

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCION DE NUEVAS CREACIONES**

2020
Bogotá, D.C.,

Abogado
EMILIO FERRERO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-031441- -00005-0000

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Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 519 TRASLADOINFORME Folios: 1

ASUNTO	Radicación	07-31441
	Trámite	011
	Evento	378
	Actuación	430
	Oficio	11 05 13
	Folios	009

Patente de Invención	☒	Patente de Modelo de Utilidad	☐
Vía Nacional	☐		
Vía PCT (Fase Nacional)	☒	Cap. I	☒ Cap. II ☐

No. Sol. Internacional	<u>PCT/EP2005/010118</u>
Fecha de Presentación Internacional	<u>20/09/2005</u>

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 38 a 66 como se radicó inicialmente.

Reivindicaciones: Folios 67 a 71 como se radicó inicialmente.

Prioridad: Folio 1 EP 04023131.8 del 29/09/2004.

2. Objeto de la invención

Título: PROCEDIMIENTO PARA LA PREPARACIÓN DE 4-{4-[CLORO-3-(TRIFLUOROMETIL)FENIL]AMINO}CARBONIL)AMINO]FENOXI}N-METILPIRIDINA-2-CARBOXAMIDA.

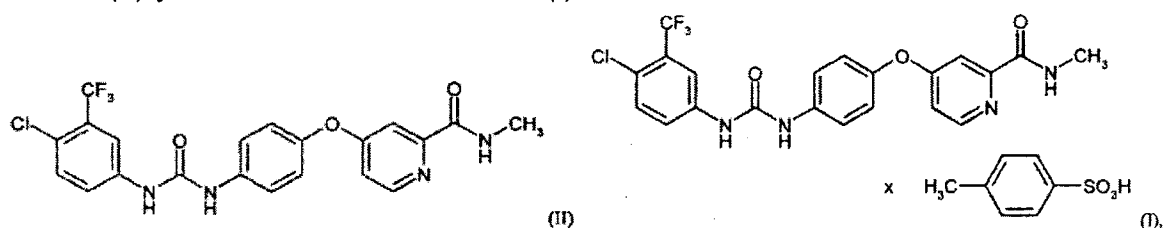
Objeto de la invención: El objeto de la invención consiste en un procedimiento para preparar 4-{4-[cloro-3-(trifluorometil)fenil]amino} carbonil)amino]fenoxi}N-metilpiridina-2-carboxamida y su sal tosilato de fórmula (I).

El problema planteado en la solicitud es proveer un proceso para preparar dicho compuesto y su sal tosilato que presente ventajas con respecto a los ya conocidos

Para solucionar este problema técnico la solicitud proporciona un procedimiento para preparar el dicho compuesto y su sal.

EXP 2007 031441

Reivindicaciones 1 a 11: Procedimientos para preparar el compuesto 4-{4-[cloro-3-(trifluorometil)fenil]amino}carbonil)amino]fenoxi}N-metilpiridina-2-carboxamida de fórmula (II) y su sal tosilato de fórmula (I).



Se catalogó la invención según la IPC así: C07D 213/081, A61K 31/44, A61K 31/185.

3. De la solicitud de Patente

Reivindicaciones (artículo 30 D 486)

La reivindicación 10 incluye las cinco etapas del proceso de la invención para obtener la sal tosilato de fórmula (I) a partir del ácido 2-picolínico, se sugiere presentar esta clausula como la independiente y las otras como dependientes de ésta

Las etapas de los procesos de las reivindicaciones 2 y 7 están comprendidas en la reivindicación 1.

4. 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 29/09/2004, se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

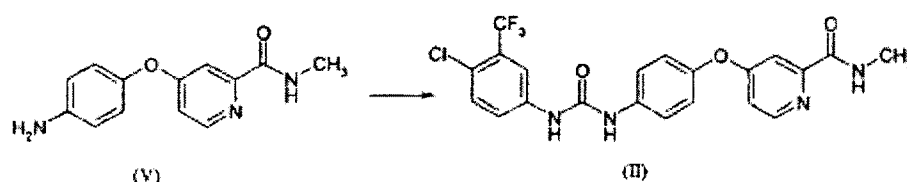
Nº	Documento	Título	Fecha de publicación
D1	US2003/181442	Omega-carboxyaryl substituted diphenyl ureas as raf kinase inhibitors	25/09/2003
D2	US2003/139605	Method and/or process for preparing omega-carboxyaryl substituted diphenyl ureas as raf kinas inhibitors	24/07/2003

5. Análisis de patentabilidad (artículo 14 D 486)

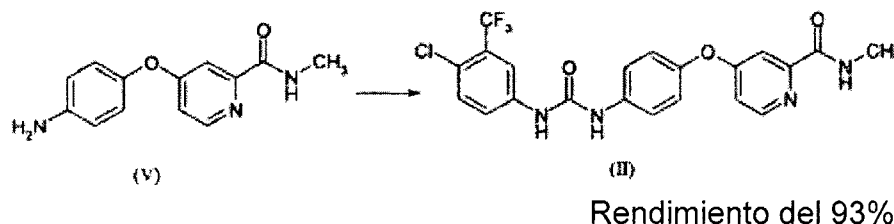
Se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación industrial para establecer la patentabilidad de la invención reivindicada en la solicitud

Nivel Inventivo: (artículo 18 D 486)

La reivindicación 2 de la solicitud se refiere a un proceso para preparar el compuesto de fórmula (II) de acuerdo al siguiente esquema:



El documento D1 describe un proceso para preparar compuestos de fórmula (II) a partir del compuesto de fórmula (V) (Método C1a pág 18)

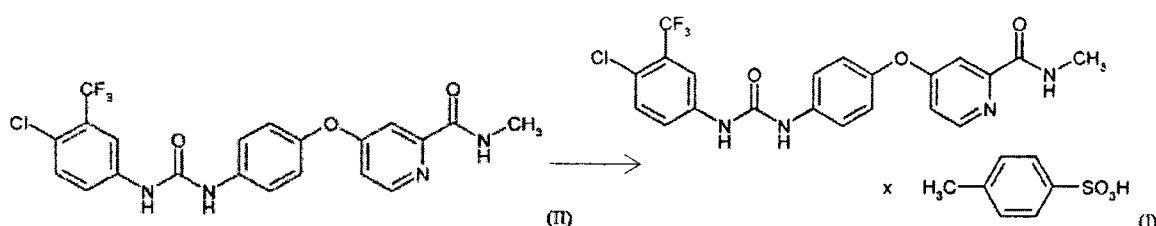


La diferencia entre el proceso de la reivindicación 2 y el descrito en D1 es que la reacción se lleva a cabo sin la presencia de CH_2Cl_2 y en lugar de éste se utiliza acetato de etilo.

El efecto dado por esta diferencia en teoría es un mayor rendimiento, sin embargo de acuerdo a la descripción (ejemplo fase 4) el rendimiento obtenido es el mismo (93%), por lo tanto esta diferencia no le otorga al proceso reivindicado una ventaja o efecto sorprendente.

Dado que D1 divulgaba un proceso para obtener el compuesto de fórmula (II) a partir del mismo compuesto de partida (V), el técnico medio basado en las enseñanzas de D1 y basado en sus conocimientos generales en la técnica, ensayaría, como es de rutina, otros solventes para llevar a cabo la reacción, derivando así de manera obvia el proceso de la reivindicación 2, por lo tanto dicho proceso no tiene nivel inventivo.

La reivindicación 7 se refiere a un procedimiento para obtener el compuesto de fórmula (I) mediante la reacción del compuesto de fórmula (II) (base) con ácido p-toluensulfónico para formar la correspondiente sal tosilo.



El documento D2 describe el compuesto de fórmula (II), sus procesos de obtención y sugiere la obtención de sales orgánicas, entre ellas tosilo de dicho compuesto (Página 3)

Es conocido por el técnico medio versado en síntesis química, la formación de sales orgánicas a partir de la reacción de la base con el correspondiente ácido. En este caso particular, el proceso de la reivindicación 7 no aporta ninguna etapa diferente a las ya conocidas y empleadas para tal fin, por lo tanto no se le puede atribuir altura inventiva a dicho proceso.

6. Conclusión

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

N°	Documento	Reivindicaciones Afectadas	Requisito que Afecta
D1	US2003/181442	2	Nivel Inventivo
D2	US2003/139605	7	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
 Directora de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha
20 AGO. 2000

CONCEPTO TECNICO No. 2609	EXAMINADOR TECNICO Código No. 202077
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US 20030181442A1

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(19) **United States**(12) **Patent Application Publication**(10) **Pub. No.: US 2003/0181442 A1****Riedl et al.**(43) **Pub. Date:****Sep. 25, 2003**(54) **OMEGA-CARBOXYARYL SUBSTITUTED
DIPHENYL UREAS AS RAF KINASE
INHIBITORS**(73) **Assignee: BAYER CORPORATION, Pittsburgh,
PA**(75) **Inventors: Bernd Riedl, Wuppertal (DE); Jacques
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(US); Joel Renick, San Diego, CA
(US); Robert N. Sibley, North Haven,
CT (US)**(21) **Appl. No.: 09/993,647**(22) **Filed: Nov. 27, 2001****Publication Classification**(51) **Int. Cl.⁷ A61K 31/54; A61K 31/537;
A61K 31/495; A61K 31/445;
A61K 31/40; A61K 31/325;
A61K 31/277**
(52) **U.S. Cl. 514/227.5; 514/237.8; 514/252.12;
514/317; 514/408; 514/596;
514/482; 514/522; 544/59;
544/162; 544/400; 546/231;
548/567; 558/417; 560/24**

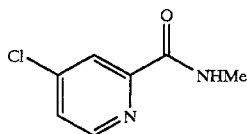
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(57)

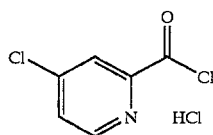
ABSTRACT

This invention relates to the use of a group of aryl ureas in treating raf mediated diseases, and pharmaceutical compositions for use in such therapy.



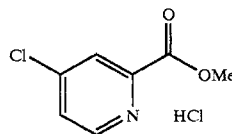
[0070] Step 1a. Synthesis of 4-chloro-N-methyl-2-pyridinecarboxamide Via the Menisci Reaction

[0071] Caution: this is a highly hazardous, potentially explosive reaction. To a stirring solution of 4-chloropyridine (10.0 g) in N-methylformamide (250 mL) at room temp. was added conc. H_2SO_4 (3.55 mL) to generate an exotherm. To this mixture was added H_2O_2 (30% wt in H_2O , 17 mL) followed by $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ (0.56 g) to generate another exotherm. The resulting mixture was stirred in the dark at room temp. for 1 h, then warmed slowly over 4 h to 45° C. When bubbling had subsided, the reaction was heated at 60° C. for 16 h. The resulting opaque brown solution was diluted with H_2O (700 mL) followed by a 10% NaOH solution (250 mL). The resulting mixture was extracted with EtOAc (3×500 mL). The organic phases were washed separately with a saturated NaCl solution (3×150 mL), then they were combined, dried (MgSO_4) and filtered through a pad of silica gel with the aid of EtOAc. The resulting brown oil was purified by column chromatography (gradient from 50% EtOAc/50% hexane to 80% EtOAc/20% hexane). The resulting yellow oil crystallized at 0° C. over 72 h to give 4-chloro-N-methyl-2-pyridinecarboxamide (0.61 g, 5.3%); TLC (50% EtOAc/50% hexane) R_f 0.50; ^1H NMR (CDCl_3) δ 3.04 (d, $J=5.1$ Hz, 3H), 7.43 (dd, $J=5.4$, 2.4 Hz, 1H), 7.96 (br s, 1H), 8.21 (s, 1H), 8.44 (d, $J=5.1$ Hz, 1H); CI-MS m/z 171 ((M+H) $^+$).



[0072] Step 1b. Synthesis of 4-chloropyridine-2-carbonyl Chloride HCl Salt Via Picolinic Acid

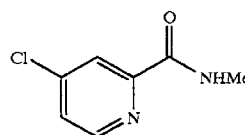
[0073] Anhydrous DIF (6.0 mL) was slowly added to SOCl_2 (180 mL) between 40 and 50° C. The solution was stirred in that temperature range for 10 min. then picolinic acid (60.0 g, 487 mmol) was added in portions over 30 min. The resulting solution was heated at 72° C. (vigorous SO_2 evolution) for 16 h to generate a yellow solid precipitate. The resulting mixture was cooled to room temp., diluted with toluene (500 mL) and concentrated to 200 mL. The toluene addition/concentration process was repeated twice. The resulting nearly dry residue was filtered and the solids were washed with toluene (2×200 mL) and dried under high vacuum for 4 h to afford 4-chloropyridine-2-carbonyl chloride HCl salt as a yellow-orange solid (92.0 g, 89%).



[0074] Step 2. Synthesis of Methyl 4-chloropyridine-2-carboxylate HCl Salt

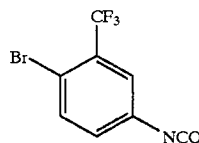
[0075] Anhydrous DMF (10.0 mL) was slowly added to SOCl_2 (300 mL) at 40–48° C. The solution was stirred at that temp. range for 10 min., then picolinic acid (100 g, 812 mmol) was added over 30 min. The resulting solution was heated at 72° C. (vigorous SO_2 evolution) for 16 h to generate a yellow solid. The resulting mixture was cooled to room temp., diluted with toluene (500 mL) and concentrated to 200 mL. The toluene addition/concentration process was repeated twice. The resulting nearly dry residue was filtered, and the solids were washed with toluene (50 mL) and dried under high vacuum for 4 hours to afford 4-chloropyridine-2-carbonyl chloride HCl salt as an off-white solid (27.2 g, 16%). This material was set aside.

[0076] The red filtrate was added to MeOH (200 mL) at a rate which kept the internal temperature below 55° C. The contents were stirred at room temp. for 45 min., cooled to 5° C. and treated with Et_2O (200 mL) dropwise. The resulting solids were filtered, washed with Et_2O (200 mL) and dried under reduced pressure at 35° C. to provide methyl 4-chloropyridine-2-carboxylate HCl salt as a white solid (110 g, 65%); mp 108–112° C.; ^1H NMR ($\text{DMSO}-d_6$) δ 3.88 (s, 3H); 7.82 (dd, $J=5.5$, 2.2 Hz, 1H); 8.08 (d, $J=2.2$ Hz, 1H); 8.68 (d, $J=5.5$ Hz, 1H); 10.68 (br s, 1H); HPLC ES-MS m/z 172 ((M+H) $^+$).



[0077] Step 3a. Synthesis of 4-chloro-N-methyl-2-pyridinecarboxamide from Methyl 4-chloropyridine-2-carboxylate

[0078] A suspension of methyl 4-chloropyridine-2-carboxylate HCl salt (89.0 g, 428 mmol) in MeOH (75 mL) at 0° C. was treated with a 2.0 M methylamine solution in THF (1 L) at a rate which kept the internal temp. below 5° C. The resulting mixture was stored at 3° C. for 5 h, then concentrated under reduced pressure. The resulting solids were suspended in EtOAc (1 L) and filtered. The filtrate was washed with a saturated NaCl solution (500 mL), dried (Na_2SO_4) and concentrated under reduced pressure to afford 4-chloro-N-methyl-2-pyridinecarboxamide as pale-yellow crystals (71.2 g, 97%); mp 4143° C.; ^1H -NMR ($\text{DMSO}-d_6$) δ 2.81 (s, 3H), 7.74 (dd, $J=5.1$, 2.2 Hz, 1H), 8.00 (d, $J=2.2$, 1H), 8.61 (d, $J=5.1$ Hz, 1H), 8.85 (br d, 1H); CI-MS m/z 171 ((M+H) $^+$).

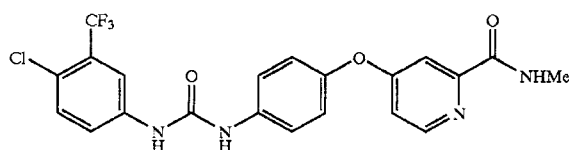


[0179] Step 2. Synthesis of 4-bromo-3-(trifluoromethyl)phenyl isocyanate

[0180] A suspension of 4-bromo-3-(trifluoromethyl)aniline HCl salt (36.8 g, 133 mmol) in toluene (278 mL) was treated with trichloromethyl chloroformate dropwise and the resulting mixture was heated at the reflux temp. for 18 h. The resulting mixture was concentrated under reduced pressure. The residue was treated with toluene (500 mL), then concentrated under reduced pressure. The residue was treated with CH_2Cl_2 (500 mL), then concentrated under reduced pressure. The CH_2Cl_2 treatment/concentration protocol was repeated and resulting amber oil was stored at -20°C . for 16 h, to afford 4-bromo-3-(trifluoromethyl)phenyl isocyanate as a tan solid (35.1 g, 86%); GC-MS m/z 265 (M^+).

[0181] C. Methods of Urea Formation

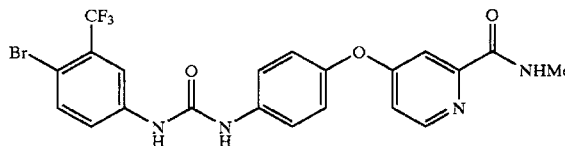
[0182] C1a. General Method for the Synthesis of Ureas by Reaction of an Isocyanate with an Aniline. Synthesis of N-(4-Chloro-3-(trifluoromethyl)phenyl)-N'-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl) Urea



[0183] A solution of 4-chloro-3-(trifluoromethyl)phenyl isocyanate (14.60 g, 65.90 mmol) in CH_2Cl_2 (35 mL) was added dropwise to a suspension of 4-(2-(N-methylcarbamoyl)-4-pyridyloxy)aniline (Method A2, Step 4; 16.0 g, 65.77 mmol) in CH_2Cl_2 (35 mL) at 0°C . The resulting mixture was stirred at room temp. for 22 h. The resulting yellow solids were removed by filtration, then washed with CH_2Cl_2 (2×30 mL) and dried under reduced pressure (approximately 1 mmHg) to afford N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl) urea as an off-white solid (28.5 g, 93%); mp $207-209^\circ\text{C}$.; $^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ 2.77 (d, $J=4.8$ Hz, 3H), 7.16 (m, 3H), 7.37 (d, $J=2.5$ Hz, 1H), 7.62 (m, 4H), 8.11 (d, $J=2.5$ Hz, 1H), 8.49 (d, $J=5.5$ Hz, 1H), 8.77 (br d, 1H), 8.99 (s, 1H), 9.21 (s, 1H); HPLC ES-MS m/z 465 ($(\text{M}+\text{H})^+$).

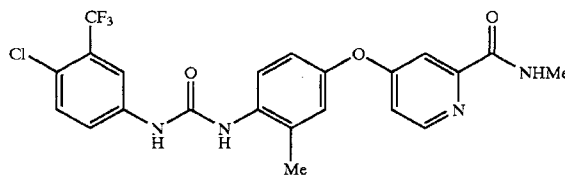
[0184] C1b. General Method for the Synthesis of Ureas by Reaction of an Isocyanate with an Aniline. Synthesis of

N-(4-Bromo-3-(trifluoromethyl)phenyl)-N'-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl) Urea



[0185] A solution of 4-bromo-3-(trifluoromethyl)phenyl isocyanate (Method B1, Step 2; 8.0 g, 30.1 mmol) in CH_2Cl_2 (80 mL) was added dropwise to a solution of 4-(2-(N-methylcarbamoyl)-4-pyridyloxy)aniline (Method A2, Step 4; 7.0 g, 28.8 mmol) in CH_2Cl_2 (40 mL) at 0°C . The resulting mixture was stirred at room temp. for 16 h. The resulting yellow solids were removed by filtration, then washed with CH_2Cl_2 (2×50 mL) and dried under reduced pressure (approximately 1 mmHg) at 40°C . to afford N-(4-bromo-3-(trifluoromethyl)phenyl)-N'-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl) urea as a pale-yellow solid (13.2 g, 90%); mp $203-205^\circ\text{C}$.; $^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ 2.77 (d, $J=4.8$ Hz, 3H), 7.16 (m, 3H), 7.37 (d, $J=2.5$ Hz, 1H), 7.58 (m, 3H), 7.77 (d, $J=8.8$ Hz, 1H), 8.11 (d, $J=2.5$ Hz, 1H), 8.49 (d, $J=5.5$ Hz, 1H), 8.77 (br d, 1H), 8.99 (s, 1H), 9.21 (s, 1H); HPLC ES-MS m/z 509 ($(\text{M}+\text{H})^+$).

[0186] C1c. General Method for the Synthesis of Ureas by Reaction of an Isocyanate with an Aniline. Synthesis of N-(4-Chloro-3-(trifluoromethyl)phenyl)-N'-(2-methyl-4-(2-(N-methylcarbamoyl)(4-pyridyloxy))phenyl) Urea



[0187] A solution of 2-methyl-4-(2-(N-methylcarbamoyl)(4-pyridyloxy))aniline (Method A5; 0.11 g, 0.45 mmol) in CH_2Cl_2 (1 mL) was treated with Et_3N (0.16 mL) and 4-chloro-3-(trifluoromethyl)phenyl isocyanate (0.10 g, 0.45 mmol). The resulting brown solution was stirred at room temp. for 6 d, then was treated with water (5 mL). The aqueous layer was back-extracted with EtOAc (3×5 mL). The combined organic layers were dried (MgSO_4) and concentrated under reduced pressure to yield N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-(2-methyl-4-(2-(N-methylcarbamoyl)(4-pyridyloxy))phenyl) urea as a brown oil (0.11 g, 0.22 mmol); $^1\text{H NMR}$ ($\text{DMSO}-d_6$) δ 2.27 (s, 3H), 2.77 (d, $J=4.8$ Hz, 3H), 7.03 (dd, $J=8.5$, 2.6 Hz, 1H), 7.11 (d, $J=2.9$ Hz, 1H), 7.15 (dd, $J=5.5$, 2.6 Hz, 1H), 7.38 (d, $J=2.6$ Hz, 1H), 7.62 (app d, $J=2.6$ Hz, 2H), 7.84 (d, $J=8.8$ Hz, 1H), 8.12 (s, 1H), 8.17 (s, 1H); 8.50 (d, $J=5.5$ Hz, 1H), 8.78 (q, $J=5.2$, 1H), 9.52 (s, 1H); HPLC ES-MS m/z 479 ($(\text{M}+\text{H})^+$).

[0188] C1d. General Method for the Synthesis of Ureas by Reaction of an Isocyanate with an Aniline. Synthesis of



US 20030139605A1

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(19) **United States**(12) **Patent Application Publication****Riedl et al.**(10) **Pub. No.: US 2003/0139605 A1**(43) **Pub. Date: Jul. 24, 2003**

(54) **METHOD AND/OR PROCESS FOR
PREPARING OMEGA-CARBOXYARYL
SUBSTITUTED DIPHENYL UREAS AS RAF
KINAS INHIBITORS**

(60) Provisional application No. 60/115,877, filed on Jan. 13, 1999. Provisional application No. 60/115,878, filed on Jan. 13, 1999.

Publication Classification

(76) Inventors: **Bernd Riedl**, Wuppertal (DE); **Jacques Dumas**, Bethany, CT (US); **Uday Khire**, Hamden, CT (US); **Timothy B. Lowinger**, Wuppertal (DE); **William J. Scott**, Guilford, CT (US); **Roger A. Smith**, Madison, CT (US); **Jill E. Wood**, North Haven, CT (US)

(51) **Int. Cl.⁷** **C07D 213/63; C07D 213/70**
(52) **U.S. Cl.** **546/291**

(57) **ABSTRACT**

This invention relates to the use of a group of aryl ureas in treating raf mediated diseases, and pharmaceutical compositions for use in such therapy of the formula

A—D—B wherein

D is —NH—C(O)—NH—

A is a substituted moiety of the formula: —L—(M—L¹)_q, and

B is a substituted or unsubstituted up to tricyclic aryl or heteroaryl moiety with at least one 6-member cyclic structure bound directly to D containing 0-4 members of the group consisting of nitrogen oxygen and sulfur.

L is a 5-6 membered cyclic structure bound directly to D,

L¹ comprises a substituted cyclic moiety having at least 5 members

M is a bridging group having at least one atom and q is an integer of from 1-3.

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(21) Appl. No.: **10/071,248**

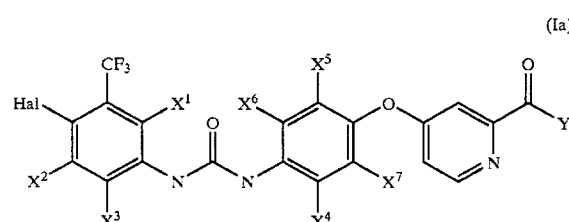
(22) Filed: **Feb. 11, 2002**

Related U.S. Application Data

(63) Continuation of application No. 09/948,915, filed on Sep. 10, 2001, which is a continuation of application No. 09/425,228, filed on Oct. 22, 1999, now abandoned, which is a continuation-in-part of application No. 09/257,266, filed on Feb. 25, 1999, now abandoned.

[0028] Suitable halogen groups include F, Cl, Br, and/or I, from one to per-substitution (i.e. all H atoms on a group replaced by a halogen atom) being possible where an alkyl group is substituted by halogen, mixed substitution of halogen atom types also being possible on a given moiety.

[0029] Preference is given to a compound of formula (Ia)



[0030] wherein,

[0031] Y is NHR,

[0032] Hal is chlorine or bromine,

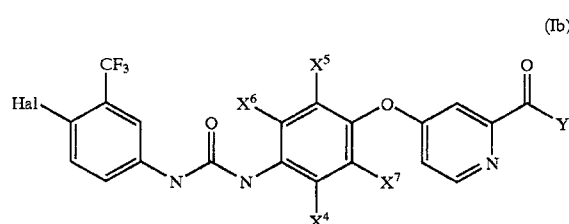
[0033] R is H, CH₃ or CH₂OH, and

[0034] X¹ to X⁷ are each, independently, H, OH or —OC(O)C₁-C₄ alkyl,

[0035] or a salt or purified stereoisomer thereof,

[0036] with the proviso that at least one of X¹ to X⁷ is OH or —OC(O)C₁-C₄ alkyl.

[0037] Further preference is given to a compound of formula (Ib),



[0038] wherein,

[0039] Y is NHR,

[0040] Hal is chlorine or bromine,

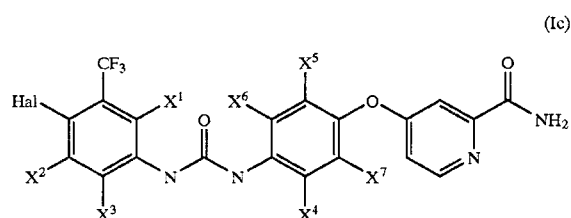
[0041] R is H, CH₃ or CH₂OH, and

[0042] X⁴ to X⁷ are each, independently, H, OH or —OC(O)C₁-C₄ alkyl,

[0043] or a salt or purified stereoisomer thereof,

[0044] with the proviso that at least one of X⁴ to X⁷ is OH or —OC(O)C₁-C₄ alkyl.

[0045] Further preference is given to a compound of formula (Ic),



[0046] wherein,

[0047] Hal is chlorine or bromine, and

[0048] X¹ to X⁷ are each, independently, H, OH or —OC(O)C₁-C₄ alkyl,

[0049] or a salt or purified stereoisomer thereof.

[0050] Preferred compounds of this invention include 4-{{4-[[{4-chloro-3-(trifluoromethyl) phenyl} amino}carbonyl]amino}2-(hydroxy)phenoxy}-2-pyridine carboxamide, 4-{{4-[[{4-chloro-3-(trifluoromethyl) phenyl} amino}carbonyl]amino}3-(hydroxy)phenoxy}-2-pyridine carboxamide, 4-{{4-[[{4-chloro-3-(trifluoromethyl) phenyl} amino}carbonyl]amino}5-(hydroxy)phenoxy}-2-pyridine carboxamide, and 4-{{4-[[{4-chloro-3-(trifluoromethyl) phenyl} amino}carbonyl]amino}6-(hydroxy)phenoxy}-2-pyridine carboxamide.

[0051] The present invention is also directed to pharmaceutically acceptable salts of formulae (I), (Ia), (Ib) and (Ic). Suitable pharmaceutically acceptable salts are well known to those skilled in the art and include basic salts of inorganic and organic acids, such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulphonic acid, trifluoromethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, 1-naphthalenesulfonic acid, 2-naphthalenesulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, and mandelic acid. In addition, pharmaceutically acceptable salts include acid salts of inorganic bases, such as salts containing alkaline cations (e.g., Li⁺Na⁺ or K⁺), alkaline earth cations (e.g., Mg²⁺, Ca²⁺ or Ba²⁺), the ammonium cation, as well as acid salts of organic bases, including aliphatic and aromatic substituted ammonium, and quaternary ammonium cations, such as those arising from protonation or peralkylation of triethylamine, N,N-diethylamine, N,N-dicyclohexylamine, lysine, pyridine, N,N-dimethylaminopyridine (DMAP), 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

[0052] A number of the compounds of formulae (I), (Ia), (Ib) and (Ic) possess asymmetric carbons and can therefore exist in racemic and optically active forms. Methods of separation of enantiomeric and diastereomeric mixtures are well known to one skilled in the art. The present invention encompasses any isolated racemic or optically active form of compounds described in Formula I which possess raf inhibitory activity.

[0053] One of ordinary skill in the art will recognize that some of the compounds of formulae (I), (Ia), (Ib) and (Ic) can exist in different geometrical isomeric forms. In addition, some of the compounds of the present invention