

Doctor

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SUPERINTENDENCIA DE INDUSTRIA

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Solicitud de Patente de Invención titulada: "Moduladores de la actividad del receptor de quimiocina y formas cristalinas"

Solicitante: Bristol-Myers Squibb Company

RESPUESTA AL AUTO NOTIFICADO POR FIJACIÓN EN LISTA NO. 421
DEL 27 DE JULIO DE 2012, OFICIO NO. 13060 (EXAMEN DE FONDO)

ÁLVARO CORREA ORDÓÑEZ, mayor de edad y vecino de Bogotá D.C., identificado tal como aparece al pie de mi firma, en mi carácter de apoderado de la sociedad en referencia, doy respuesta al auto emanado por ese Despacho dentro del término de prórroga solicitado en mi memorial 09-019203-00006-0000 de fecha 3 de octubre de 2012:

1. Objeciones del Examinador

1.1 Excepción a la patentabilidad

Su Despacho menciona que las reivindicaciones 10-12 no son patentables.

Con el objeto de atender a la anterior observación, informo a su Despacho que las reivindicaciones 10-12 se cancelaron del pliego reivindicatorio.

1.2 Título de la invención

Su Despacho sugiere que el título de la invención se modifique. Para atender a la anterior observación informamos a su Despacho que teniendo en cuenta que las reivindicaciones de proceso se cancelaron el título se modifica de la siguiente forma:

“Moduladores de la actividad del receptor de quimiocina, y formas cristalinas”

1.3 Unidad de Invención

Su Despacho menciona que la solicitud no cumple con el requisito de unidad de invención porque se refiere a 3 grupos inventivos.

Con el objeto de atender a la anterior observación, se presenta un nuevo pliego reivindicatorio conformado por 9 reivindicaciones que se refiere solo a un grupo inventivo. El examinador podrá notar que el nuevo pliego reivindicatorio solo contiene una reivindicación independiente dirigida al compuesto N-((1R,2S,5R)-5-(*tert*-butilamino)-2-((S)-2-oxo-3-(6-(trifluorometil)quinazolin-4-ilamino)pirrolidin-1-il)ciclohexil)acetamida, o una sal farmacéuticamente aceptable del mismo. Las otras reivindicaciones son reivindicaciones dependientes.

1.4 Claridad de las reivindicaciones

El examinador menciona que la reivindicación 1 no es clara pues debería incluir todos los aspectos que caracterizan el compuesto.

Al respecto, informamos a su Despacho que no se entiende la anterior observación pues la reivindicación 1 es un compuesto específico, tal como se muestra a continuación:

"Un compuesto, caracterizado porque es N-((1R,2S,5R)-5-(tert-butilamino)-2-((S)-2-oxo-3-(6-(trifluorometil)quinazolin-4-ilamino)pirrolidin-1-il)ciclohexil)acetamida, o una sal farmacéuticamente aceptable del mismo."

Por otro lado, el examinador podrá notar que las expresiones: *"como se listan en la tabla 7"* y *"de conformidad con la Figura 2"* ya no aparecen en el pliego reivindicatorio.

Es importante mencionar que el pliego reivindicatorio que ahora se presenta está de conformidad con el otorgado en Europa EP 2 046 779 B1, exceptuando las reivindicaciones 9 a 11 que fueron canceladas para la solicitud Colombiana.

La reivindicación 6 incluye la tabla 3 de la descripción y en la reivindicación 7 se incluyó la figura 2.

La referencia a la forma N-2 ya no se establece en el nuevo pliego reivindicatorio.

El examinador podrá notar que el cristal está claramente definido en las reivindicaciones 3 a 7, mediante los parámetros de unidad de celda, mediante los patrones de difracción de rayos X en polvo, y mediante las coordenadas atómicas fraccionales.

Teniendo en cuenta las modificaciones efectuadas, el nuevo pliego reivindicatorio cumple a cabalidad con el artículo 30 de la Decisión 486.

1.5 Nivel inventivo

Su Despacho afirma que los documentos D1 (WO2005021500) y D2 (US2005054627) afectan el nivel inventivo de las reivindicaciones 1 a 8 de la presente invención y en forma resumida argumenta lo siguiente:

"La diferencia entre la invención, definida en la reivindicación 1 y el compuesto de D1 consiste en la presencia de una acetamida sobre el ciclohexilo, mientras que en D1 el grupo que figura en el ciclohexilo corresponde a un carboxilo."

La diferencia entre la invención, definida en la reivindicación 1 y el compuesto de D2 consiste en la presencia de una acetamida sobre el ciclohexilo mientras que en D2 el grupo que figura sobre el ciclohexilo corresponde a un radical alquilo (...)

Se hace necesario realizar la caracterización completa del polimorfo de manera que se defina claramente y se logre identificar como tal, aunque no se ha encontrado anticipado en el estado de la técnica, no es posible determinar el polimorfo como tal motivo de la presente invención, debido a que no se encuentra debidamente caracterizado (...)

No se encuentran efectos diferentes por el hecho de tener un ordenamiento diferente en las estructuras, la diferencia es el DRX y demás parámetros del estado sólido, pero no hay evidencias de un efecto inesperado (...)

En consecuencia, la persona del oficio normalmente versada en la materia, obtendría el compuesto en una forma cristalina u otra, para la misma función a nivel de los receptores MCP-I sin que se presente ningún efecto inesperado, por lo cual se considera obvia..."

2. Argumentos en favor de la patentabilidad de la presente invención

2.1 Novedad

Su Despacho reconoce la novedad de la presente invención, por lo tanto, el requisito a sustentar es el nivel invento.

2.2 Nivel inventivo

El nivel inventivo de una solicitud se encuentra definido en el Artículo 18 de la Decisión 486 y se establece cuando *"si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica"*.

Contrario a lo que plantea el Examinador, los documentos D1 (WO 2005021500) y D2 (US2005054627) no afectan el nivel inventivo de la presente solicitud por cuanto no es posible derivar la presente invención a partir de las enseñanzas presentadas en dichos documentos.

Se hace notar a su Despacho que los documentos D1 y D2 fueron citados por mi representada en la descripción de la solicitud en estudio. Además dichos documentos fueron citados como anterioridades en el informe de búsqueda internacional de la solicitud PCT/US2007/074377. No obstante, el informe del examen preliminar internacional sobre la patentabilidad de esta invención, claramente establece que el compuesto reclamado así como su forma cristalina, no habían sido previamente descritos.

Además, en la descripción de la presente invención se establece textualmente:

"WO2005021500 A1 (incorporado en la presente para referencia y se asigna a la solicitud presente) describe compuestos que modulan la actividad MCP-1, MCP-2, MCP-3 y MCP-4 por medio de CCR2. La referencia también describe varios procesos para preparar estos compuestos incluyendo síntesis de etapa múltiple que incluye la introducción y la eliminación posterior de grupos protectores.

Es deseable encontrar nuevos compuestos con características farmacológicas mejoradas comparadas con moduladores de la quimiocina conocida. Por ejemplo, es deseable encontrar nuevos compuestos con actividad inhibidora CCR-2 mejorada y selectividad para CCR-2 contra otros receptores acoplados a la proteína G (esto es, receptor 5HT2A). También es deseable encontrar compuestos con características ventajosas y mejoradas en una o más de las siguientes categorías:

- (a) propiedades farmacológicas (esto es, solubilidad, permeabilidad, receptibilidad para formulaciones de liberación sostenida);*
- (b) requerimientos de dosis (por ejemplo, dosis inferiores y/o dosis una vez diaria);*
- (c) factores los cuales disminuyen las características a través de un pico de concentración de sangre (esto es, liberación y/o volumen de la distribución);*
- (d) factores que incrementan la concentración de fármaco activo al receptor (esto es, proteína enlazada, volumen de distribución);*

(e) *factores que disminuyen la responsabilidad de interacciones clínicas fármaco-fármaco (inhibición o inducción de la enzima P450 de citocromo, tales como inhibición de CYP 2D6, ver G.K. Dresser, J.D. Spence, D.G. Bailey, Clin. Pharmacolkinet. 2000, 38, 41-57, la cual se incorpora en la presente para referencia);*

(f) *factores que disminuyen el potencial para efectos secundarios adversos (por ejemplo, receptores acoplados a la proteína G superiores a la selectividad farmacológica, reactividad metabólica o química potencial, penetración CNS limitada, selectividad del canal de ion). Es específicamente deseado encontrar compuestos que tienen una combinación deseada de las características farmacológicas antes mencionadas."*

El informe preliminar internacional sobre la patentabilidad también menciona que la presente invención cumple con el requisito de nivel inventivo pues el problema técnico objetivo se soluciona con la provisión de nuevos compuestos con características farmacológicas mejoradas comparado con moduladores de quimiocina conocidos de D1 y D2 (que también fueron citados en la solicitud).

Se menciona también que las características farmacológicas mejoradas de los compuestos de la solicitud en estudio comparados con los de D1 y D2 se demuestran en las tablas, datos (in vivo, in vitro también como los datos farmacocinéticos in vivo) proporcionados por el solicitante en particular por el ejemplo 1 que compara los compuestos de la solicitud en estudio con varios ejemplos de los documentos D1 y D2.

Es importante mencionar nuevamente que el nuevo pliego reivindicatorio que se presenta se relaciona con un compuesto específico: N-((1R,2S,5R)-5-(tert-butilamino)-2-((S)-2-oxo-3-(6-(trifluorometil)quinazolin-4-ilamino)pirrolidin-1-il)ciclohexil)acetamida, o una sal farmacéuticamente aceptable del mismo y como reivindicaciones dependientes se tiene: La forma cristalina de N-((1R,2S,5R)-5-(tert-butilamino)-2-((S)-2-oxo-3-(6-(trifluorometil)quinazolin-4-ilamino)pirrolidin-1-il)ciclohexil)acetamida, o una sal farmacéuticamente aceptable del mismo.

Los compuestos de la presente invención demostraron tener características farmacológicas mejoradas en comparación con los compuestos de los documentos D1 y D2. Esto claramente es un indicio de nivel inventivo. Así mismo, se debe notar que las formas cristalinas reclamadas son las formas cristalinas de un producto nuevo e inventivo. Si el producto es nuevo e inventivo, las reivindicaciones dependientes de las formas cristalinas también son novedosas e inventivas. Tal como lo reconoció el reporte del examen preliminar internacional. La altura inventiva también fue reconocida por la Oficina de Patentes Europea.

Por lo anteriormente expuesto, se puede concluir que la solicitud en estudio no solamente es novedosa como ya lo ha reconocido su Despacho sino que también cumple con el requisito de altura inventiva.

En este orden de ideas, tenemos que la invención propuesta por el solicitante cumple con los requisitos de patentabilidad y de esta manera es susceptible de ostentar el título de patente de invención.

3. Solicitudes concedidas en otros países para esta misma invención.

A manera informativa, pongo en conocimiento del Examinador que la patente EP 2 046 779 equivalente a la presente solicitud colombiana ha sido otorgada. Aún cuando entiendo que estas decisiones de ninguna manera obligan al Despacho para decidir de igual forma, considero que por tratarse de una pregunta fáctica la determinación de la existencia de novedad, nivel inventivo y aplicación industrial, las decisiones de otras oficinas de patentes constituyen un antecedente persuasivo en la materia.

En virtud de lo anterior, solicito que se acepten las razones expuestas en el presente documento y en consecuencia, se otorgue el privilegio de patente de invención para el invento que se tramita en este expediente.

Atentamente,



ÁLVARO CORREA ORDÓÑEZ
C.C.No.79.143.366 de Usaquén
T.P.20.281

Anexos:

- Capítulo reivindicatorio modificado conformado por 9 reivindicaciones.
- Copia de la carátula y reivindicaciones de la patente EP 2 046 779.
- Copia del Examen Preliminar Internacional de la solicitud internacional PCT/US2007/074377

BM_ALMGT/BOGDMS-#1297270-V1-P2009_000032-0720.DOC

REIVINDICACIONES

1. Un compuesto, caracterizado porque es N-
((1R,2S,5R)-5-(*tert*-butilamino)-2-((S)-2-oxo-3-(6-
5 (trifluorometil)quinazolin-4-ilamino)pirrolidin-1-
il)ciclohexil)acetamida, o una sal farmacéuticamente
aceptable del mismo.

2. Compuesto de conformidad con la reivindicación 1,
10 caracterizado porque es una forma cristalina de N-
((1R,2S,5R)-5-(*tert*-butilamino)-2-((S)-2-oxo-3-(6-
(trifluorometil)quinazolin-4-ilamino)pirrolidin-1-
il)ciclohexil)acetamida, o una sal farmacéuticamente
aceptable del mismo.

15 3. La forma cristalina de conformidad con las
reivindicaciones 1-2, caracterizada porque los parámetros de
unidad de celda son iguales a los siguientes:

20 Dimensiones de celda:

$$a = 18.7240(4)$$

$$b = 8.0171(2)$$

$$c = 19.6568(5)$$

25 $\alpha = 90$

- 2 -

$$\beta = 114.935(2)$$

$$\gamma = 90$$

$$V(\text{\AA}^3) = 2675.7 (1)$$

Grupo de espacio $P2_12_12_1$

5 Moléculas/célula unitaria 2

en donde el cristal está a una temperatura de +22°C (T.A).

10 4. La forma cristalina de conformidad con las reivindicaciones 1-3, caracterizada porque el patrón de difracción de rayos X en polvo comprende tres o más de los valores 2θ ($\text{CuK}\alpha$ $\lambda=1.5418\text{\AA}$) seleccionados de 5.5, 9.1, 12.1, 14.0 y 19.2 a una temperatura de 22°C.

15 5. La forma cristalina de conformidad con las reivindicaciones 1-4, caracterizada además porque el patrón de difracción de rayos X en polvo comprende cuatro o más de los valores 2θ ($\text{CuK}\alpha$ $\lambda=1.5418\text{\AA}$) seleccionados del grupo que consiste de 5.5, 9.1, 12.1, 14.0 y 19.2, a una temperatura de
20 de 22°C.

6. La forma cristalina de conformidad con las reivindicaciones 1-5, caracterizada porque las coordenadas atómicas fraccionales son las siguientes:

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Átomo	X	Y	Z	Átomo	X	Y	Z
N1	0.7824	1.3195	0.3238	C71	0.9289	1.4591	0.5167
N2	0.1685	0.3056	-0.0178	H72	0.9378	1.4237	0.5668
H3	0.1633	0.1989	-0.0196	H73	0.9764	1.4359	0.5102
N4	0.6223	0.8215	0.1887	C74	0.8719	1.7574	0.6080
N5	0.2627	0.4840	-0.0849	C75	0.6719	1.2862	0.4846
N6	0.6868	0.9765	0.2943	H76	0.6246	1.2933	0.4390
H7	0.7030	0.9877	0.3420	H77	0.6814	1.3914	0.5103
N8	0.4185	0.9718	0.0742	H78	0.6660	1.2009	0.5162
N9	0.0989	0.0258	-0.1003	C79	0.9173	1.6199	0.6639
N10	0.7913	1.3680	0.4754	H80	0.8851	1.5217	0.6541
H11	0.7826	1.4618	0.4918	H81	0.9305	1.6578	0.7142
N12	0.5331	0.6005	0.1813	H82	0.9647	1.5943	0.6584
N13	0.3353	0.7474	0.0475	C83	0.9176	1.9198	0.6225
H14	0.3028	0.6896	0.0583	H84	0.9680	1.8999	0.6220
N15	0.8501	1.6946	0.5311	H85	0.9252	1.9631	0.6707
N16	0.4567	1.1267	0.1887	H86	0.8887	1.9992	0.5842
O17	0.7470	1.1042	0.4435	C87	0.7960	1.7901	0.6131
O18	0.2114	0.7470	-0.1165	H88	0.7660	1.8705	0.5758
O19	0.2229	0.5239	0.0583	H89	0.8064	1.8325	0.6620
O20	0.8588	1.0890	0.3360	H90	0.7667	1.6881	0.6048
F21	0.5881	0.9034	0.4961	C91	0.2069	0.3753	0.0494
F22	0.4828	0.7754	0.4659	C92	0.1886	0.3981	-0.1294
F23	0.5874	0.6500	0.5199	H93	0.1617	0.4641	-0.1751

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C24	0.1049	-0.1653	-0.0049	C94	0.1345	0.3960	-0.0889
H25	0.1473	-0.2167	-0.0125	H95	0.1249	0.5115	-0.0787
H26	0.0773	-0.2487	0.0097	C96	0.3636	0.8982	0.1612
H27	0.1257	-0.0826	0.0338	C97	0.0560	0.3169	-0.1396
C28	0.0052	-0.2107	-0.1371	H98	0.0300	0.3865	-0.1836
H29	-0.0334	-0.1565	-0.1806	H99	0.0226	0.3123	-0.1131
H30	-0.0204	-0.2889	-0.1178	C100	0.0655	0.1409	-0.1647
H31	0.0423	-0.2685	-0.1506	H101	0.0138	0.0994	-0.1999
C32	-0.0102	0.0236	-0.0618	C102	0.2651	0.6526	-0.0801
H33	0.0176	0.1111	-0.0276	C103	0.3727	0.8727	0.0930
H34	-0.0371	-0.0447	-0.0399	C104	0.3129	0.8065	0.1831
H35	-0.0478	0.0713	-0.1077	H105	0.2826	0.7213	0.1525
C36	0.6347	0.8573	0.2590	C106	0.4090	1.0275	0.2081
C37	0.7956	1.1614	0.3094	C107	0.1998	0.2249	-0.1544
C38	0.5429	0.6399	0.2526	H108	0.2268	0.1548	-0.1108
C39	0.5969	0.8058	0.3661	H109	0.2321	0.2314	-0.1820
H40	0.6303	0.8901	0.3943	C110	0.0479	-0.0823	-0.0781
C41	0.5928	0.7673	0.2949	C111	0.3943	0.5437	-0.0102
C42	0.7174	1.0886	0.2543	H112	0.4319	0.5306	0.0416
H43	0.7243	1.0288	0.2140	H113	0.4226	0.5469	-0.0417
C44	0.8437	1.4188	0.3806	C114	0.1202	0.1477	-0.2041
H45	0.8919	1.4020	0.3733	H115	0.0955	0.2128	-0.2496
C46	0.8266	1.6034	0.3730	H116	0.1283	0.0355	-0.2179
H47	0.7791	1.6255	0.3797	C117	0.3076	0.8411	0.2485
H48	0.8177	1.6396	0.3230	C118	0.2292	0.2619	0.1158
C49	0.5524	0.7201	0.3942	H119	0.2846	0.2720	0.1469

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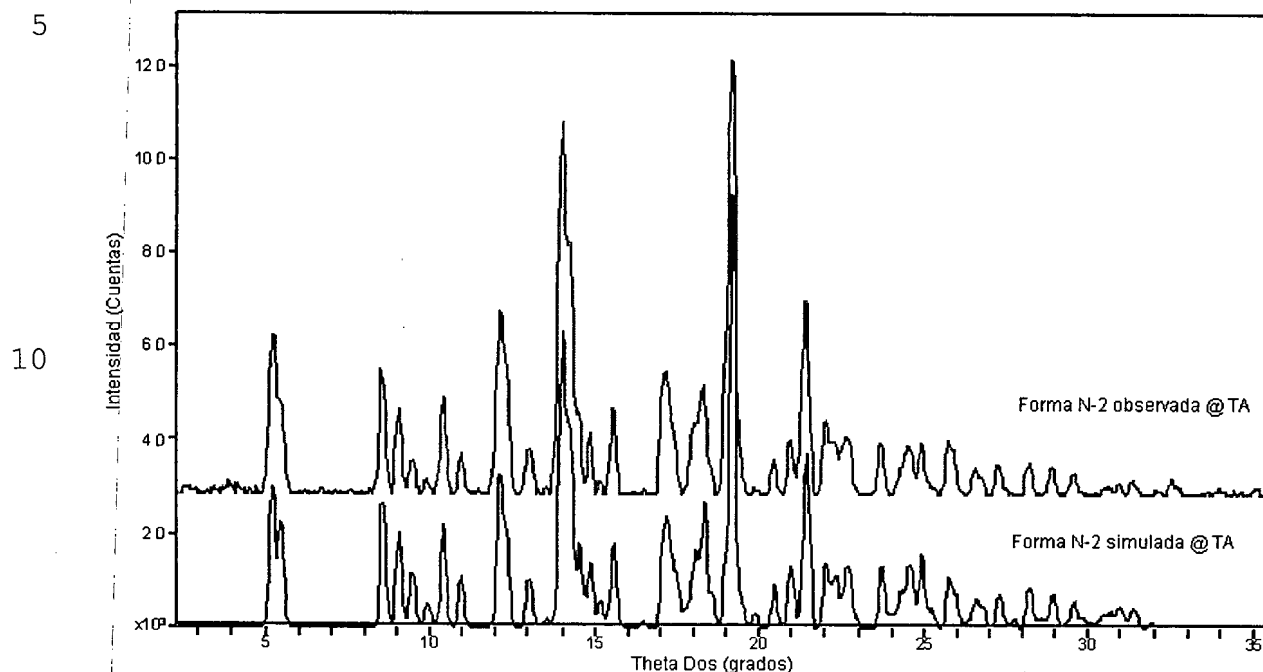
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C50	0.6668	1.2414	0.2237	H120	0.2172	0.1487	0.0989
H51	0.6690	1.2785	0.1776	H121	0.2001	0.2924	0.1441
H52	0.6125	1.2182	0.2137	C122	0.3349	0.4024	-0.0337
C53	0.8609	1.3569	0.4595	H123	0.3502	0.3144	-0.0588
H54	0.8773	1.2398	0.4636	H124	0.3290	0.3556	0.0092
C55	0.4991	0.5496	0.2836	C125	0.3458	0.7009	-0.0200
H56	0.4668	0.4624	0.2569	H126	0.3682	0.7937	-0.0371
C57	0.7010	1.3718	0.2841	C127	0.4561	1.0941	0.1233
H58	0.6975	1.4822	0.2628	H128	0.4859	1.1659	0.1085
H59	0.6744	1.3722	0.3171	C129	0.4030	1.0567	0.2762
C60	0.9137	1.6472	0.5099	H130	0.4339	1.1390	0.3084
H61	0.9621	1.7039	0.5438	C131	0.2548	0.7395	0.2713
C62	0.7404	1.2441	0.4666	C132	0.3536	0.9679	0.2955
C63	0.5039	0.5898	0.3526	H133	0.3500	0.9907	0.3403
H64	0.4747	0.5300	0.3726	F134	0.1847	0.7359	0.2156
C65	0.5722	0.6959	0.1556	F135	0.2364	0.8060	0.3220
H66	0.5642	0.6734	0.1065	F136	0.2859	0.5920	0.2960
C67	0.8949	1.7014	0.4308	F137	0.1977	0.8329	0.2710
H68	0.9412	1.6866	0.4211	F138	0.2168	0.6170	0.2301
H69	0.8818	1.8193	0.4256	F139	0.2934	0.6790	0.3395
C70	0.5532	0.7632	0.4678	H140	0.8280	1.7679	0.5060
				H141	0.1330	-0.0400	-0.1062

7. La forma cristalina de conformidad con las reivindicaciones 1-6, caracterizada porque tiene un patrón de difracción de rayos X en polvo de conformidad con:



8. La Composición farmacéutica, caracterizada porque comprende el compuesto de conformidad con las reivindicaciones 1-7, y un portador o diluyente farmacéuticamente aceptable.

9. La composición farmacéutica de la reivindicación 8, que comprende además uno o más de otros ingredientes activos.



(11) EP 2 046 779 B1

(12) EUROPEAN PATENT SPECIFICATION

- (45) Date of publication and mention of the grant of the patent:
18.05.2011 Bulletin 2011/20

(21) Application number: 07813363.4

(22) Date of filing: 26.07.2007
- (51) Int Cl.:
C07D 403/12^(2006.01) C07D 207/273^(2008.01)
A61K 31/4025^(2006.01)

(86) International application number:
PCT/US2007/074377

(87) International publication number:
WO 2008/014360 (31.01.2008 Gazette 2008/05)

(54) MODULATORS OF CHEMOKINE RECEPTOR ACTIVITY, CRYSTALLINE FORMS AND PROCESS
MODULATOREN DER CHEMOKINREZEPTORAKTIVITÄT, KRISTALLINE FORMEN UND VERFAHREN
MODULATEURS DE L'ACTIVITÉ DU RÉCEPTEUR DE CHIMIOKINE, FORMES CRISTALLINES ET PROCÉDÉ

(84) Designated Contracting States: AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IS IT LI LT LU LV MC MT NL PL PT RO SE SI SK TR Designated Extension States: HR (30) Priority: 28.07.2006 US 834235 P 21.03.2007 US 896026 P 25.07.2007 US 782742 (43) Date of publication of application: 15.04.2009 Bulletin 2009/16 (60) Divisional application: 10001989.2 / 2 194 051 (73) Proprietor: Bristol-Myers Squibb Company Princeton NJ 08543-4000 (US) (72) Inventors: • CARTER, Percy, H. Princeton, NJ 08543 (US)	• DUNCIA, John, V. Princeton, NJ 08543 (US) • MUDRYK, Boguslaw, M. New Brunswick, NJ 08903 (US) • RANDAZZO, Michael, E. New Brunswick, NJ 08903 (US) • XIAO, Zili Princeton, NJ 08543 (US) • YANG, Michael, G. Princeton, NJ 08543 (US) • ZHAO, Rulin Princeton, NJ 08543 (US) (74) Representative: Beacham, Annabel Rose Dehns St Bride's House 10 Salisbury Square London EC4Y 8JD (GB) (56) References cited: WO-A-2005/021500 US-A1- 2005 054 627
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Note: Within nine months of the publication of the mention of the grant of the European patent in the European Patent Bulletin, any person may give notice to the European Patent Office of opposition to that patent, in accordance with the Implementing Regulations. Notice of opposition shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

TABLE 13

Determination of in vivo receptor occupancy of Example 1 in blood of hCCR2 KI mice in the 48-hour TG peritonitis model						
Dose (mg/kg)	Concentration of Mouse MCP-1 in plasma (nM)	Concentration of free Examples 1 in plasma (nM) (fold IC90 CCR2 binding)	% mouse MCP-1 bound CCR2	% of Example 1-bound CCR2	% free CCR2	% inhibition of monocyte/macrophage infiltration ^a
100	0.015	53 (1.8)	0.04	97.6	2.4	78
25	0.017	14 (0.5)	0.16	91.2	8.6	74
1	0.005	1.4 (0.05)	0.26	51.4	48.3	24
0 (vehicle)	0	0	0	0	100	0

Section 3. Chronic Efficacy Studies

Experimental autoimmune encephalomyelitis (EAE) Methods

[0302] To assess the effect of Example 1 on chronic models of disease, we used the EAE model of multiple sclerosis in hCCR2 KI mice. To study the effect of Example 1 on EAE model, 10 mice per group were used. On day 0, hCCR2 KI mice were immunized subcutaneously with a total of 200 µl of 300 µg myelin oligodendrocyte glycoprotein (MOG) 35-55 (Genemed Synthesis) mixed 1:1 with 300 µg Mycobacterium tuberculosis (H37Ra) (Becton-Dickinson) in incomplete Freund's adjuvant (IFA) (Sigma-Aldrich). On day 0 (two hours post-immunization) and day 2, mice were injected intraperitoneally with 100 µl of 400 ng pertussis toxin. Clinical scoring began on day 10, continued three times per week throughout the study, and was based on a scale of 0-5: 0, no signs of disease; 0.5, partial tail weakness; 1, limp tail or waddling gait with tail tonic; 1.5, waddling gait with partial tail weakness; 2, waddling gait with limp tail (ataxia); 2.5 (ataxia with partial limb paralysis; 3, full paralysis of one limb; 3.5, full paralysis of one limb with partial paralysis of a second limb; 4, full paralysis of two limbs; 4.5, moribund; 5, death. Oral dosing of Example 1 at 25 mg/kg and 55 mg/kg (BID) was initiated on day 1.

Results

[0303] Example 1 at both doses reduced the area under curve (AUC) of the clinical score by 49% (p < 0.05) (Figure 22). The IC50 is 3.7 nM for Example 1 in ¹²⁵I-mouse MCP-1 binding to hCCR2-expressing cells, hPBMCs (mimicking hCCR2 KI setting). Based on this IC50 value, the 25 and 55 mg/kg doses resulted in a free plasma trough concentration of 1- and 3-fold the binding IC90. Histological evaluation of the spinal cord on Day 22 did not demonstrate a significant difference in total inflammatory cellular infiltrate between mice treated with Example 1 versus vehicle. A marked neutrophil infiltrate was observed in mice treated with compound.

Claims

1. A compound that is N-((1R,2S,5R)-5-(*tert*-butylamino)-2-((S)-2-oxo-3-(6-(trifluoromethyl)quinazolin-4-ylamino)pyrrolidin-1-yl)cyclohexyl)acetamide, or a pharmaceutically acceptable salt thereof.
2. A compound of claim 1 that is a crystalline form of N-((1R,2S,5R)-5-(*tert*-butylamino)-2-((S)-2-oxo-3-(6-(trifluoromethyl)quinazolin-4-ylamino)pyrrolidin-1-yl)cyclohexyl)acetamide, or a pharmaceutically acceptable salt thereof.
3. The crystalline form of claims 1-2 characterized by unit cell parameters substantially equal to the following:

EP 2 046 779 B1

Cell dimensions:

a = 18.7240(4)
b = 8.0171(2)
c = 19.6568(5)
 $\alpha = 90$
 $\beta = 114.935(2)$
 $\gamma = 90$
 $V(\text{\AA}^3) = 2675.7(1)$

Space group $P2_12_12_1$
Molecules/unit cell 2

wherein said crystal is at a temperature of about +22°C (RT).

4. The crystalline form of claims 1-3 **characterized by** a powder x-ray diffraction pattern comprising three or more of 2 θ values ($\text{CuK}\alpha$ $\lambda=1.5418$ Å) selected from 5.5, 9.1, 12.1, 14.0 and 19.2, at a temperature of about 22°C.
5. The crystalline form of claims 1-4 further **characterized by** a powder x-ray diffraction pattern comprising four or more of 29 values ($\text{CuK}\alpha$ $\lambda=1.5418$ Å) selected from 5.5, 9.1, 12.1, 14.0 and 19.2 at a temperature of about 22°C.
6. The crystalline form of claims 1-5 **characterized by** fractional atomic coordinates substantially as listed in Table 3.
7. The crystalline form of claims 1-6 having a power x ray diffraction pattern substantially according to Figure 2.
8. A pharmaceutical composition comprising a compound of claims 1-7, and a pharmaceutically acceptable carrier or diluent.
9. A compound according to claims 1-8 for use in treating a disease in a mammal, wherein the disease is selected from diabetes, obesity, metabolic syndrome, stroke, neuropathic pain, ischemic cardiomyopathy, psoriasis, hypertension, scleroderma, osteoarthritis, aneurism, fever, cardiovascular disease, Crohn's disease, congestive heart failure, autoimmune diseases, HIV-infection, HIV-associated dementia, psoriasis, idiopathic pulmonary fibrosis, transplant arteriosclerosis, physically- or chemically-induced brain trauma, inflammatory bowel disease, alveolitis, colitis, systemic lupus erythematosus, nephrotoxic serum nephritis, glomerulonephritis, asthma, multiple sclerosis, atherosclerosis, vasculitis, vulnerable plaques, rheumatoid arthritis, restenosis, venous neointimal hyperplasia, dialysis-graft neointimal hyperplasia, arterio-venous shunt intimal hyperplasia, organ transplantation, chronic allograft nephropathy, and cancer.
10. A compound of claim 9 wherein the disease is selected from diabetes, obesity, Crohn's disease, systemic lupus erythematosus, glomerulonephritis, multiple sclerosis, atherosclerosis, restenosis, and organ transplantation.
11. A compound of claims 9-10 wherein the disease is selected from multiple sclerosis, atherosclerosis, Crohn's disease, and diabetes.
12. A pharmaceutical composition of claim 8, further comprising one or more other active ingredients.

Patentansprüche

1. Verbindung, die N-((1R, 2S, 5R)-5-(tert-Butylamino)-2-((S)-2-oxo-3-(6-trifluormethyl)chinazolin-4-ylamino)pyrrolidin-1-yl)cyclohexyl)acetamid ist, oder ein pharmazeutisch akzeptierbares Salz davon.
2. Verbindung nach Anspruch 1, die eine kristalline Form von N-((1R, 2S, 5R)-5-(tert-Butylamino)-2-((S)-2-oxo-3-(6-trifluormethyl)chinazolin-4-ylamino)pyrrolidin-1-yl)cyclohexyl)acetamid ist, oder ein pharmazeutisch akzeptierbares Salz davon.
3. Kristalline Form nach den Ansprüchen 1-2, **gekennzeichnet durch** Parameter der Einheitszelle, die im Wesentlichen gleich den folgenden sind:

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

Applicant's or agent's file reference 11079 PCT	FOR FURTHER ACTION		See item 4 below
International application No. PCT/US2007/074377	International filing date (day/month/year) 26 July 2007 (26.07.2007)	Priority date (day/month/year) 28 July 2006 (28.07.2006)	
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237			
Applicant BRISTOL-MYERS SQUIBB COMPANY			

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 bis.1(a).

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒ Box No. I	Basis of the report
☐ Box No. II	Priority
☐ Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒ Box No. IV	Lack of unity of invention
☒ Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐ Box No. VI	Certain documents cited
☐ Box No. VII	Certain defects in the international application
☒ Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis .2).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Date of issuance of this report 03 February 2009 (03.02.2009)
	Authorized officer Nora Lindner e-mail: pt11.pct@wipo.int

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference see form PCT/ISA/220	FOR FURTHER ACTION See paragraph 2 below
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International application No. PCT/US2007/074377	International filing date (day/month/year) 26.07.2007	Priority date (day/month/year) 28.07.2006
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International Patent Classification (IPC) or both national classification and IPC
INV. C07D403/12 C07D207/273 A61K31/4025 C07D317/72

Applicant
BRISTOL-MYERS SQUIBB COMPANY

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 eprmu d Fax: +49 89 2399 - 4465	Date of completion of this opinion see form PCT/ISA/210	Authorized Officer Goss, Ilaria Telephone No. +49 89 2399-8292
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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2007/074377

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))
3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ on paper
 - ☐ in electronic form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in electronic form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43bis.1 and 64.1) is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43bis.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

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Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has, within the applicable time limit:
- ☒ paid additional fees
 - ☐ paid additional fees under protest and, where applicable, the protest fee
 - ☐ paid additional fees under protest but the applicable protest fee was not paid
 - ☐ not paid additional fees
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with
 - ☒ not complied with for the following reasons:
see separate sheet
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☒ all parts.
 - ☐ the parts relating to claims Nos.

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	<u>1-20</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-20</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-20</u>
	No: Claims	

2. Citations and explanations

see separate sheet

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Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

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AUTHORITY (SEPARATE SHEET)**

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Re Item IV

Lack of unity of invention

1. The application in suit refers to several different topics/aspects (see the list of inventions defined above wherein the main two concepts have been grouped together). Claim 1 and dependent claims thereupon refers to new compounds with improved pharmacological characteristics (and the crystalline forms). The main structural difference of the claimed end-compounds to the many structurally related compounds of prior art documents resides mainly in the specific acetamide group at position 1 as well as the tert-butylamino substituent of the cyclohexyl and its solid state. The closest prior art is represented by the compounds disclosed in D1 as well as D2 describing the general formula as well as specific compounds structurally close related to those now claimed. In another aspect, the invention provides new and/or improved processes to prepare such compounds and intermediates therefore (independent claim 20 relating to structurally different classes of compounds).

2. According to Rule 13(1), 1st sentence, PCT, the requirements of unity of invention in the sense of a technical relationship may be met, when all claimed alternatives belong either to a class of compounds which may be expected to behave in the same way in the context of the claimed inventions ("MARKUSH-claims"); to a new process and related intermediates (giving the distinguishing structural contribution to the end products) or whatsoever. The technical relationship involves those common special technical features that define a contribution over the state of the art (Rule 13(1), 2nd sentence, PCT). However, such contribution cannot be recognized on the basis of this expectation if for some aspects of the invention a specific prior art should be taken into consideration since the problem is that of the provision of new compounds with advantages vis-à-vis the class of compounds already shown in the prior art to behave in the manner disclosed in the application and for another topic the prior art is a totally different one (all the processes/approaches to preparing the desired end product with less drawbacks and the provision of intermediates not showing the distinguishing novelty rendering feature) and thus lacking a common technical feature. In particular claim 20 relates to intermediates showing different structures among which i) many 1,4-dioxo-spiro[4.5]dec-8-yl core structure bound to the 2-oxo-1-pyrrolidinyl ring, ii) one compound showing the 4-oxocyclohexyl structure and iii) one carrying a 4-tert-butylamino substituent at position 3 of the pyrrolidine ring. As also recognized by the applicant on page 25, the coupling of a cyclohexanone of formula II with a suitable amino acid of formula III to give amide IV is known from D1 (as well as from other documents as referred to on page 80, line 20) however not these specific intermediates for transforming the carboxylic acid moiety into isocyanate or an amide moiety.

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Therefore unity is present among the process of claim 17 and all intermediates claimed in claim 20 which are seen as being closely interrelated.

3. As far as the first invention as defined above is concerned, the compound differs from those of the citations in view of the specific substitution pattern (acetamide group) claimed in independent claim 1. The intermediates claimed in claim 20 are of heterogeneous nature form, however, a unitary inventive concept with process claim 17 using the same, specific compounds' class. Thus the problem underlying the application is not considered to be a unique one and the contribution seen as common technical/structural feature can not, therefore, qualify as a unifying element.

4. There is a lack of unity mainly a priori but also a posteriori and the different inventions and/or groups of inventions, not belonging to a common inventive concept, have to be formulated as different subject(s) in the order chosen by the applicant.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

V.1 Reference is made to the following documents:

D1: WO 2005/021500 A (SQUIBB BRISTOL MYERS CO [US]; CARTER PERCY H [US];
CHERNEY ROBERT J [U] 10 March 2005 (2005-03-10) cited in the application

D2: US 2005/054627 A1 (CARTER PERCY H [US] ET AL) 10 March 2005 (2005-03-10)
cited in the application

V.2 Claims 10 to 16 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv)/67.1(iv) PCT.

The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as patentable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a product, in particular substances or compositions for in a first or further medical use.

V.3 Novelty and inventive step (Invention 1)

Claim 1 and dependent claims thereon refer to a specific acetamide derivative of one of the many MCP-1 to MPC-4 via CCR2 modulators known from D1 and/or D2, or a pharmaceutically acceptable salt or solvate having unexpected combination of desirable pharmacological characteristics (see page 13, paragraph [0030]).

The compound claimed as well as its crystalline forms have not been previously described. Novelty can be thus recognized for the whole subject-matter claimed.

The problem underlying invention 1 of the present application is seen in the provision of

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new compounds with improved pharmacological characteristics compared with known chemokine modulators known from D1 and D2 (also cited in the application). According to many tables provided, data (in vivo, in vitro as well as in vivo pharmacokinetic data) are provided for Example 1 of the present invention compared to those of many examples from both D1 as well as D2.

From the data provided it appears that, indeed, the general pharmacological as well as pharmacokinetic profile of example 1 (which form is exactly meant?) is quasi the result of the better values of different compounds compared with. The applicant should kindly confirm it and take shortly position on that (also regarding the question of the general definition Example 1 without reference at the specific form used for the parameters obtained.

The application involves an inventive step.

V.4 Novelty and inventive step (invention 2)

Claim 17 (dependent claims thereupon) as well as intermediates claim 20 appear to satisfy the requirements of Art.33(2) PCT for the following reasons.

Claim 17 refers to a process for preparing a compound having formula X starting from V via VI forming a ketal and transforming it further. Both Claims 18 and 19 further specify the nature of the intermediate involved in the process of claim 17 and claim 20 relates to specific compounds of formula VII, VIII, IX and X. None of the documents reported in the search report describes either the specific individual compounds of claim 20 nor the process for preparing X as claimed in claim 17 (see also the previous international patents cited on page 79, Example 1, 2nd Alternative preparation).

Thus novelty can be recognized for the whole subject-matter of invention 2.

With regard to the problem underlying the second invention, it is seen in the provision of an alternative process for preparing the desired end product with less drawbacks and related intermediates according to claim 20. As already anticipated under novelty, none of the documents cited in the search report and/or referred to in the description anticipates the specific claimed step according to claim 17. No obviousness objection can be raised and the many examples provided indeed show that the problem has been solved. In this respect it is worth noting that all compounds of formula VII to X (from CO_2H ->isocyanate->carbamate via azidocarbonyl as well as the acetamido derivatives) are considered to be closely interrelated and indeed so linked with the process described in claim 17 as to form a unitary inventive concept, thus representing the special technical features of the whole inventive process.

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Re Item VIII

Certain observations on the international application

With regard to the use of the definition "...the N-2 Form" in claim 2, the applicant is reminded that it is not sufficient to simply define a specific polymorph with the term "Form X or Y" since the claims must be drafted in terms of the technical features of the invention as otherwise the person skilled in the art would absolutely not know which distinct crystal structure is exactly meant.

The form comprised and meant according to claim 2 must be clearly defined by the diffraction pattern or another special technical feature in order to define the crystalline material claimed.