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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 06-122131- -00003-0000

Fecha: 2008-05-28 17:03:29 Dep. 2020 NUECREACION
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 538 PETICION Folios: 2

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

Trámite : 011

Evento : 378

Actuación : 538

Referencia : Expediente No. **06.122.131**
Asunto : Solicitud de patente para: **INDAZOLES SUSTITUIDOS, COMPOSICIONES QUE LOS CONTIENEN, PROCEDIMIENTO DE PREPARACIÓN Y SU USO**
Solicitante : **AVENTIS PHARMA S.A.**
Publicada en : Gaceta No. 583 del 18 de diciembre de 2007
Fecha solicitud : 4 de diciembre de 2006

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 \$420.000.00, que corresponde a la tasa fijada según lo dispuesto en la Resolución No. 44372 del 26 de diciembre de 2007.

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

COLO-12457-841-010-0
JGG\JGG\ID-126614\WPC12457
No. M-2008-126614\JGG

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 06-122131- -00003-0000

Fecha: 2008-05-28 17:03:29 Dep 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 538 PETICION Folios: 2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

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FECHA : MAYO 12 DE 2008

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	1075023	12/05/2008	73,795,000.00

***** CONCEPTO *****

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

SON: CUATROCIENTOS VEINTE MIL PESOS

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Li et al.(10) **Pub. No.: US 2003/0199511 A1**(43) **Pub. Date: Oct. 23, 2003**(54) **KINASE INHIBITORS**

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(21) Appl. No.: **10/317,914**(22) Filed: **Dec. 12, 2002****Related U.S. Application Data**

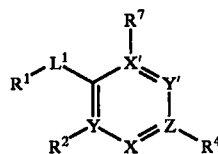
(60) Provisional application No. 60/341,474, filed on Dec. 17, 2001. Provisional application No. 60/341,356, filed on Dec. 13, 2001.

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(57) **ABSTRACT**

Compounds having the formula



(I)

are useful for inhibiting protein kinases. Also disclosed are compositions which inhibit protein kinases and methods of inhibiting protein kinases in a patient.

6.8 mmol) at -78°C ., stirred for 30 min. at -78°C . To the reaction methyl iodide (2 ml) was added dropwise at -78°C . The resulting solution was warmed up to room temperature. The mixture was quenched with water. The reaction solution was partitioned between ethylacetate and water. The organic layer was washed (brine), dried (Na_2SO_4), filtered and concentrated under vacuum. Purification on silica gel with 30% ethyl acetate/hexane to provide the title compound (410 mg, 75%). MS (DCI/ NH_3) m/e 162 ($\text{M}+1$)⁺.

Example 445B

5-{5-[(2S)-2-Amino-3-(1H-indol-3-yl)-propoxy]-pyridin-3-yl}-3,3-dimethyl-1,3-dihydro-indol-2-one

[0931] The title compound was prepared by substituting Example 445A for Example 444A in Example 444. ^1H NMR (300 MHz, D_6 -DMSO) δ 11.03 (s; 1H), 10.49 (s; 1H), 8.56 (s; 1H), 8.31 (s; 1H), 8.18 (s; 2H), 7.70 (s; 1H), 7.64 (s; 1H), 7.61 (d; 1H; J=7.5 Hz), 7.57 (d; 1H; J=7.5 Hz), 7.38 (d; 1H; J=8.7 Hz), 7.27 (s; 1H), 7.10 (t; 1H; J=8.7 Hz), 7.01 (t; 1H; J=8.7 Hz), 6.96 (d; 1H; J=8.7 Hz), 4.33 (m; 1H), 4.17 (m; 1H), 3.84 (m; 1H), 3.17 (m; 2H), 1.31 (s; 6H); MS (DCI/ NH_3) m/e 427 ($\text{M}+1$)⁺.

EXAMPLE 446

5-{5-[(2S)-2-Amino-3-(1H-indol-3-yl)-propoxy]-pyridin-3-yl}-1,3,3-trimethyl-1,3-dihydro-indol-2-one

Example 446A

1,3,3-Trimethyl-1,3-dihydro-indol-2-one

[0932] The title compound was prepared by substituting Example 445A for Example 102A in Example 112. MS (DCI/ NH_3) m/e 176 ($\text{M}+1$)⁺.

Example 446B

5-{5-[(2S)-2-Amino-3-(1H-indol-3-yl)-propoxy]-pyridin-3-yl}-1,3,3-trimethyl-1,3-dihydro-indol-2-one

[0933] The title compound was prepared by substituting Example 446A for Example 444A in Example 444. ^1H NMR (300 MHz, D_6 -DMSO) δ 11.03 (s; 1H), 8.60 (s; 1H), 8.32 (s; 1H), 8.20 (s; 2H), 7.78 (s; 1H), 7.67 (d; 1H; J=7.5 Hz), 7.62 (d; 1H; J=7.5 Hz), 7.39 (d; 1H; J=8.7 Hz), 7.29 (s; 1H), 7.14 (d; 1H; J=8.7 Hz), 7.10 (t; 1H; J=8.7 Hz), 7.01 (t; 1H; J=8.7 Hz), 4.35 (m; 1H), 4.28 (m; 1H), 3.83 (m; 1H), 3.19 (s; 3H), 3.17 (m; 2H), 1.33 (s; 6H); MS (DCI/ NH_3) m/e 441 ($\text{M}+1$)⁺.

EXAMPLE 447

5-{5-[(2S)-2-Amino-3-(1H-indol-3-yl)-propoxy]-pyridin-3-yl}-3-ethyl-1,3-dihydro-indol-2-one

[0934] The title compound was prepared by substituting iodoethane for iodomethane in Example 444. ^1H NMR (300 MHz, D_6 -DMSO) δ 11.04 (s; 1H), 10.51 (s; 1H), 8.53 (s; 1H), 8.30 (s; 1H), 8.16 (s; 2H), 7.64 (s; 1H), 7.62 (d; 1H; J=7.5 Hz), 7.53 (d; 1H; J=7.5 Hz), 7.38 (d; 1H; J=8.7 Hz), 7.28 (s; 1H), 7.10 (t; 1H; J=8.7 Hz), 7.01 (t; 1H; J=8.7 Hz), 6.93 (d; 1H; J=8.7 Hz), 4.33 (m; 1H), 4.16 (m; 1H), 3.84 (m;

1H), 3.49 (t; 1H; J=7.5), 3.14 (m; 2H), 1.85 (m; 2H), 1.09 (d; 3H; J=7.5 Hz); MS (DCI/ NH_3) m/e 427 ($\text{M}+1$)⁺.

EXAMPLE 448

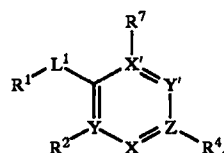
5-{5-[(2S)-2-Amino-3-(1H-indol-3-yl)-propoxy]-pyridin-3-yl}-3-benzyl-1,3-dihydro-indol-2-one

[0935] The title compound was prepared by substituting benzyl chloride for iodomethane in Example 444. ^1H NMR (300 MHz, D_6 -DMSO) δ 11.04 (s; 1H), 10.48 (s; 1H), 8.38 (s; 1H), 8.27 (s; 1H), 8.15 (s; 2H), 7.62 (d; 1H; J=7.5 Hz), 7.44 (d; 1H; J=7.5 Hz), 7.40 (s; 1H), 7.39 (d; 1H; J=8.7 Hz), 7.29 (s; 1H), 7.17 (m; 5H), 7.10 (t; 1H; J=8.7 Hz), 7.01 (t; 1H; J=8.7 Hz), 6.82 (d; 1H; J=8.7 Hz), 4.30 (m; 1H), 4.12 (m; 1H), 3.86 (m; 1H), 3.40 (m; 1H), 3.17 (m; 2H), 3.01 (m; 1H); MS (DCI/ NH_3) m/e 489 ($\text{M}+1$)⁺.

[0936] It will be evident to one skilled in the art that the present invention is not limited to the foregoing illustrative examples, and that it can be embodied in other specific forms without departing from the essential attributes thereof. It is therefore desired that the examples be considered in all respects as illustrative and not restrictive, reference being made to the appended claims, rather than to the foregoing examples, and all changes which come within the meaning and range of equivalency of the claims are therefore intended to be embraced therein.

What is claimed is:

1. A compound of formula (I)



(I)

or a therapeutically acceptable salt thereof, wherein

X is selected from the group consisting of $\text{C}(\text{R}^8)$ and N; wherein R^8 is selected from the group consisting of hydrogen, alkyl, amino, carboxy, cyano, halo, hydroxy, and amido;

X' is selected from the group consisting of C and N;

Y is selected from the group consisting of C and N;

Y' is selected from the group consisting of $\text{C}(\text{R}^9)$ and N; wherein R^9 is selected from the group consisting of hydrogen and $-\text{L}^2-\text{L}^3(\text{R}^6)(\text{R}^6)$;

Z is selected from the group consisting of C and N;

provided that 0, 1, or 2 of X, X', Y, Y', and Z are N;

L^1 is selected from the group consisting of a bond, $-\text{O}-$, $-\text{NR}^5-$, alkenyl, alkynyl, $-\text{C}(\text{O})-$, $-\text{S}-$, $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$, $-\text{S}(\text{O})_2\text{N}(\text{R}^5)-$, $-\text{N}(\text{R}^5)\text{S}(\text{O})_2-$, $-\text{C}(\text{R}^{12})_2-$, $-\text{C}(\text{R}^{12})_2\text{N}(\text{R}^5)-$, $-\text{N}(\text{R}^5)\text{C}(\text{O})-$, and $-\text{C}(\text{O})\text{N}(\text{R}^5)-$; wherein each group is drawn with its left end attached to R^1 and its right end attached to the aromatic ring;

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H9

- (1S)-1-(1H-Indol-3-ylmethyl)-2-(5-isoquinolin-5-yl-pyridin-3-yloxy)-ethylamine;
- 6-{5-[(2S)-2-Amino-3-(1H-indol-3-yl)-propoxy]-pyridin-3-yl}-2H-isoquinolin-1-one;
- (1S)-2-[5-(3-Chloro-isoquinolin-6-yl)-pyridin-3-yloxy]-1-(1H-indol-3-ylmethyl)-ethylamine;
- (1S)-2-[(3,4'-Bipyridinyl-5-yloxy)-1-(1H-indol-3-ylmethyl)-ethylamine trifluoroacetic acid];
- (1S)-1-(1H-Indol-3-ylmethyl)-2-[5-(2-pyridin-2-yl-vinyl)-pyridin-3-yloxy]-ethylamine;
- (1S)-1-(1H-Indol-3-ylmethyl)-2-(5-pyridin-3-ylethynyl-pyridin-3-yloxy)-ethylamine trifluoroacetic acid salt;
- (1S)-2-[5-(2-Fluoro-pyridin-4-ylethynyl)-pyridin-3-yloxy]-1-(1H-indol-3-ylmethyl)-ethylamine trifluoroacetic acid salt;
- (1S)-4-{5-[2-Amino-3-(1H-indol-3-yl)-propoxy]-pyridin-3-ylethynyl}-pyridin-2-ol trifluoroacetic acid salt;
- (1S)-2-[6-Chloro-5-(1-chloro-isoquinolin-6-yl)-pyridin-3-yloxy]-1-(1H-indol-3-ylmethyl)-ethylamine trifluoroacetic acid salt;
- Bis-[3-(4-Bromo-phenyl)-allyl]-{2-[5-(2-pyridin-4-yl-vinyl)-pyridin-3-yloxy]-ethyl}-amine hydrochloride;
- N⁴-[3-(2-Amino-ethoxy)-phenyl]-pyrimidine-2,4-diamine hydrochloride;
- trans-[4-(2-{5-[(2S)-2-Amino-3-(1H-indol-3-yl)-propylamino]-pyridin-3-yl}-vinyl)-pyrimidin-2-yl]-carbamic acid ethyl ester trifluoroacetic acid salt;
- 1-Amino-6-{5-[(2S)-2-amino-3-(1H-indol-3-yl)-propoxy]-pyridin-3-yl}-isoquinoline trifluoroacetic acid salt;
- 6-{5-[(2S)-2-amino-3-(1H-indol-3-yl)-propoxy]-pyridin-3-yl}-1-chloro-isoquinoline trifluoroacetic acid salt;
- (2S)-2-Amino-3-(1H-indol-3-yl)-N-[5-(2-pyridin-4-yl-vinyl)-pyridin-3-yl]-propionamide;
- (2S)-2-Amino-3-(naphtha-1-yl)-N-[5-(2-pyridin-4-yl-vinyl)-pyridin-3-yl]-propionamide hydrochloride;
- (2S)-2-Amino-3-phenyl-N-[5-(2-pyridin-4-yl-vinyl)-pyridin-3-yl]-propionamide hydrochloride;
- S-2-Amino-3-(imidazol-4-yl)-N-[5-(2-pyridin-4-yl-vinyl)-pyridin-3-yl]-propionamide hydrochloride;
- (1R)-2-(1H-indol-3-yl)-1-[[5-(5-isoquinolin-6-ylpyridin-3-yl)oxy]methyl]ethylamine;
- (1S)-5-{5-[2-Amino-3-(1H-indol-3-yl)-propoxy]-pyridin-3-yl}-1H-indazol-3-ylamine;
- (1S)-6-{5-[2-Amino-3-(1H-indol-3-yl)-propoxy]-pyridin-3-yl}-1H-indazol-3-ylamine;
- 2-Amino-N-[(1S)-1-(1H-indol-3-ylmethyl)-2-(5-isoquinolin-6-yl-pyridin-3-yloxy)-ethyl]-acetamide;
- (2S)-2-Amino-N-[(1S)-1-(1H-indol-3-ylmethyl)-2-(5-isoquinolin-6-yl-pyridin-3-yloxy)-ethyl]-propionamide;
- 2-Dimethylamino-N-[(1S)-1-(1H-indol-3-ylmethyl)-2-(5-isoquinolin-6-yl-pyridin-3-yloxy)-ethyl]-acetamide;
- (1S)-1-(1H-Indol-3-ylmethyl)-2-[5-(3-methyl-1H-indazol-5-yl)-pyridin-3-yloxy]-ethylamine;
- (1S)-1-(1H-Indol-3-ylmethyl)-2-{5-[3-(1H-pyrrol-2-yl)-1H-indazol-5-yl]-pyridin-3-yloxy}-ethylamine;
- (1S)-1-(1H-Indol-3-ylmethyl)-2-[5-(3-phenyl-1H-indazol-5-yl)-pyridin-3-yloxy]-ethylamine;
- (1S)-2-[5-(3-Cyclopropyl-1H-indazol-5-yl)-pyridin-3-yloxy]-1-(1H-indol-3-ylmethyl)-ethylamine;
- (1S)-2-[5-(3-Ethyl-1H-indazol-5-yl)-pyridin-3-yloxy]-1-(1H-indol-3-ylmethyl)-ethylamine;
- (1S)-1-(1H-Indol-3-ylmethyl)-2-{5-[3-(i-methyl-1H-imidazol-2-yl)-1H-indazol-5-yl]-pyridin-3-yloxy}-ethylamine;
- (1S)-1-(1H-Indol-3-ylmethyl)-2-[5-(3-thiazol-2-yl-1H-indazol-5-yl)-pyridin-3-yloxy]-ethylamine;
- (1S)-2-[5-[3-(1H-Imidazol-2-yl)-1H-indazol-5-yl]-pyridin-3-yloxy]-1-(1H-indol-3-ylmethyl)-ethylamine;
- (1S)-1-(1H-Indol-3-ylmethyl)-2-[5-(3-thiophen-2-yl-1H-indazol-5-yl)-pyridin-3-yloxy]-ethylamine;
- (1S)-1-(1H-Indol-3-ylmethyl)-2-[5-(3-morpholin-4-yl-1H-indazol-5-yl)-pyridin-3-yloxy]-ethylamine;
- (1S)-2-[5-(1,3-Dimethyl-1H-indazol-5-yl)-pyridin-3-yloxy]-1-(1H-indol-3-ylmethyl)-ethylamine;
- (1S)-1-(1H-Indol-3-ylmethyl)-2-[3-(3-methyl-1H-indazol-5-yl)-phenoxy]-ethylamine;
- (1S)-1-(1H-Indol-3-ylmethyl)-2-{5-[3-(4-methyl-piperazin-1-yl)-1H-indazol-5-yl]-pyridin-3-yloxy}-ethylamine;
- (1S)-(5-{5-[2-Amino-3-(1H-indol-3-yl)-propoxy]-pyridin-3-yl}-1H-indazol-3-yl)-dimethyl-amine;
- (1S)-(4-(5-(2-Amino-3-(1H-indol-3-yl)-propoxy)-pyridin-3-yl)-benzyl)-phenyl-amine;
- (1S)-(4-(5-(2-Amino-3-(1H-indol-3-yl)-propoxy)-pyridin-3-yl)-phenyl)-methanol;
- (1S)-2-(5-(4-Fluoro-phenyl)-pyridin-3-yloxy)-1-(1H-indol-3-ylmethyl)-ethylamine;
- (1S)-4-(5-(2-Amino-3-(1H-indol-3-yl)-propoxy)-pyridin-3-yl)-benzoic acid;
- (1S)-2-(3-Bromo-5-isoquinolin-6-yl-phenoxyoxy)-1-(1H-indol-3-ylmethyl)-ethylamine;
- N⁴-(3-(5-(2-Amino-3-(1H-indol-3-yl)-propoxy)-pyridin-3-yl)-phenyl)-pyrimidine-2,4-diamine;
- (1S)-3-(2-Amino-3-(1H-indol-3-yl)-propoxy)-5-isoquinolin-6-yl-phenylamine;
- 4-(5-Isoquinolin-6-yl-pyridin-3-yl)-piperazine-1-carboxylic acid tert-butyl ester;
- 6-(5-Piperazin-1-yl-pyridin-3-yl)-isoquinoline;
- ((2S)-2-Amino-5-(5-(2-amino-3-(1H-indol-3-yl)-propoxy)-pyridin-3-yl)-phenyl-(3-chloro-phenyl-methanone);
- (1S)-N-6-(3-(5-(2-Amino-3-(1H-indol-3-yl)-propoxy)-pyridin-3-yl)-phenyl)-9H-purine-2,6-diamine;

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LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX,
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(54) Title: AMINOINDAZOLE DERIVATIVES, PREPARATION METHOD THEREOF AND USE OF INTERMEDIATES OF
SAID METHOD AS MEDICAMENTS AND PHARMACEUTICAL COMPOSITIONS CONTAINING SAME

(54) Titre : DERIVES D'AMINOINDAZOLES, PROCEDE DE PREPARATION ET INTERMEDIAIRES DE CE PROCEDE A
TITRE DE MEDICAMENTS ET COMPOSITIONS PHARMACEUTIQUES LES RENFERMANT

(57) Abstract: The invention relates to novel indazole derivatives having general formula (I): wherein R is O, S or NH; R3 is an alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryl, heterocycle, cycloalkyl, alkenyl, etc. radical; said radicals being optionally substituted with 1 or more substituents; R4, R5, R6 and R7 are selected independently from the following radicals: hydrogen, halogen, CN, NO₂, NH₂, OH, COOH, C(O)OR8, -O-C(O)R8, NR8R9, NHC(O)R8, C(O)NR8R9, NHC(S)R8, C(S)NR8R9, SR8, S(O)R8, SO₂R8, NHSO₂R8, SO₂NR8R9, trifluoromethyl, trifluoromethoxy, alkyl, alcoxy, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycle, cycloalkyl, alkenyl, etc.; said radicals being optionally substituted with 1 or more substituents.

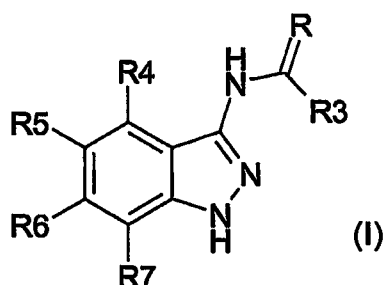
(57) Abrégé : La présente invention concerne les nouveaux dérivés d'indazole de formule générale (I): dans laquelle: R est soit O, S ou NH; R3 est un radical alkyle, aryle, arylalkyle, hétéroaryle, hétéroarylalkyle, aryle, hétérocycle, cycloalkyle, alkényle; ces radicaux étant éventuellement substitués par 1 ou plusieurs substituants; R4, R5, R6 et R7 sont indépendamment l'un de l'autre choisis parmi les radicaux suivant hydrogène, halogène, CN, NO₂, NH₂, OH, COOH, C(O)OR8, -O-C(O)R8, NR8R9, NHC(O)R8, C(O)NR8R9, NHC(S)R8, C(S)NR8R9, SR8, S(O)R8, SO₂R8, NHSO₂R8, SO₂NR8R9, trifluorométhyle, trifluorométhoxy, alkyle, alcoxy, aryle, arylalkyle, hétéroaryle, hétéroarylalkyle, hétérocycle, cycloalkyle, alkényle; ces radicaux étant éventuellement substitués par 1 ou plusieurs substituants.

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REVENDEICATIONS

1. Composés de formule (I)



dans laquelle

5 R est soit O, S ou NH

R3 est un radical (1-6C)alkyle, aryle, aryle(1-6C)alkyle, hétéroaryle, hétéroaryle(1-6C)alkyle, aryle ou hétéroaryle fusionné à un cycloalkyle (1-10C), hétérocycle, cycloalkyle, adamantyle, polycycloalkyles, alkényle, alkynyle ; ces radicaux étant éventuellement substitués par 1 ou plusieurs substituants choisis parmi halogène, CN, NO₂, NH₂, OH, OR₈, COOH, C(O)OR₈, -O-C(O)R₈, NR₈R₉, NHC(O)R₈, C(O)NR₈R₉, SR₈, S(O)R₈, SO₂R₈, NHSO₂R₈, SO₂NR₈R₉, C(S)NR₈R₉, NHC(S)R₈, -O-SO₂R₈, -SO₂-O-R₈, aryle, hétéroaryle, formyle, trifluorométhyle, trifluorométhylsulfanyle, trifluorométhoxy ;

R4, R5, R6 et R7 sont indépendamment l'un de l'autre choisis parmi les radicaux suivant hydrogène, halogène, CN, NO₂, NH₂, OH, COOH, C(O)OR₈, -O-C(O)R₈, NR₈R₉, NHC(O)R₈, C(O)NR₈R₉, NHC(S)R₈, C(S)NR₈R₉, SR₈, S(O)R₈, SO₂R₈, NHSO₂R₈, SO₂NR₈R₉, -O-SO₂R₈, -SO₂-O-R₈, trifluorométhyle, trifluorométhoxy, (1-6C)alkyle, (1-6C)alcoxy, aryle, aryle(1-6C)alkyle, hétéroaryle, hétéroaryle(1-6C)alkyle, hétérocycle, cycloalkyle, alkényle, alkynyle, adamantyle, polycycloalkyles ; ces radicaux étant éventuellement substitués par 1 ou plusieurs substituants choisis parmi halogène, CN, NO₂, NH₂, OH, OR₁₀, COOH, C(O)OR₁₀, -O-C(O)R₁₀, NR₁₀R₁₁, NHC(O)R₁₀, C(O)NR₁₀R₁₁, NHC(S)R₁₀, C(S)NR₁₀R₁₁,

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1H-indazol-3-yl)-2,2,2-trifluoroacetamide, N-(6-chloro-1H-indazol-3-yl)-2-thiophenecarboxamide, N-(6-chloro-1H-indazol-3-yl)-2,2,2-trifluoroacetamide, N-(6-chloro-1H-indazol-3-yl)-4-(hexyloxy)-benzamide, 3-chloro-N-(6-chloro-1H-indazol-3-yl)-benzamide, 4-chloro-N-(6-chloro-1H-indazol-3-yl)-benzamide, N-(5-nitro-1H-indazol-3-yl)-acetamide.

7. Composé selon la revendication 4 caractérisé par le fait qu'il est choisi parmi :

Acide (2Z) 4-[(6-chloro-1H-indazol-3-yl)amino]-4-oxo-2-buténoïque

Acide (2E) 4-[(6-chloro-1H-indazol-3-yl)amino]-4-oxo-2-buténoïque

(2E) 4-[(6-chloro-1H-indazol-3-yl)amino]-4-oxo-2-buténoate d'éthyle

10 (2Z) 4-[(6-chloro-1H-indazol-3-yl)amino]-4-oxo-2-buténoate d'éthyle

Acide 4-[(6-chloro-1H-indazol-3-yl)amino]-4-oxo-2-butanoïque

Acide (2Z) 4-[(5-bromo-1H-indazol-3-yl)amino]-4-oxo-2-buténoïque

Acide (2E) 4-[(6-chloro-1H-indazol-3-yl)amino]-4-oxo-2-buténoïque

Acide (2E) 4-[(5-bromo-1H-indazol-3-yl)amino]-4-oxo-2-buténoïque

15 Acide (2Z) 4-[(6-chloro-1H-indazol-3-yl)amino]-4-oxo-2-buténoïque

Acide 4-[(5-bromo-1H-indazol-3-yl)amino]-4-oxo-2-butanoïque

(2E) N-(6-chloro-1H-indazol-3-yl)-2-buténamide

(2Z) N-(6-chloro-1H-indazol-3-yl)-2-buténamide

N-(6-chloro-1H-indazol-3-yl)-3-buténamide, chlorhydrate

20 4-[(6-chloro-1H-indazol-3-yl)amino]-4-oxo-2-butanoate de méthyle

N-(6-chloro-1H-indazol-3-yl)-acétamide

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N-[6-chloro-1H-indazol-3-yl]-1-piperazineacétamide

N-[6-chloro-1H-indazol-3-yl]-4-[(2-méthoxyéthyl)amino]-cyclohexanecarboxamide

4-amino-N-[6-chloro-1H-indazol-3-yl]-1-piperidinecarboxamide

N-[6-chloro-1H-indazol-3-yl]-4-morpholinylcarboxamide

- 5 leur racémiques, énantiomères, diastéréoisomères et leurs mélanges, leurs tautomères et leurs sels pharmaceutiquement acceptables.

8. Composé selon l'une quelconque des revendications 4 à 5 caractérisé par le fait qu'il est choisi parmi :

Acide (2Z) 4-[(6-chloro-1H-indazol-3-yl)amino]-4-oxo-2-buténoïque

- 10 (2E) 4-[(6-chloro-1H-indazol-3-yl)amino]-4-oxo-2-buténoate d'éthyle

Acide 4-[(6-chloro-1H-indazol-3-yl)amino]-4-oxo-2-butanoïque

Acide (2Z) 4-[(5-bromo-1H-indazol-3-yl)amino]-4-oxo-2-buténoïque

Acide (2E) 4-[(6-chloro-1H-indazol-3-yl)amino]-4-oxo-2-buténoïque

Acide 4-[(5-bromo-1H-indazol-3-yl)amino]-4-oxo-2-butanoïque

- 15 (2E) N-(6-chloro-1H-indazol-3-yl)-2-buténamide

N-(6-chloro-1H-indazol-3-yl)-3-buténamide, chlorhydrate

4-[(6-chloro-1H-indazol-3-yl)amino]-4-oxo-2-butanoate de méthyle

N-(6-chloro-1H-indazol-3-yl)-acétamide

N-(6-chloro-1H-indazol-3-yl)-butanamide

- 20 (2E) N-(6-bromo-1H-indazol-3-yl)-2-buténamide

(2E) N-(5-méthyl-1H-indazol-3-yl)-2-buténamide

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- N-[[6-chloro-1-[(2-triméthylsilyléthoxy)méthyl]-indazol-3-yl]]-propénamide
- N-[[6-chloro-1-(2-triméthylsilyléthoxy)méthyl]-indazol-3-yl]]-butanamide
- N-[[6-(3-pyridyl)-1-[(2-triméthylsilyléthoxy)méthyl]-indazol-3-yl]]-butanamide
- N-[6-(3-pyridyl)-1H-indazol-3-yl]-butanamide
- 5 N-[[6-phenyl]-1-[(2-triméthylsilyléthoxy)méthyl]-indazol-3-yl]]-butanamide
- N-[[6-(furan-3-yl)-1-[(2-triméthylsilyléthoxy)méthyl]-indazol-3-yl]]-butanamide
- N-[[[6-(4-benzyloxy)phenyl]-1-[(2-triméthylsilyléthoxy)méthyl]-indazol-3-yl]]-butanamide
- N-[[6-(3,5-difluorophenyl)-1-[(2-triméthylsilyléthoxy)méthyl]-indazol-3-yl]]-
- 10 butanamide
- N-[[6-(3-thienyl)-1-[(2-triméthylsilyléthoxy)méthyl]-indazol-3-yl]] butanamide
- N-[6-(2-phényléthyl)-1-[[2-(triméthylsilyl)éthoxy]méthyl]-1H-indazol-3-yl]-butanamide
- N-[6-[4-(méthylthio)phényl]-1-[[2-(triméthylsilyl)éthoxy]méthyl]-1H-indazol-3-yl]-
- 15 butanamide
- N-[6-(4-méthoxyphényl)-1-[[2-(triméthylsilyl)éthoxy]méthyl]-1H-indazol-3-yl]-butanamide
- N-[6-[4-(trifluorométhoxy)phényl]-1-[[2-(triméthylsilyl)éthoxy]méthyl]-1H-indazol-3-yl]-butanamide
- 20 N-[(6-(2-propényl)-1-[[2-(triméthylsilyl)éthoxy]méthyl]-1H-indazol-3-yl]-butanamide
- N-[6-(4-fluorophényl)-1-[[2-(triméthylsilyl)éthoxy]méthyl]-1H-indazol-3-yl]-butanamide

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(72) Inventors; and

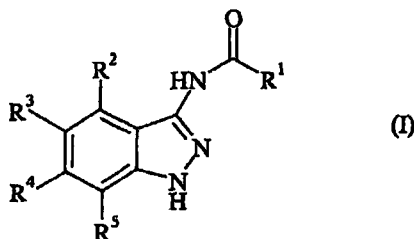
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Published:

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ance Notes on Codes and Abbreviations" appearing at the begin-
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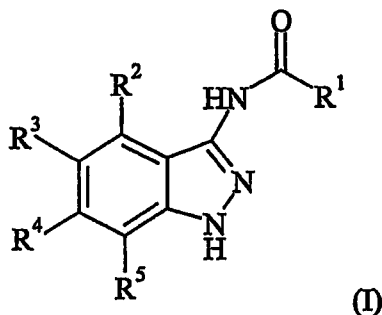
(54) Title: (1-H-INDAZOL-3-YL) -AMIDE DERIVATIVES AS GSK-3 INHIBITORS



(57) Abstract: Compounds of formula (I), or a salt thereof, or a solvate thereof, wherein, R¹, R², R³, R⁴ and R⁵ are as defined in the specification, a process for preparing such compounds, a pharmaceutical composition containing such compounds and the use of such compounds as GSK-3 inhibitors.

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126Claims

1. A compound of formula (I),



or a salt thereof, or a solvate thereof, wherein,

R¹ is unsubstituted or substituted alkyl, unsubstituted or substituted cycloalkyl,
 10 unsubstituted or substituted alkenyl, unsubstituted or substituted cycloalkenyl,
 unsubstituted or substituted aryl, aralkyl wherein the aryl and the alkyl moieties may each
 independently be unsubstituted or substituted, aralkenyl wherein the aryl and alkenyl
 moieties may each independently be unsubstituted or substituted, unsubstituted or
 substituted heterocyclyl, or heterocyclylalkyl wherein the heterocyclyl and the alkyl
 15 moieties may each independently be unsubstituted or substituted, unsubstituted or
 substituted heteroaryl, heteroarylalkyl wherein the heteroaryl and the alkyl moieties may
 each independently be unsubstituted or substituted;

R² is H;

R³ is H, halo, alkyl, unsubstituted or substituted aryl or unsubstituted or substituted
 20 heteroaryl;

R⁴ is H, unsubstituted or substituted aryl; unsubstituted or substituted heteroaryl,
 unsubstituted or substituted heterocyclyl; or -X-aryl;

R⁵ is H;

X is O, NH, S or S(O)_n and

25 n is 1 or 2;

PATENT SPECIFICATION

Inventors: RALPH GOWER DAVIES MOORE and PETER THOMAS WOITACH, JR.

816.382



Date of Application and filing Complete Specification: March 15, 1957.

No. 8684/57.

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International Classification:—C07c, d. G03c, f.

COMPLETE SPECIFICATION

Light-Sensitive Layers for Photomechanical Reproduction

We, GENERAL ANILINE & FILM CORPORATION, a corporation of the State of Delaware, United States of America, located at 230 Park Avenue, New York, New York, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention pertains to light sensitive layers for photomechanical reproduction, and particularly to the use in the preparation of such light sensitive layers of photo-sensitive diazo derivatives of heterocyclic nitrogenous bases.

The use in the lithographic art of diazo compounds for the preparation of light sensitive layers for photomechanical reproduction is well known. In their earliest application these compounds were employed in conjunction with hydrophilic colloids, such as gelatin and the like, with the idea of utilizing their ability to harden the colloids under exposure to light to thereby render the colloid ink-receptive in the hardened areas. More recently, it has been found possible to dispense with the colloid and employ the photodecomposition product of the diazo itself to form an ink-receptive image, for example, on metal surfaces. The diazonium salts heretofore found useful in such application, typified by the reaction products of formaldehyde with diazotised p-phenylene diamines, are generally characterized by the fact that while the photodecomposition products are highly water resistant and hence ink and grease receptive, the diazonium salts, per se, are usually readily soluble and removable by treatment with water.

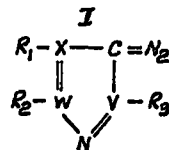
It has been possible to prepare printing plates in this manner which function satisfactorily to some extent. However, the performance of such plates is far from optimum due

to poor stability, especially in the absence of a colloid, of the diazo coated but unprocessed plates. Consequently, considerable research has been directed toward the finding of diazo compounds which would permit the formation of printing plates having a long working life and free from the objections inherent in those utilizing the water soluble diazonium salts.

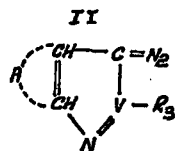
We have now found that it is possible to prepare light-sensitive layers which yield excellent printing images by the use of water insoluble diazo compounds. These compounds may be typified by the general formula:



wherein Z and Y represent the atoms necessary to complete a 5-membered heterocyclic ring system in which the only hetero atoms are nitrogen atoms, there being no more than 3 such hetero atoms in the ring. While any compounds embraced by this formula are suitable for our purpose, we prefer to employ those compounds of the following formulae:



and



[Price 3s. 6d.]

Price 3s. 6d.

Price 25p

3 mls. monoethanolamine
20 mls. triethanolamine
60 mls. ethylene glycol
120 mls. glycerol.

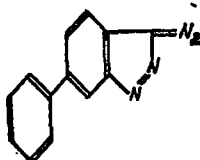


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- 5 This removed the diazo compound from the non-irradiated areas but left the diazo photo-decomposition products intact. A subsequent swabbing of the developed plate with the product sold by Addressograph Multigraph Corporation as "PLATEX" readied the plate for offset printing. Positive copies were obtained.

EXAMPLE XI

- 15 A grained aluminium foil was coated with a solution containing one gram of 3-diazo-6-phenylindiazole having the structure.



- 20 in 100 mls. of methyl cellosolve and dried. The dried foil was exposed to ultraviolet light beneath a negative original. The exposed plate was treated with a solution of the following composition:

- 25 1.5 mls. monoethanolamine
10.0 mls. triethanolamine
25.0 mls. glycerol
63.5 mls. ethylene glycol.

- 30 The unexposed diazo compound was thus removed, leaving a visible positive image on a clean background. After a rinse and treatment with a 5% aqueous solution of phosphoric acid, the plate could be inked to give a positive printing image.

- 35 3-Diazo-6-phenylindiazole was made as follows: 3-amino-4-biphenylcarbonitrile (Jones, J. Org. Chem. 10, 537 (1945)) was diazotized and reductively cyclized with stannous chloride to 3-amino-6-phenylindiazole, m.p. 228-30°. This intermediate was then diazotized in dilute aqueous hydrochloric acid. The resultant yellow slurry was treated with sodium acetate solution and the product was isolated by filtration. It was purified by dissolving in dilute hydrochloric acid and precipitating with sodium acetate solution in the form of fine yellow crystals which were sensitive to light and melted with decomposition at 235° after partial decomposition at about 130°.

EXAMPLE XII

- 50 A paper of high wet strength was lacquered as in Example X. This was sensitized with a solution consisting of: 0.63 gram of 3-diazo-2,4-diphenyl-3H-pyrroline of the probable formula:

0.50 grams of vinyl acetate, sold by Bakelite Corporation as "AYAC," 0.95 gram of a copolymer of vinyl acetate and crotonic acid sold by Monsanto Chemical Company as "POLYMER C-3" and 100 grams of methyl isobutyl ketone.

After being dried, the plate was exposed beneath a negative original to the radiation of a mercury arc. Imagewise development was accomplished with a solution consisting of:

1.5 mls. monoethanolamine
10.0 mls. triethanolamine
25.0 mls. glycerol
63.5 mls. ethylene glycol.

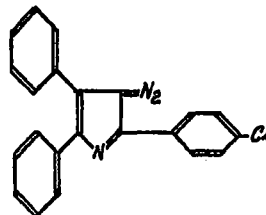
The plate was then fixed with "PLAYTEX" solution and run on an offset duplicator. positive copies were obtained. Similar results could be obtained by imagewise development with a solution comprising:

15 mls. diethanolamine
85 mls. ethylene glycol

The compound 3-diazo-2,4-diphenyl-3H-pyrroline was prepared by diazotizing 3-amino-2,4-diphenylpyrrole (Gabriel, Berichte 41, 1132-40 (1908)) in acetic acid solution with aqueous sodium nitrite. Addition of water precipitated yellow crystals which were sensitive to light and melted with decomposition at 170° C.

EXAMPLE XIII

Presensitized plates were made according to the procedure employed in Example XII except that an equal amount of 2-p-chlorophenyl-3-diazo-4,5-diphenyl-3H-pyrroline of the following structure was used instead of 3-diazo-2,4-diphenyl-3H-pyrroline:



Imagewise development after exposure under a negative could be accomplished with either of the developing solutions employed in Example XII. Positive copies were obtained when these plates were run on an offset duplicator.

The 2-p-chlorophenyl-3-diazo-4,5-diphenyl-3H-pyrroline was made in the following

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogado
Emilio Ferrero
Apoderado

ASUNTO	Radicación	06 122131
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	
	Folios	016- 9409

Patente de Invención	☒	Patente de Modelo de Utilidad	☐
Vía Nacional	☐		
Vía PCT (fase nacional)	☒	Cap. I	☒ Cap. II ☐
No. Sol. Internacional	PCT/FR2005/001335		
Fecha de Presentación Internal.	01/06/2005		

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

1. Documentos estudiados

- 1.1. Descripción: Folios 59 - 132
- 1.2. Reivindicaciones: Folios 133 - 139
- 1.3. Prioridad: Presentada en Francia el 04.06.04, bajo el número 0406042

2. Objeto de la invención

- Título de la solicitud: "Indazoles sustituidos, composiciones que los contienen, procedimiento de preparación y su uso"

Según las reivindicaciones 1-32 se refiere a derivados de fenil-indazoles de fórmula (I) y composiciones farmacéuticas que los contienen. Tales compuestos son inhibidores de quinasa y son activos en el tratamiento de cáncer, y procesos inflamatorios.

El problema planteado en esta solicitud es la necesidad de más compuestos inhibidores de quinasa.

Para solucionar este problema técnico la solicitud en estudio proporciona los compuestos de la presente solicitud que son activos sobre quinasas Aurora 2, CDK4, KDR y Tie2.

- Clasificación Internacional de Patentes A 61 K 31/416

3. De la solicitud de Patente

3.1. Reivindicaciones (artículo 30 D 486)

- Los términos “arilo”, “heteroarilo”, “alquilo”, “alquileo”, “alquinilo”, “cicloalquilo”, “heterociclilo” que se encuentran a lo largo del capítulo reivindicatorio son muy amplios y pueden comprender compuestos que no se encuentran dentro de la descripción

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

- El contenido de las reivindicaciones 28-32, que trata de “El uso de un producto...”, no es patentable, debido a que la legislación vigente únicamente contempla los productos y procedimientos como objeto de patente.

5. Determinación del Estado de la Técnica

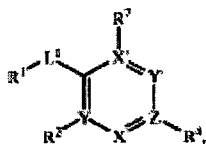
Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es 04.06.04, se buscaron documentos del estado de la técnica relacionados, con fecha de publicación anterior a esta.

Nº	Documento	Título	Fecha de Publicación
D1	US 20030199511	“Inhibidores de quinasa”	23.10.03
D2	WO 03078403	“Derivados de aminoindazoles, su procedimiento de preparación e intermediarios de dicho procedimiento como medicamentos y composiciones farmacéuticas que los contienen”	25.09.03
D3	WO 03051847	“Derivados de (1H-indazol-3-il)-amida como inhibidores GSK-3”	26.06.03
D4	GB 816382	“Placas sensibles a la luz para reproducción fotomecánica”	15.07.59

6. Análisis de patentabilidad (artículo 14 D486)

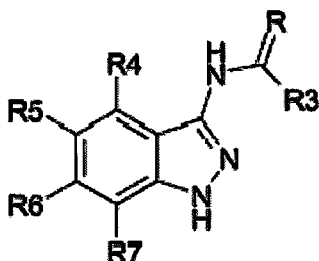
6.1. Novedad (artículo 16 D486)

- La publicación US 2003199511 enseña compuestos inhibidores de



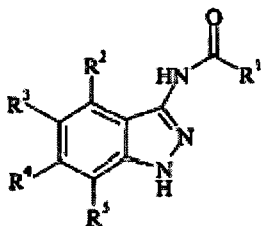
quinasa de fórmula: , específicamente, se enseñan los compuestos de la reivindicación 12

- La publicación WO 03078403 enseña compuestos de fórmula

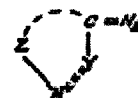


, especialmente los compuestos de las reivindicaciones 7, 8 y 17

- EL documento WO 0351847 revela compuestos de fórmula

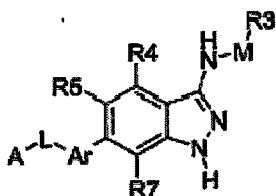


, especialmente los compuestos de los ejemplos 5-10, 13, 14, 17.30, 32, 34 y 35



- La solicitud GB 816382 enseña compuestos de fórmula , específicamente, se revela el compuesto intermediario 3-amino-6-fenilindazol (ver ejemplo XI)

- La presente solicitud enseña compuestos de la fórmula



Comparando elemento por elemento, se aprecia que muchos de los compuestos de la presente solicitud ya habían sido revelados en D1-D4, tal como se ha ido explicando.

En conclusión, los elementos característicos de los compuestos de la presente

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solicitud son revelados en D1-D4 y puede afectar la novedad de la presente solicitud..

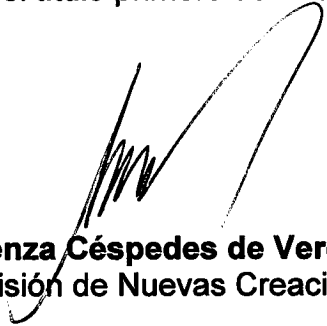
7. Conclusión:

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

N°	Documento	Reivindicaciones Afectadas	Requisito que Afecta
D1	US 20030199511	1-27	Novedad
D2	WO 03078403	1-27	Novedad
D3	WO 03051847	1-27	Novedad
D4	GB 816382	1-27	Novedad

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo 5 del título primero de la Circular Única N° 10 de 2001.


Álix Carmenza Céspedes de Vergel
Jefe de División de Nuevas Creaciones

14 AGO. 2018

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

CONCEPTO TECNICO No. 2595	EXAMINADOR TECNICO Código No.202024
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