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Clarke, Modet & C^o

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E. S. D.

Re: Expediente No. 06.016.492

Solicitud de patente a nombre de NOVARTIS AG Y IRM LLC

Yo, DILIA MARIA RODRIGUEZ D'ALEMAN, actuando como apoderada sustituta de acuerdo con la sustitución presentada el 4 de noviembre de 2009, identificada como aparece al pie de mi firma, domiciliada en la carrera 11 A No. 86-53, piso 6, obrando como apoderada de la sociedad NOVARTIS AG Y IRM LLC, domiciliada en Basilea Suiza y Hamilton HM XL Bermuda, respectivamente, solicitante de la patente de la referencia, en respuesta al oficio No. 15342 notificado por fijación en lista el 26 de noviembre de 2010, relacionado con el concepto técnico de fondo No. 3687, nos permitimos informar lo siguiente:

1. Nivel inventivo

El señor examinador manifiesta en el folio 432, párrafos 5 y 6 que: *“La materia reclamada es ahora afectada por Nivel Inventivo por el documento D2, no siendo este documento la anterioridad más cercana; se encontró otro documento como anterioridad más cercana, el cual es WO 03/048133 (D3), en donde los compuestos son derivados de pirimidina y se relaciona con inhibidores de tirosina cinasa para el tratamiento de enfermedades proliferativas como el cáncer.*

La única diferencia con D3 es que la solicitud tiene ausencia de un grupo alquilo unido al grupo amino que se encuentra en la posición 2 de la pirimidina, mientras que en D3 existe un grupo alquilo C1-4 (Pág. 65, línea 22); y D2 divulga derivados de pirimidina, en donde hay ausencia de un grupo alquilo unido al grupo amino que se encuentra en la posición 2 de la pirimidina (ver tabla comparativa).”

En relación con los argumentos anteriormente señalados por el señor examinador y presentados en el concepto técnico No. 3687, respetuosamente nos permitimos manifestar que se está malinterpretando la descripción del documento WO 03/048133 (D).

En efecto, cuando se hace una lectura cuidadosa de las opciones para el sustituyente R4 en la fórmula (I) de D3, se puede observar que se establece que es un anillo heteroaromático de cinco miembros, y no es un anillo fenílico, (véase por favor anexo 1, página 9 y 10 de D3).

Adicionalmente, R1 también representa una anillo heteroaromático de 6 miembros. Ahora bien, la referencia que se hace D3 en la página 65, entre las líneas 12 a 13 en cuanto a “un anillo de 5 ó 6 miembros” no hace mención al R1, sino a un sustituyente opcional de R1, es decir, R1 representa un anillo heteroaromático de 5 ó 6 miembros..., siendo el anillo opcionalmente sustituido por al menos un sustituyente seleccionado de...un anillo no saturado de 5 ó 6 miembros..., esto se puede corroborar y ver aún más claro en las páginas 5 y 6 de D3 en el anexo 1.

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Por lo tanto, los compuestos en D3 difieren de los compuestos de la presente invención en muchos aspectos y no simplemente en la presencia de un grupo alquilo de 1 a 4 átomos de carbono que corresponde al R2 en la fórmula (I) de D3. Adicionalmente, el documento D3 no hace mención alguna a la inhibición de FAK y ALK.

Así las cosas, para un experto en la materia técnica correspondiente que conociera los compuestos divulgados en D3, no sería evidente la ausencia de un grupo alquilo unido al grupo amino que se encuentra en la posición 2 de la pirimidina y por lo tanto, los compuestos reclamados en la solicitud en estudio son inventivos sobre las enseñanzas de los documentos D2 y D3 toda vez que D3 no puede suplir las deficiencias en D2 para llegar de manera evidente a la materia divulgada en la presente invención, específicamente a los compuestos que resuelven el problema de la inhibición específica de quinasas, principalmente FAK y ALK

Habiendo atendido cabalmente las objeciones presentadas por ese despacho, atentamente solicitamos se conceda el privilegio de patente de invención a la solicitud en estudio o si el examinador considera que subsisten razones para objetar la presente invención ruego expedir otro examen de fondo con los debidos motivos y razones que sustenten su objeción con el fin de que mi mandante tenga la posibilidad de exponer sus argumentos con base en la interpretación de los artículos 45 de la Decisión 486 -el cual otorga la facultad al examinador para emitir los exámenes de fondo-, 35 y 59 del Código Contencioso Administrativo que señala que: *"habiéndose dado oportunidad a los interesados para expresar sus opiniones, y con base en las pruebas e informes disponibles, se tomará la decisión que será motivada al menos en forma sumaria si afecta a particulares"* y *"(..) deberá proferirse la decisión definitiva. Esta se motivará en sus aspectos de hecho y de derecho, y en los de conveniencia si es el caso"*, respectivamente (El subrayado es nuestro).

En consecuencia, solicitamos a ese despacho pronunciarse en relación con todos los argumentos presentados en este memorial dando estricta aplicación al principio del debido proceso consagrado en el artículo 29 de la Constitución Nacional

Señor Superintendente,


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3

ANEXO 1

PÁGINAS 5, 6, 9 Y 10 DE D3 (WO 03/048133)

WO 03/048133 - 5 - PCT/SE02/02221

and R⁴, or R^{7a} and R^{8a}, or R⁹ and R¹⁰, or R¹¹ and R¹², or R^{11a} and R^{12a}, or R¹³ and R¹⁴, or R¹⁵ and R¹⁶, or R^{17a} and R^{18a} are attached. In the definition of R¹, it should be noted that the unsaturated 5- to 6-membered ring may have alicyclic or aromatic properties.

Examples of "C₁-C₆alkyl" and "C₁-C₆alkyl" include methyl, ethyl, isopropyl and *n*-butyl. Examples of "C₁-C₆alkoxycarbonyl" include methoxycarbonyl, ethoxycarbonyl, *n*- and *t*-butoxycarbonyl. Examples of "C₁-C₆alkoxy" and "C₁-C₆alkoxy" include methoxy, ethoxy and propoxy. Examples of "C₁-C₆alkylcarbonylamino" include formamido, acetamido and propionylamino. Examples of "S(O)_mC₁-C₆alkyl" wherein m is 0 to 2 include methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl and ethylsulphonyl. Examples of "C₁-C₆alkylcarbonyl" include propionyl and acetyl. Examples of "C₂-C₆alkenyl" are vinyl, allyl and 1-propenyl. Examples of "C₃-C₆cycloalkyl" are cyclopropyl, cyclopentyl and cyclohexyl.

A "5- or 6-membered heteroaromatic ring comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur" is a fully unsaturated, aromatic monocyclic ring containing 5 or 6 atoms of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur, which may, unless otherwise specified, be carbon or nitrogen linked. Suitably a "5- or 6-membered heteroaromatic ring comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur" is pyridyl, imidazolyl, isoxazolyl, pyrazolyl, furyl, pyrazinyl, pyridazinyl, pyrimidinyl, pyrrolyl or thienyl; said pyridyl, imidazolyl, isoxazolyl, pyrazolyl, furyl, pyrazinyl, pyridazinyl, pyrimidinyl, pyrrolyl or thienyl.

An "unsaturated 5- to 6-membered ring which may comprise at least one ring heteroatom selected from nitrogen, oxygen and sulphur" is a fully or partially unsaturated, monocyclic ring containing 5 or 6 atoms optionally of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur, and which may, unless otherwise specified, be carbon or nitrogen linked. Suitably an "unsaturated 5- to 6-membered ring which may comprise at least one ring heteroatom selected from nitrogen, oxygen and sulphur" is phenyl or pyridyl.

A "5- membered heteroaromatic ring comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur" is a fully unsaturated, aromatic monocyclic ring containing 5 atoms of which at least one is a heteroatom selected from nitrogen, oxygen and sulphur, which may, unless otherwise specified, be carbon or nitrogen linked. Suitably a "5-membered heteroaromatic ring comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur" is pyrazolyl.

WO 03/048133 - 6 - PCT/SE02/02221

R¹ represents an optionally substituted 5- or 6-membered heteroaromatic ring comprising at least one ring heteroatom (e.g. one, two, three or four ring heteroatoms independently) selected from nitrogen, oxygen and sulphur. Examples of heteroaromatic rings include thienyl (e.g. 3-thienyl), pyrazolyl (e.g. 4-pyrazolyl), isoxazolyl (e.g. 5-isoxazolyl), thiadiazolyl, pyrrolyl (e.g. 2-pyrrolyl), furanyl (2- or 3-furanyl), thiazolyl, triazolyl, tetrazolyl, imidazolyl (e.g. 4-imidazolyl), pyrazinyl (e.g. 2-pyrazinyl), pyridazinyl (e.g. 3-pyridazinyl), pyrimidinyl (e.g. 4- or 5-pyrimidinyl) and pyridyl (2-, 3- or 4-pyridyl).

In R¹, the 5- or 6-membered heteroaromatic ring is optionally substituted by at least one substituent (e.g. one, two, three or four substituents independently) selected from C₁-C₆, particularly C₁-C₆alkyl (such as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *tert*-butyl, *n*-pentyl or *n*-hexyl), C₁-C₆, particularly C₁-C₆alkoxy (such as methoxy, ethoxy, *n*-propoxy, *n*-butoxy, *tert*-butoxy, *n*-pentoxy or *n*-hexoxy) (each of the C₁-C₆alkyl and C₁-C₆alkoxy substituent groups being optionally substituted by at least one substituent, e.g. one, two, three or four substituents independently, selected from halogen (such as fluorine, chlorine bromine or iodine), amino, hydroxyl and trifluoromethyl), halogen (such as fluorine, chlorine, bromine or iodine), nitro, cyano, -NR²R⁶, carboxyl, hydroxyl, C₂-C₆, particularly C₂-C₆alkenyl (such as ethenyl), C₃-C₆cycloalkyl (cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl), C₁-C₆, particularly C₁-C₆alkoxycarbonyl (such as methoxycarbonyl or ethoxycarbonyl), C₁-C₆, particularly C₁-C₆alkylcarbonyl (such as methylcarbonyl, ethylcarbonyl, *n*-propylcarbonyl, isopropylcarbonyl, *n*-butylcarbonyl, *n*-pentylcarbonyl or *n*-hexylcarbonyl), C₁-C₆, particularly C₁-C₆alkylcarbonylamino (such as methylcarbonylamino or ethylcarbonylamino), phenylcarbonyl, -S(O)_mC₁-C₆, particularly C₁-C₆alkyl, -C(O)NR²R⁶, -SO₂NR²R⁶, and an optionally substituted unsaturated 5- to 6-membered ring which may comprise at least one ring heteroatom (e.g. one, two, three or four ring heteroatoms independently) selected from nitrogen, oxygen and sulphur.

Examples of the unsaturated 5- to 6-membered ring include phenyl, cyclopentenyl, cyclohexenyl, thienyl (e.g. 3-thienyl), pyrazolyl (e.g. 4-pyrazolyl), isoxazolyl (e.g. 5-isoxazolyl), thiadiazolyl, pyrrolyl (e.g. 2-pyrrolyl), furanyl (2- or 3-furanyl), thiazolyl, triazolyl, tetrazolyl, imidazolyl (e.g. 4-imidazolyl), pyrazinyl (e.g. 2-pyrazinyl), pyridazinyl (e.g. 3-pyridazinyl), pyrimidinyl (e.g. 4- or 5-pyrimidinyl) and pyridyl (2-, 3- or 4-pyridyl). The ring may itself be optionally substituted by at least one substituent (e.g. one, two, three or four substituents independently) selected from C₁-C₆, particularly C₁-C₆alkyl (such as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *tert*-butyl, *n*-pentyl or *n*-hexyl), C₁-C₆.

pyrazin-2-yl, 2-methylpyrazin-5-yl, pyridazin-3-yl, pyrimidin-4-yl, 1-methylpyrrol-2-yl and thien-3-yl.

R² represents a C₁-C₆alkyl group (such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl or *tert*-butyl) optionally substituted by at least one substituent (e.g. one, two, three or four substituents independently) selected from halogen (e.g. fluorine, chlorine, bromine or iodine), hydroxyl and C₁-C₃alkoxy (e.g. methoxy, ethoxy and n-propoxy).

In one embodiment of the invention, R² represents CH₃ or (CH₂)₂.

In a further embodiment R² represents a C₁-C₆alkyl group.

In an additional embodiment R² represents methyl, ethyl and propyl.

R³ represents hydrogen, halogen (e.g. fluorine, chlorine, bromine or iodine) or trifluoromethyl.

In one embodiment of the invention, R³ represents chlorine or bromine.

In a further embodiment R³ represents hydrogen or halogen.

In an additional embodiment R³ represents hydrogen, chloro or bromo.

R⁴ represents an optionally substituted 5-membered heteroaromatic ring comprising at least one ring heteroatom (e.g. one, two, three or four ring heteroatoms independently) selected from nitrogen, oxygen and sulphur. Examples of rings include thienyl (e.g. 3-thienyl), pyrazolyl (e.g. 4-pyrazolyl), isoxazolyl (e.g. 5-isoxazolyl), thiadiazolyl, pyrrolyl (e.g. 2-pyrrolyl), furanyl (2- or 3-furanyl), thiazolyl, triazolyl, tetrazolyl, imidazolyl (e.g. 4-imidazolyl).

The 5-membered heteroaromatic ring in R⁴ is optionally substituted by at least one substituent (e.g. one, two, three or four substituents independently) selected from C₁-C₆, particularly C₁-C₆alkyl (such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, *tert*-butyl, n-pentyl or n-hexyl), C₁-C₆, particularly C₁-C₆alkoxy (such as methoxy, ethoxy, n-propoxy, n-butoxy, *tert*-butoxy, n-pentoxy or n-hexoxy) (each of the C₁-C₆alkyl and C₁-C₆alkoxy substituent groups being optionally substituted by at least one substituent, e.g. one, two, three or four substituents independently, selected from halogen (such as fluorine, chlorine bromine or iodine), amino, hydroxyl and trifluoromethyl), halogen (such as fluorine, chlorine, bromine or iodine), nitro, cyano, -NR¹³R¹⁴, carboxyl, hydroxyl, C₂-C₆, particularly C₂-C₆alkenyl (such as ethenyl), C₃-C₆cycloalkyl (cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl), C₁-C₆, particularly C₁-C₆alkoxycarbonyl (such as methoxycarbonyl or ethoxycarbonyl), C₁-C₆, particularly C₁-C₆alkylcarbonyl (such as methylcarbonyl, ethylcarbonyl, n-propylcarbonyl, isopropylcarbonyl or n-butylcarbonyl), C₁-C₆, particularly

C₁-C₆alkylcarbonylamino (such as methylcarbonylamino or ethylcarbonylamino), phenylcarbonyl, -S(O)₂C₁-C₆, particularly C₁-C₆alkyl, -C(O)NR¹³R¹⁴ and -SO₂NR¹³R¹⁴.

In one embodiment of the invention, R⁴ represents a 5-membered heteroaromatic ring comprising one or two ring heteroatoms selected from nitrogen and oxygen, the ring being optionally substituted by at least one substituent selected from C₁-C₆alkyl, C₁-C₆alkoxy, halogen, nitro, cyano, -NR¹³R¹⁴, carboxyl, hydroxyl, C₂-C₆alkenyl, C₃-C₆cycloalkyl, C₁-C₆alkoxycarbonyl, C₁-C₆alkylcarbonyl, C₁-C₆alkylcarbonylamino, phenylcarbonyl, -S(O)₂C₁-C₆alkyl, -C(O)NR¹³R¹⁴ and -SO₂NR¹³R¹⁴.

In a further embodiment of the invention, R⁴ represents a 5-membered heteroaromatic ring comprising two ring nitrogen atoms, the ring being optionally substituted by at least one substituent selected from C₁-C₆alkyl, C₁-C₆alkoxy, halogen and C₃-C₆cycloalkyl.

In an additional embodiment R⁴ represents a 5-membered heteroaromatic ring comprising at least one ring heteroatom selected from nitrogen, the ring being optionally substituted by at least one substituent selected from C₁-C₆alkyl and C₃-C₆cycloalkyl.

In an additional further embodiment R⁴ represents pyrazolyl, the ring being optionally substituted by at least one substituent selected from methyl, ethyl, isopropyl, propyl, *t*-butyl and cyclopropyl.

In another further embodiment R⁴ represents 5-methylpyrazol-3-yl, 5-ethylpyrazol-3-yl, 5-isopropylpyrazol-3-yl, 5-propylpyrazol-3-yl, 5-*t*-butylpyrazol-3-yl and 5-cyclopropylpyrazol-3-yl.

R⁵ and R⁶ each independently represent hydrogen, C₁-C₆, particularly C₁-C₆alkyl (such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl or *tert*-butyl) or C₃-C₆cycloalkyl (cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl), or R⁵ and R⁶ together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle (such as pyrrolidinyl or piperidinyl).

R⁷ and R⁸ each independently represent hydrogen, C₁-C₆, particularly C₁-C₆alkyl (such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl or *tert*-butyl) or C₃-C₆cycloalkyl (cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl), or R⁷ and R⁸ together with the nitrogen atom to which they are attached form a 4- to 6-membered saturated heterocycle (such as pyrrolidinyl or piperidinyl).

R⁹ and R¹⁰ each independently represent hydrogen, C₁-C₆, particularly C₁-C₆alkyl (such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl or *tert*-butyl) or C₃-C₆cycloalkyl (cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl), or R⁹ and R¹⁰ together with the