1H, NH), 10.41 (s, 1H, NH), 7.89 (d, 2H), 7.32 (d, 2H), 7.22 (t, 1H), 6.88 (m, 2H), 6.79 (m, 1H), 4.45 (d, 2H), 4.22 (q, J=7 Hz, 2H), 3.72 (s, 3H, OCH₃), 2.21 (s, 3H, CH₃), 2.19 (s, 3H, CH₃), 1.28 (t, J=7 Hz, 3H). MS m/z 407 [M+1].

Example 22

4-[4-(4-Methoxy-benzylcarbamoyl)-phenyl]-3,5-dimethyl-1H-pyrrole-2-carboxylic Acid Ethyl Ester

[0339]



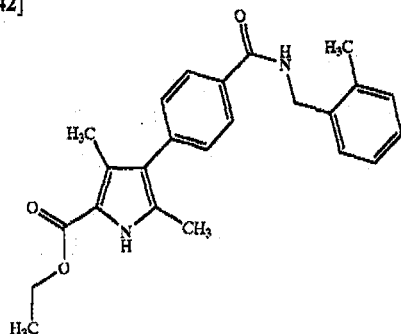
[0340] 4-(4-Carboxy-phenyl)-3,5-dimethyl-1H-pyrrole-2-carboxylic acid ethyl ester (100 mg, 0.35 mmol) was converted to acid chloride using oxalyl chloride (1.2 eq.) and DMF (1 drop) in DCM (20 mL). To the reaction was added 4-methoxy-benzylamine (96 mg, 0.7 mmol) and sodium bicarbonate (500 mg) to give 61 mg (30%) of the titled compound.

[0341] ¹HNMR (400 MHz, DMSO-d₆) δ 11.5 (br s, 1H, NH), 8.9 (t, 1H, NH), 7.88 (d, 2H), 7.31 (d, 2H), 7.23 (d, 2H), 6.87 (d, 2H), 4.40 (d, 2H), 4.22 (q, J=7 Hz, 2H), 3.07 (s, 3H, OCH₃), 2.21 (s, 3H, CH₃), 2.18 (s, 3H, CH₃), 1.28 (t, J=7 Hz, 3H). MS m/z 407 [M+1].

Example 23

3,5-Dimethyl-4-[4-(2-methyl-benzylcarbamoyl)-phenyl]-1H-pyrrole-2-carboxylic Acid Ethyl Ester

[0342]



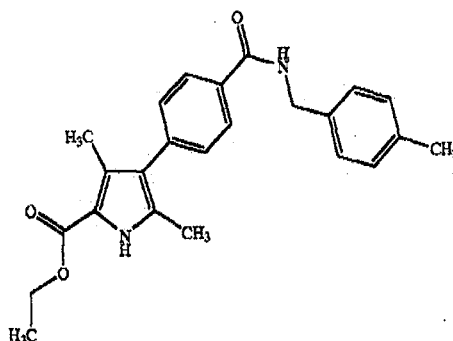
[0343] 4-(4-Carboxy-phenyl)-3,5-dimethyl-1H-pyrrole-2-carboxylic acid ethyl ester (100 mg, 0.35 mmol) was converted to acid chloride using oxalyl chloride (1.2 eq.) and DMF (1 drop) in DCM (20 mL). To the reaction was added 2-methyl-benzylamine (85 mg, 0.7 mmol) and sodium bicarbonate (500 mg) to give 28 mg of the titled compound.

[0344] ¹HNMR (400 MHz, DMSO-d₆) 811.49 (br s, 1H, NH), 8.9 (s, 1H, NH), 7.91 (d, 2H), 7.32 (d, 2H), 7.23 (m, 1H), 7.12 (m, 3H), 4.45 (d, 2H), 4.22 (q, J=7 Hz, 2H), 2.31 (s, 3H, CH₃), 2.22 (s, 3H, CH₃), 2.19 (s, 3H, CH₃), 1.28 (t, J=7 Hz, 3H). MS m/z 391 [M+1].

Example 24

3,5-Dimethyl-4-[4-(4-methyl-benzylcarbamoyl)-phenyl]-1H-pyrrole-2-carboxylic Acid Ethyl Ester

[0345]



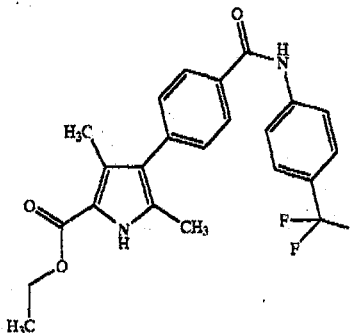
[0346] 4-(4-Carboxy-phenyl)-3,5-dimethyl-1H-pyrrole-2-carboxylic acid ethyl ester (100 mg, 0.35 mmol) was converted to acid chloride using oxalyl chloride (1.2 eq.) and DMF (1 drop) in DCM (20 mL). To the reaction was added 4-methyl-benzylamine (85 mg, 0.7 mmol) and sodium bicarbonate (500 mg) to give 32 mg (15%) of the titled compound.

[0347] ¹HNMR (400 MHz, DMSO-d₆) δ 11.53 (br s, 1H, NH), 8.9 (t, 1H, NH), 7.89 (d, 2H), 7.31 (d, 2H), 7.19 (d, 2H), 7.11 (d, 2H), 4.42 (d, J=6 Hz, 2H), 4.22 (q, J=7 Hz, 2H), 2.25 (s, 3H, CH₃), 2.21 (s, 3H, CH₃), 2.18 (s, 3H, CH₃), 1.28 (t, J=7 Hz, 3H). MS m/z 391 [M+1].

Example 25

1,3,5-Trimethyl-4-[4-(4-trifluoromethyl-phenylcarbamoyl)-phenyl]-1H-pyrrole-2-carboxylic Acid Ethyl Ester

[0348]

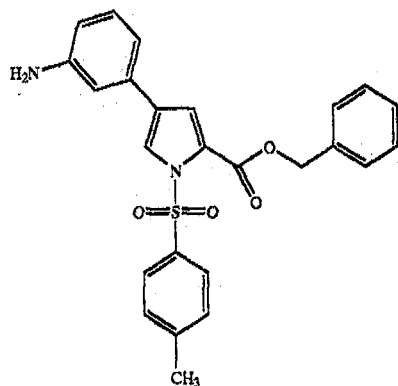


12H), 6.54 (s, 1H, NH), 6.37 (s, 1H, NH), 5.2 (s, 2H), 2.92 (m, 1H, CH), 2.42 (s, 3H, CH₃), 1.25 (d, J=7 Hz, 6H, 2xCH₃). MS m/z 606 [M-1].

Example 37

4-(3-Amino-phenyl)-1-(toluene-4-sulfonyl)-1H-pyrrole-2-carboxylic Acid Benzyl Ester

[0393]



[0394] A solution of sodium carbonate (2.3 g, 21 mmol) in 10 mL of water was added to a mixture of 4-iodo-1-(toluene-4-sulfonyl)-1H-pyrrole-2-carboxylic acid benzyl ester (2 g, 4 mmol; from Example 31) and 3-aminophenylboronic acid hemisulfate (1.2 g, 6.3 mmol) in DMF (40 mL) under nitrogen. After stirring at room temperature for one hour, to the mixture was added Pd(OAc)₂ (94 mg, 0.42 mmol). It was then heated to 70° C. under nitrogen for overnight. The reaction was filtered through celite, washing with ether. The aqueous layer was acidified with 6N HCl (dropwise) at 0° C. to pH 2. The precipitate was collected by vacuum filtration and dried to give the titled compound as a brown solid.

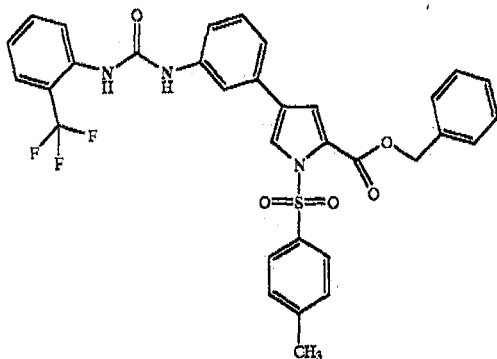
[0395] ¹HNMR (400 MHz, DMSO-d₆) δ 8.09 (d, J=2 Hz, 1H), 7.91 (d, J=8 Hz, 2H), 7.41 (d, J=8 Hz, 2H), 7.37 (d, J=2 Hz, 1H), 7.34 (m, 6H), 7.02 (m, 1H), 6.87 (m, 1H), 6.49 (m, 1H), 5.19 (s, 2H), 5.09 (br s, 2H, NH₂), 2.37 (s, 3H, CH₃).

[0396] MS m/z 445 [M-1].

Example 38

1-(Toluene-4-sulfonyl)-4-{3-[3-(2-trifluoromethyl-phenyl)-ureido]-phenyl}-1H-pyrrole-2-carboxylic Acid Benzyl Ester

[0397]



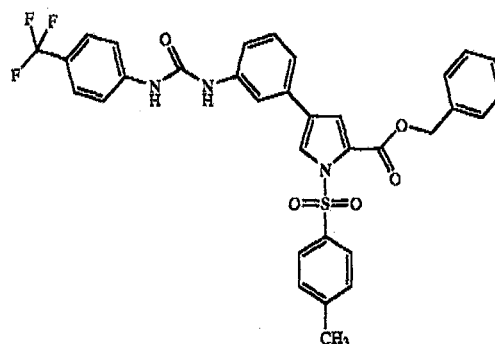
[0398] A mixture of 4-(3-amino-phenyl)-1-(toluene-4-sulfonyl)-1H-pyrrole-2-carboxylic acid benzyl ester (150 mg, 0.336 mmol; from Example 37) and trifluoro-o-tolyl isocyanate (1.5 eq.) in DCM (4 mL) was stirred at room temperature for 5 hours. The reaction was concentrated to give 155 mg (73%) of the titled compound as an off-white solid.

[0399] ¹HNMR (400 MHz, DMSO-d₆) δ 9.48 (s, 1H, NH), 8.22 (d, J=2 Hz, 1H), 8.15 (s, 1H, NH), 7.95 (d, J=8 Hz, 2H), 7.77 (m, 1H), 7.65 (m, 4H), 7.48 (d, J=2 Hz, 1H), 7.44 (d, J=8 Hz, 2H), 7.37 (m, 8H), 5.22 (s, 2H, OCH₂), 5.40 (s, 3H, CH₃). MS m/z 635 [M+1].

Example 39

1-(Toluene-4-sulfonyl)-4-{3-[3-(4-trifluoromethyl-phenyl)-ureido]-phenyl}-1H-pyrrole-2-carboxylic Acid Benzyl Ester

[0400]



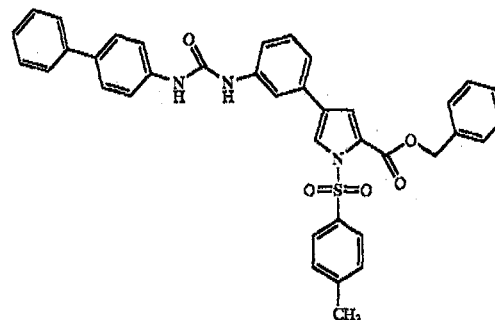
[0401] A mixture of 4-(3-amino-phenyl)-1-(toluene-4-sulfonyl)-1H-pyrrole-2-carboxylic acid benzyl ester (150 mg, 0.336 mmol; from Example 37) and trifluoro-p-tolyl isocyanate (1.5 eq.) in DCM (4 mL) was stirred at room temperature for 5 hours. The reaction was concentrated to give 156 mg (73%) of the titled compound as an off-white solid.

[0402] ¹HNMR (400 MHz, DMSO-d₆) δ 9.48 (s, 1H, NH), 9.12 (s, 1H, NH), 8.22 (d, J=2 Hz, 1H), 7.95 (d, J=8 Hz, 2H), 7.81 (m, 1H), 7.65 (m, 4H), 7.48 (d, J=2 Hz, 1H), 7.44 (d, J=8 Hz, 2H), 7.37 (m, 8H), 5.23 (s, 2H, CH₂), 2.40 (s, 3H, CH₃). MS m/z 634 [M+1].

Example 40

4-[3-(3-Biphenyl-4-yl-ureido)-phenyl]-1-(toluene-4-sulfonyl)-1H-pyrrole-2-carboxylic Acid Benzyl Ester

[0403]



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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCION DE NUEVAS CREACIONES

2020
Bogotá, D.C.

Abogado
✓ **EMILIO FERRERO**

ASUNTO

Radicación 07-79188
Trámite 011
Evento 378
Actuación 430
Oficio
Folios 009 **05868**

Patente de Invención

☒

Patente de Modelo de Utilidad

☐

Vía Nacional

☐

Vía PCT (Fase Nacional)

☒

Cap. I

☒

Cap. II

☐

No. Sol. Internacional

PCT/FR2006/000220

Fecha de Presentación Internacional

01/02/2006

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

Descripción: Folios 46 a 107 como se radicó inicialmente.

Reivindicaciones: Folios 108 a 115 como se radicó inicialmente.

Prioridad: Folio 2 FR 0501092 del 03/02/2005.

2. Análisis de la Prioridad

Se acepta la reivindicación de prioridad ya que esta solicitud fue presentada dentro del plazo establecido (Art. 9 D 486) y su contenido técnico corresponde con el de la prioridad reivindicada.

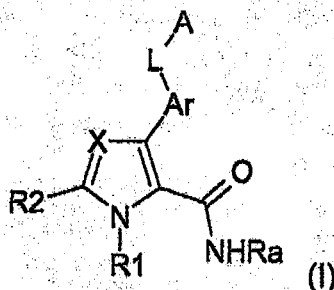
3. Objeto de la invención

Título: 1-H-PIRROL-2-CARBOXAMIDAS E IMIDAZOL-5-CARBOXAMIDAS Y SU USO COMO MODULADORES DE QUINASAS FAK, KDR Y TIE2 PARA EL TRATAMIENTO DEL CÁNCER.

Objeto: La solicitud consiste en compuestos derivados de pirrol de fórmula general (I) con actividad moduladora de quinasas FAK, KDR y TIE2 así como sus composiciones farmacéuticas.

El problema planteado es proveer nuevos compuestos moduladores de quinasas FAK, KDR y TEK con mejores propiedades de potencia y selectividad con respecto a los ya existentes con actividad antiproliferativa.

Para solucionar este problema técnico la solicitud proporciona derivados de 1-H-pirrol-2-carboxamida de fórmula (I) y sus composiciones farmacéuticas.



Se catalogó la invención según la IPC así: C07D 233/90, A61K 31/4164 y A61P 35/00

4. Reivindicaciones relativas a uso o a uso distinto (artículos 14 y 21 D 486)

Las reivindicaciones 22 a 25 se refieren al uso de compuestos de fórmula (I), lo cual no se considera como invención y por lo tanto no es patentable

5. De la solicitud de Patente

Título: Se recomienda modificar el título de forma tal que se excluya el término uso, ya que corresponde a materia no patentable.

Descripción (artículo 28 D 486)

La gran cantidad de compuestos formados por los sustituyentes de la fórmula general (I) no corresponden a la invención ya que los esquemas de síntesis indicados en la descripción (folios 61 a 63) indican solamente la síntesis de derivados de 1-H pirrol-2-carboxamida e imidazol-2-carboxamida donde los sustituyentes R1, Ra, R3, Ar, L y A son:

SUSTITUYENTE	SOPORTE EN LA DESCRIPCION
R1, R3 y Ra	Hidrógeno
Ar y A	Fenilo sustituido
L	NH-CO-NH

Por lo anterior, es evidente que la descripción no contiene la información suficiente para que una persona versada en la materia pueda obtener tal diversidad de compuestos.

De igual forma los ensayos de la actividad biológica están reportados solo para los compuestos con dichas sustituciones.

Reivindicaciones (artículo 30 D 486)

En el capítulo reivindicatorio se encuentran términos tales como arilo, arilo sustituido, alquilo, heteroarilo y heterociclo que son muy generales y no son concisos.

Los sustituyentes R1, Ra, R3, Ar, L y A de la fórmulas (I) de la reivindicación independiente generan un gran número de compuestos que no corresponden a la invención de acuerdo a lo sustentado en la descripción.

Se sugiere al solicitante que limite los compuestos de fórmula (I) a aquellos que evidentemente correspondan a la invención y demuestren tener la actividad moduladora de quinasas mencionada en la descripción.

6. Determinación del Estado de la Técnica

El estado de la técnica se determinó con base en la fecha de presentación de la solicitud de prioridad 03/02/2005 y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

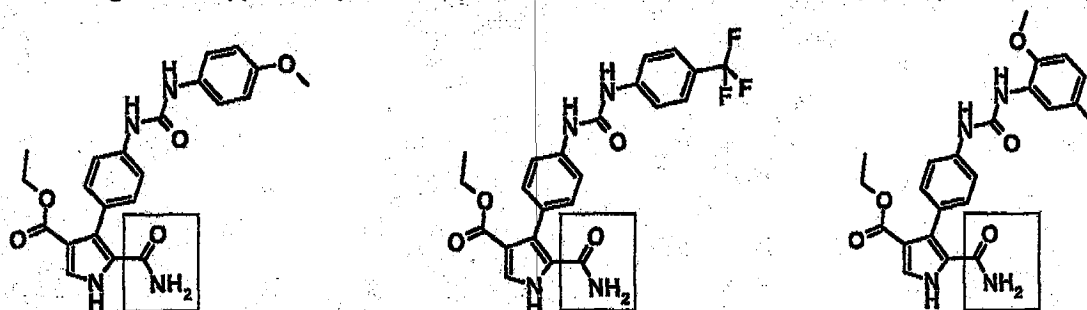
N°	Documento	Título	Fecha de publicación
D1	US 2004138269	Substituted pyrroles as kinase inhibitors	15/07/2004
D1. Divulga compuestos derivados de 3-fenil-1H-pirrol moduladores de proteínas quinasas			

7. Análisis de patentabilidad (artículo 14 D 486)

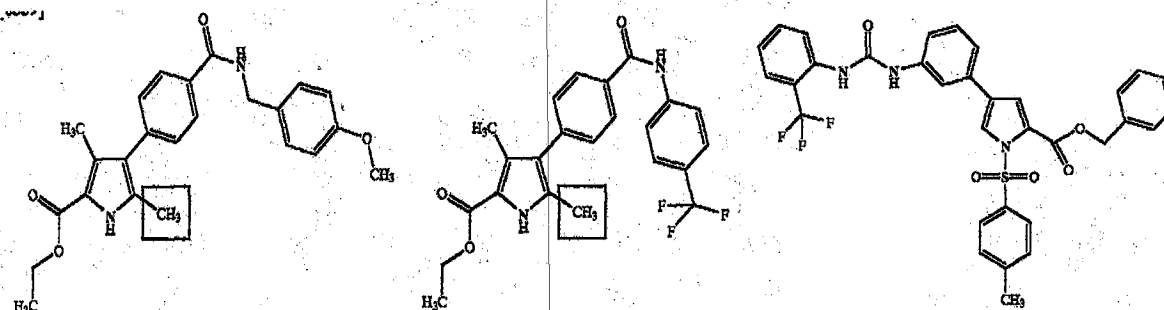
Se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación industrial para establecer la patentabilidad de la invención reivindicada en la solicitud

Nivel Inventivo: (artículo 18 D 486)

La solicitud reclama compuestos derivados de pirrol moduladores de quinasas de fórmula general (I). Compuestos preferidos tienen la fórmula (Ejemplos 19, 22 y 34):



El documento D1 divulga derivados de pirrol moduladores de quinasas y sus procesos de síntesis. Entre ellos los compuestos (ejemplos 22, 25 y 40):



Los compuestos de la solicitud solo se diferencian de los divulgados por D1 en el grupo 2-carboxamido en lugar de metil en la posición 2 del anillo de 1H-pirrol (recuadro).

No se evidencia en la descripción un efecto técnico asociado a dicha diferencia ya que los valores de CI_{50} de afinidad a proteínas quinasas indicados en la descripción (del orden nanomolar), no superan a los divulgados para los compuestos de D1 (páginas 38 - 40).

Por lo tanto, el problema técnico objetivo que pretende resolver esta invención se puede formular así: "cómo modificar compuestos derivados de pirrol inhibidores de quinasas FAK y TIE-2 conocidos en D1 para conseguir compuestos más potentes y/o selectivos".

Sin embargo, compuestos inhibidores de quinasas con este núcleo estructural y los procesos de síntesis para modificar sus sustituyentes ya eran divulgados en D1.

Así las cosas, el técnico medio, enfrentado al problema de encontrar nuevos compuestos derivados de pirrol con propiedades inhibidoras de quinasas, encuentra en D1 los procesos para sintetizarlos y la motivación a modificar los sustituyentes de dicho núcleo esencial, entre ellos el metil de la posición 2, obteniendo así compuestos que no ostentan ningún efecto técnico sorprendente o inesperado (CI_{50} nanomolar), por lo tanto los compuestos de la solicitud se derivan de manera evidente de las enseñanzas de D1, por lo cual carecen de nivel inventivo.

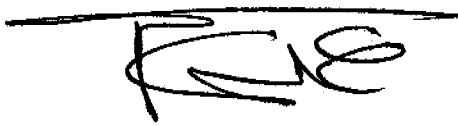
8. Conclusión

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

Nº	Documento	Reivindicaciones Afectadas	Requisito que Afecta
D1	US 2004138269	1 a 21	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.


JOSE LUIS SALAZAR LOPEZ
 Director de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha
01 ABR. 2011

CONCEPTO TECNICO No. 516	EXAMINADOR TECNICO Código No. 202077
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