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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Act 412 REPOSPRESRECU Folios: 23

Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

DIVISIÓN DE NUEVAS CREACIONES

E. _____ S. _____

Re: PI.-GLAXOSMITHKLINE LLC.-Solicitud de Patente de Invención en Fase Nacional PCT para "COMPUESTO 4-(8-METOXI-1((1-METOXIPROPAN-2-IL)-2(TETRAHIDRO-2H-PIRAN-4-IL)-1H-IMIDAZO[4,5-C]QUINOLIN-7-IL)-3,5-DIMETIL ISOXAZOL COMO INHIBIDOR BROMODOMINIO".- Clase C07D 471/04. -Expediente número 14-011.125.-

Yo, **ALICIA LLOREDA RICAURTE**, mayor, vecina de esta ciudad, identificada con la cédula de ciudadanía número 39.690.713 de Usaquén, Representante Legal en Bogotá para todos los asuntos relacionados con la Propiedad Industrial de la sociedad **GLAXOSMITHKLINE LLC**, organizada y existente de conformidad con las leyes del Estado de Delaware, Estados Unidos de América, domiciliada en Wilmington, Delaware, Estados Unidos de América, atentamente manifiesto a usted que interpongo **RECURSO DE REPOSICIÓN** contra la Resolución Número **39059** dictada por el señor Superintendente de Industria y Comercio el 30 de Julio de 2015, y notificada mediante listado único de notificaciones de propiedad industrial del 4 de Agosto de 2015, por medio de la cual se niega el privilegio de patente solicitado para la invención contenida en el expediente de la referencia.

I. FUNDAMENTOS DE DERECHO

Como fundamento de mi recurso me permito manifestar ante ese Despacho que el contenido de la Resolución Número **39059** evidencia que durante el examen técnico realizado a la solicitud en cuestión de ninguna manera se consideró el alcance, objeto e importancia de la invención denegada en su verdadera dimensión, esto es, no se consideró el valioso aporte técnico que representa para el arte en cuestión el compuesto químico específico que es revelado en la solicitud denegada.

En efecto, a pesar de los argumentos proporcionados por el solicitante en respuesta al Concepto Técnico emitido por ese Despacho el 17 de Febrero de 2014, en la Resolución impugnada este Despacho mantiene las objeciones frente al nivel inventivo de la solicitud, argumentando básicamente que:

"...la persona del oficio normalmente versada en la materia, estaría motivada en enlazar un radical éter alquílico al nitrógeno de la posición 1 del anillo imidazol de las estructuras reveladas en el documento D1 de acuerdo con lo divulgado en el documento D2, para llegar así al objeto de la reivindicación 1 de la solicitud. Por lo cual, la materia reclamada se considera obvia."

Así como también que:

"...este Despacho manifiesta que si bien es cierto, el mecanismo de acción presentado por los compuestos reclamados es diferente al mecanismo de acción presentado para los compuestos divulgados en el documento D2, no es menos cierto que tanto los compuestos reclamados como los divulgados en el documento D2 resuelven el mismo problema técnico, es decir, que ambos tipos de compuestos son útiles en el tratamiento del cáncer e infecciones virales, por lo anterior, el mecanismo de acción no se puede considerar como una característica técnica esencial del compuesto".

Por consiguiente, a continuación me permito demostrar ante ese Despacho que la materia revelada en la solicitud de patente en cuestión cumple a cabalidad con el requisito de nivel inventivo exigido por el artículo 18 de la Decisión 486 de 2000.

1) Consideraciones técnicas frente a las enseñanzas del arte previo

Me permito manifestar ante ese Despacho que el compuesto químico específico revelado en la solicitud de patente denegada presenta un inequívoco carácter inventivo con respecto a las enseñanzas de las anterioridades mencionadas en la Resolución Número **39059**, esto es, frente a los documentos **WO 2011/054846 (D1)** y **US 2004/0147543 (D2)**. En este sentido, a continuación me permito realizar un análisis comparativo detallado entre la información revelada en la presente solicitud y las enseñanzas brindadas por dichas anterioridades.

Dicha modificación estructural, sin embargo, de ninguna manera resulta evidente para la persona medianamente versada en la materia a partir de las enseñanzas del documento D1, tal y como se estableció explícitamente en el reporte preliminar internacional sobre patentabilidad que fue expedido por la Oficina Europea de Patentes actuando como Autoridad de Búsqueda Internacional (El anexo I del presente memorial corresponde a una copia completa de dicho Reporte):

"3. Nivel inventivo

La materia reivindicada también cumple con los requerimientos del Artículo 33(3) del PCT por las siguientes razones.

El estado del arte más cercano para la presente solicitud es representado por D1. D1 divulga el mismo grupo de compuestos de imidazoquinolina. El sustituyente en la posición 1 del anillo de imidazol es, sin embargo, diferente y no puede ser un grupo alcoxialquilo, en lo absoluto. En la presente solicitud, la variación estructural, es decir, la sustitución con 1-metoxipropan-2-il presuntamente conduce a derivados de imidazoquinolina con las mismas propiedades/actividad cualitativa como aquellas descritas en D1. En vista de la parte experimental en las páginas 29f y la otra información como es dada en la descripción, podría asumirse que los compuestos reivindicados exhiben en realidad la actividad presunta.

En la ausencia de datos experimentales u otra información apropiada que pudiera demostrar un efecto inesperado o sorprendente, el problema afrontado en la presente solicitud puede ser visto como proporcionar derivados de imidazoquinolinas adicionales con propiedades inhibitorias de bromodominio. El intercambio del sustituyente en la posición 1 de acuerdo con lo divulgado en D1 por un sustituyente alcoxialquilo, en particular con un grupo metoxipropan-2-il, no es obvio porque D1 no da pista alguna sobre dicho grupo."

En efecto, no existe enseñanza alguna en el documento D1 que hubiera podido sugerirle a la persona medianamente versada en la materia lo siguiente:

- Escoger específicamente el compuesto químico del ejemplo 223 de dicha anterioridad como punto de partida para el desarrollo en cuestión;
- Reemplazar únicamente el radical fluorofeniletil de dicho compuesto del ejemplo 223 de D1 por un grupo metoxipropan-2-il; y

- Asumir como obvio o esperable que el nuevo compuesto químico obtenido presentara actividad biológica efectiva como inhibidor de bromodominio y por ende con actividad terapéutica para el tratamiento de problemas inmunológicos o alérgicos.

Lo anterior corresponde a una prueba fehaciente de que la materia revelada en la solicitud de patente en cuestión de ninguna manera es evidente a partir de las enseñanzas del documento D1 y por lo tanto cumple a cabalidad con el requisito de nivel inventivo exigido por el artículo 18 de la Decisión 486 de 2000.

Ahora bien, tal y como se analizará en el siguiente numeral, no existe motivación técnica alguna (diferente al hindsight) para combinar las enseñanzas de D1 y D2, y adicionalmente -y tan sólo en gracia de discusión-, la combinación de dichas anterioridades ni siquiera llevaría a la persona medianamente versada a desarrollar de manera evidente el compuesto químico revelado por el solicitante en la presente invención.

1.3. El documento D2 no complementa de manera alguna las enseñanzas del documento D1

En relación con el documento D2 resulta relevante destacar en primer lugar que dicha anterioridad divulga una serie de compuestos derivados de imidazoquinolina, los cuales, de acuerdo con los inventores de dicha anterioridad, son capaces de inhibir la biosíntesis de citocina.

Como consecuencia de lo anterior, es claro que la persona medianamente versada en la materia que tuviera como objetivo técnico desarrollar compuestos químicos que actuaran como inhibidores de bromodominio de la familia BET (alternativos a aquellos divulgados en el documento D1), de ninguna manera se habría visto motivado a combinar las enseñanzas de dichos documentos D1 y D2 debido a que el documento D2 de ninguna manera aborda el mismo problema técnico, esto es, debido a que el documento D2 tiene un propósito técnico diferente al de los compuestos revelados en D1 y la solicitud de patente en cuestión.

Ahora bien, tan sólo en gracia de discusión, asumiendo entonces que la persona medianamente versada en la materia se viera motivada por alguna razón a combinar las enseñanzas de D1 y D2, resulta determinante resaltar que dicho documento D2 corresponde a la divulgación de una cantidad excesivamente amplia de compuestos químicos que abarcan una altísima variedad de alternativas químicas estructurales.

Sin embargo, a lo largo de todos los ejemplos químicos divulgados en D2 no existe un solo compuesto que se caracterice por comprender un grupo metoxipropan-2-il como aquel que hace parte del compuesto revelado en la presente invención y que constituye la diferencia estructural frente a los compuestos del documento D1.

En este sentido me permito aclarar a ese Despacho que el compuesto químico divulgado en el ejemplo 207 de D2 (el cual fue resaltado por el señor Examinador como parte de la Resolución aquí impugnada) se caracteriza porque comprende un grupo metoxipropan-1-il, el cual, como es evidente, no equivale al grupo metoxipropan-2-il del compuesto químico de la presente invención.

Sumado a lo anterior, resulta muy poco probable que la persona medianamente versada en la materia encontrara obvio combinar las enseñanzas de los documentos D1 y D2, interesándose únicamente en tomar el grupo metoxipropan-1-il de D2 (ignorando por completo los demás aspectos estructurales de los compuestos divulgados en dicha anterioridad), modificarlo por el grupo metoxipropan-2-il e incluirlo a manera de modificación exclusiva precisamente en el compuesto 223 del documento D1.

Así, por ejemplo, resulta conveniente preguntarse ¿Por qué dicha persona medianamente versada en la materia decidiría de manera obvia ignorar que todos los compuestos divulgados en D2 presentan como característica estructural esencial un grupo amino primario sobre el anillo fusionado?

O ¿Por qué la persona medianamente versada en la materia encontraría evidente ignorar que el compuesto del ejemplo 207 de D2 presenta otras diferencias estructurales con respecto al compuesto revelado en la presente invención, tales como el grupo denotado como 'R', la carencia de un sustituyente metoxi y la carencia del grupo tetrahidropirano?

Lo anterior sugiere entonces que la decisión de ese Despacho de desconocer la existencia de nivel inventivo en la materia revelada en la solicitud de patente en cuestión es simplemente el resultado de haber llevado a cabo un análisis en retrospectiva, actuación que, tal y como se analiza en el siguiente numeral, no resulta válida para intentar demostrar una supuesta falta de nivel inventivo de una solicitud de patente en particular.

1.4. El análisis en retrospectiva no es válido para evaluar el nivel inventivo de una solicitud de patente

Finalmente y aparte de los argumentos técnicos proporcionados previamente, de la manera más atenta me permito señalar que en el numeral 2.13.6.3 de la Guía para examen de solicitudes de patente de invención y modelo de utilidad, se describe lo siguiente en relación con las características de un análisis de patentabilidad realizado en retrospectiva:

"2.13.6.3 Análisis ex post facto o retrospectivo o hindsight

Es importante tener en cuenta que una invención reivindicada que, a primera vista, parece evidente, puede ser inventiva. Una vez formulada una nueva idea, a menudo se puede demostrar teóricamente el modo en el que se podría llegar a ella, a partir de algo conocido, a través de una serie de etapas aparentemente fáciles. El examinador de patentes debe evitar el uso de un análisis ex post facto de este tipo.¹³⁸

Es decir, el estado de la técnica se debe examinar sin el beneficio del conocimiento ofrecido retrospectivamente por la invención reivindicada. La indicación o la sugerencia que permita llegar a la invención reivindicada deben proceder del estado de la técnica o de los conocimientos generales de la persona del oficio normalmente versada en la materia, y no basarse en la divulgación del solicitante.

Uno de los factores que deben tomarse en consideración para establecer si la persona del oficio normalmente versada en la materia hubiera estado motivada a combinar los documentos del estado de la técnica es la probabilidad razonable de éxito como resultado de tal combinación de sugerencias del estado de la técnica, consideradas colectivamente.

En cualquier caso, el examinador de patentes deberá esforzarse por hacer una evaluación práctica conforme a la realidad. Deberá tener en cuenta todo lo que se sabe en cuanto a los antecedentes de la invención reivindicada y dar el valor justo a los argumentos o pruebas pertinentes presentados por el solicitante¹³."

Con base en lo anterior me permito manifestar nuevamente ante ese Despacho que la estructura del compuesto químico específico revelado en la presente invención, así como su actividad biológica efectiva como inhibidor de bromodominio, de ninguna manera resultan evidentes para la persona medianamente versada en la materia a partir de las enseñanzas del estado de la técnica anterior, y sólo un estudio de patentabilidad en

retrospectiva permitiría que dicha persona medianamente versada en la materia pensara en combinar las enseñanzas de los documentos D1 y D2 señalados por ese Despacho.

2) Concesión de la patente en otros países y regiones

Aparte de todo lo mencionado hasta el momento, atentamente me permito señalar ante ese Despacho que la Oficina de marcas y patentes de Estados Unidos y la Oficina Europea de patentes han reconocido los méritos de patentabilidad de la materia técnica en cuestión, y como consecuencia de ello han otorgado la patente US 9,067,936 y expedido el certificado de intención de conceder la patente, respectivamente (*Los anexos II y III del presente recurso corresponden a una copia de tales documentos*).

Ahora bien, ante todo es preciso señalar que con la información mencionada anteriormente de ninguna manera pretendo desconocer la independencia de la que goza la Superintendencia de Industria y Comercio al momento de analizar los méritos de patentabilidad de una solicitud, de acuerdo con las disposiciones del Convenio de París para la protección de la propiedad industrial.

Sin embargo, sí considero de gran importancia resaltar el hecho de que la materia técnica revelada en la solicitud de patente en cuestión corresponde a materia que ha sido catalogada como novedosa, inventiva e industrialmente aplicable por los Examinadores de la Oficina Europea de patentes y de la Oficina de marcas y patentes de Estados Unidos, hecho que evidentemente representa un claro indicio de que la materia técnica revelada en la solicitud de patente en estudio cumple a cabalidad con los requisitos de patentabilidad establecidos en la Decisión Andina 486 de 2000.

II. CONCLUSIONES

Con base en los argumentos técnicos mostrados previamente, me permito manifestar ante ese Despacho que la materia revelada en la solicitud de patente en cuestión presenta un inequívoco carácter inventivo frente a las enseñanzas del documento citado en la Resolución Número **39059** aquí impugnada, cumpliendo de esta manera con las disposiciones establecidas en el artículo 18 de la Decisión 486 de 2000, y por lo tanto demostrando ser merecedora del privilegio de patente requerido.

III. PETICIÓN

En vista de todo lo anterior, ruego a usted proceder a estudiar nuevamente la solicitud a la luz de los argumentaciones presentadas y proceder a revocar la Resolución Número **39059**, con el fin de que se conceda el privilegio de patente a la presente invención.

IV. PODER

En este punto me permito señalar ante ese Despacho que una copia del documento de poder que acredita mi calidad de Representante Legal en Bogotá para todos los asuntos relativos a la Propiedad Industrial de la sociedad peticionaria fue presentado junto con mi petitorio de 21 de Enero de 2014.

V. ANEXOS

Anexo al presente recurso me permito presentar:

- i) Copia del Reporte de Examen Preliminar Internacional sobre patentabilidad expedido para la solicitud de patente en cuestión por parte de la Oficina Europea de patentes actuando como Autoridad de búsqueda Internacional;
- ii) Copia de la carátula y capítulo reivindicatorio de la patente US 9,067,936 B2; y,
- iii) Copia del documento expedido por la Oficina Europea de patentes notificando la intención de conceder la solicitud de patente equivalente.

VI. DOMICILIO

Mi dirección es Calle 72 No. 5-83, Piso 6º, Bogotá D.C.

Del Señor Superintendente,



ALICIA LLOREDA RICAURTE

T.P. 53.215

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 ADS/PB64734	FOR FURTHER ACTION	See item 4 below
International application No. PCT/EP2012/065918	International filing date (day/month/year) 15 August 2012 (15.08.2012)	Priority date (day/month/year) 17 August 2011 (17.08.2011)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant GLAXOSMITHKLINE LLC		

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 5 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: <table border="0"><tr><td>☒</td><td>Box No. I</td><td>Basis of the report</td></tr><tr><td>☐</td><td>Box No. II</td><td>Priority</td></tr><tr><td>☐</td><td>Box No. III</td><td>Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</td></tr><tr><td>☐</td><td>Box No. IV</td><td>Lack of unity of invention</td></tr><tr><td>☒</td><td>Box No. V</td><td>Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</td></tr><tr><td>☐</td><td>Box No. VI</td><td>Certain documents cited</td></tr><tr><td>☐</td><td>Box No. VII</td><td>Certain defects in the international application</td></tr><tr><td>☐</td><td>Box No. VIII</td><td>Certain observations on the international application</td></tr></table>		☒	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
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☐	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 18 February 2014 (18.02.2014) Authorized officer Nora Lindner e-mail: pt05.pct@wipo.int
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PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

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

International application No.
PCT/EP2012/065918

International filing date (day/month/year)
15.08.2012

Priority date (day/month/year)
17.08.2011

International Patent Classification (IPC) or both national classification and IPC
INV. C07D471/04 A61K31/4745 A61P29/00 A61P37/00

Applicant
GLAXOSMITHKLINE LLC

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 and 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.

Name and mailing address of the ISA:



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0
Fax: +49 89 2399 - 4465

Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

Von Daacke, Axel
Telephone No. +49 89 2399-8286



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2012/065918

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, this opinion has been established on the basis of a sequence listing filed or furnished:
 - a. (means)
 - ☐ on paper
 - ☐ in electronic form
 - b. (time)
 - ☐ in the international application as filed
 - ☐ together with the international application in electronic form
 - ☐ 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 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. 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>1-15</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-15</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-15</u>
	No: Claims	

2. Citations and explanations

see separate sheet

V REASONED STATEMENT

1. PRIOR ART

Reference is made to the following document:

- D1 WO 2011/054846 A1 (GLAXOSMITHKLINE LLC [US]; BOUILLOT ANNE MARIE JEANNE [FR]; DONCHE FRED) 12 May 2011 (2011-05-12) cited in the application

Claims 12-15 relate to a subject-matter considered by this Authority to be covered by the provision of Rule 39.1(iv)/67.1(iv) PCT.

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

2. NOVELTY

The claimed subject-matter is considered to be novel (Article 33(2) PCT). The essential structural difference between the claimed compounds and those of D1 relates in the presence of the 1-methoxypropan-2-yl substituent

3. INVENTIVE STEP

The claimed subject-matter does also fulfil the requirements of Article 33(3) PCT for the following reasons.

The closest state of the art for the present application is represented by D1. D1 discloses the same group of imidazoquinoline compounds. The substituent in 1-position of the imidazole ring is, however, different and cannot be an alkoxyalkyl group, at all. In the present application, the structural variation, i.e. the 1-methoxypropan-2-yl substitution is alleged to lead to imidazoquinoline derivatives with the same qualitative activity/properties as those described in D1. In view of the experimental part on pages 29f and the other information as given in the description, it can be assumed that the claimed compounds do actually exhibit the alleged activity.

In the absence of experimental data or other appropriate information which would demonstrate a surprising or unexpected effect the problem underlying the present application may be seen in providing further imidazoquinoline derivatives with bromodomaine inhibiting properties. The exchange of the 1-substituents as disclosed in D1 by an alkoxyalkyl substituent, in particular a methoxypropan-2-yl group, is not obvious because D1 gives no hint to such a group.

4. INDUSTRIAL APPLICABILITY

The claimed object is considered as susceptible of industrial application because it can be made or used in the industry (Article 33(4) PCT).



US009067936B2

GlaxoSmithKline LLC

Exp.

14-011-125

ii)

(12) **United States Patent**
Demont et al.

(10) **Patent No.:** **US 9,067,936 B2**
(45) **Date of Patent:** **Jun. 30, 2015**

(54) **4-(8-METHOXY-1-((1-METHOXYPROPAN-2-YL)-2-(TETRAHYDRO-2H-PYRAN-4-YL)-1H-IMIDAZO[4,5-C]QUINOLIN-7-YL)-3,5-DIMETHYLISOXAZOLE AND ITS USE AS BROMODOMAIN INHIBITOR**

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CPC *C07D 471/04* (2013.01); *A61K 31/4745* (2013.01)

(58) **Field of Classification Search**
None
See application file for complete search history.

(56) **References Cited**

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(57) **ABSTRACT**

Novel quinoline compounds pharmaceutical compositions containing such compounds and their use in therapy.

12 Claims, 5 Drawing Sheets

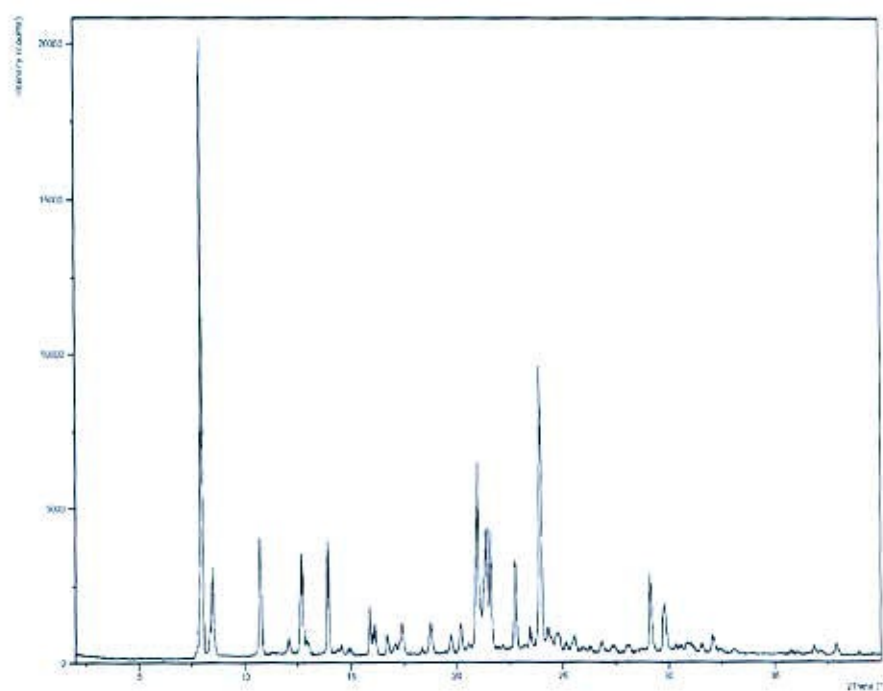


Figure 1

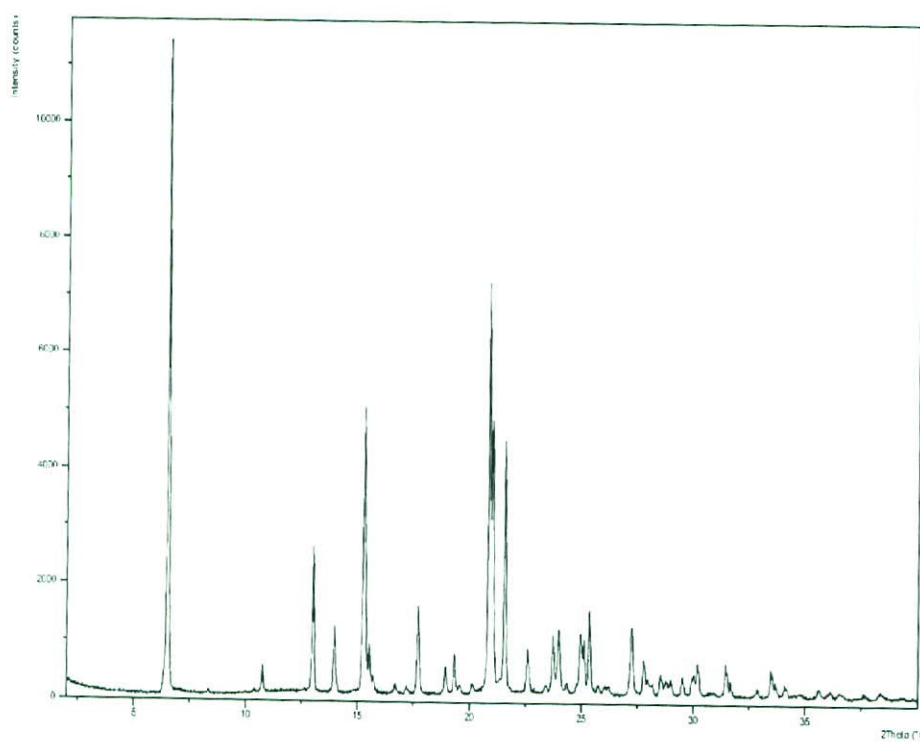


Figure 2

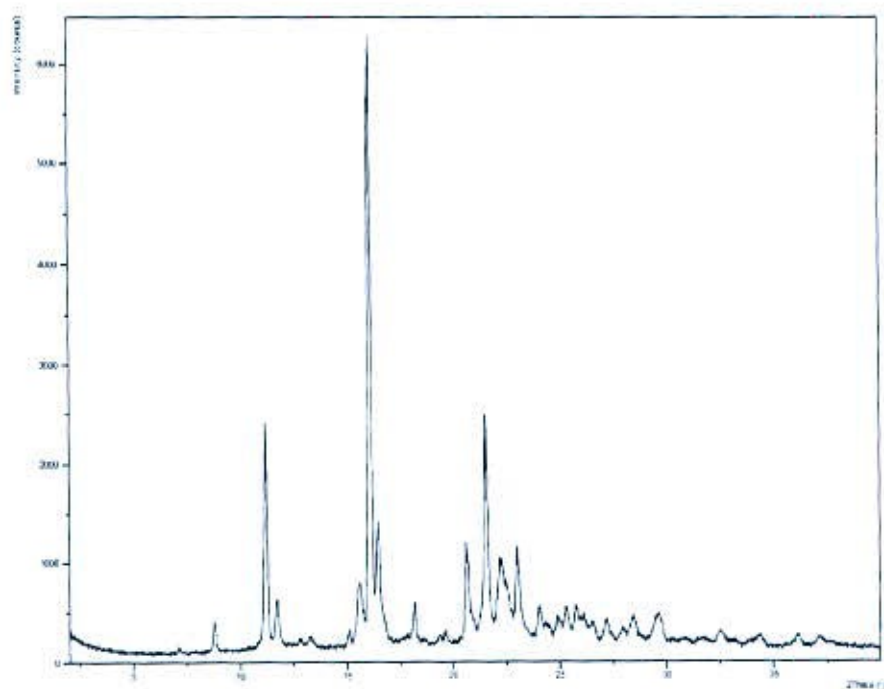


Figure 3

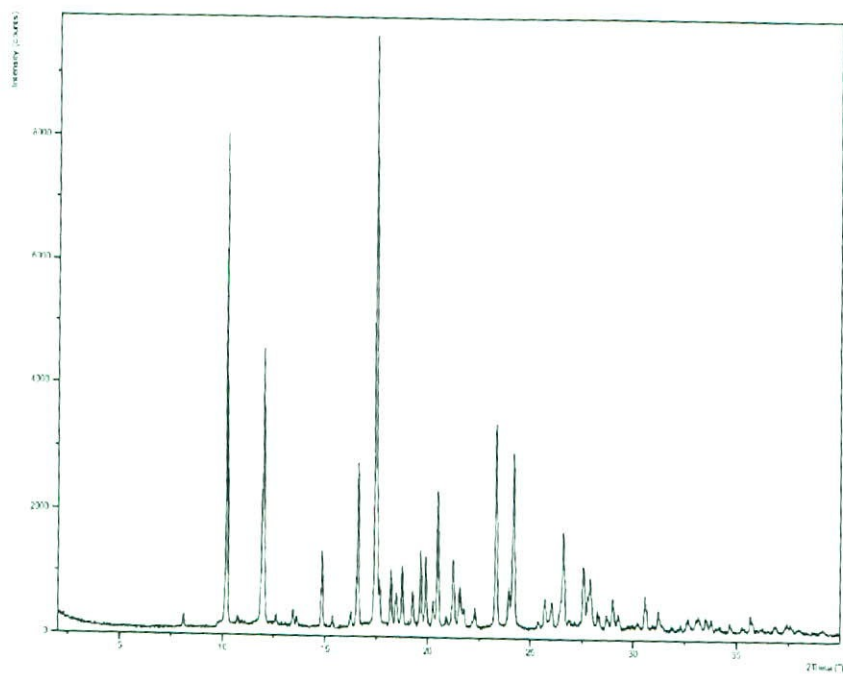


Figure 4

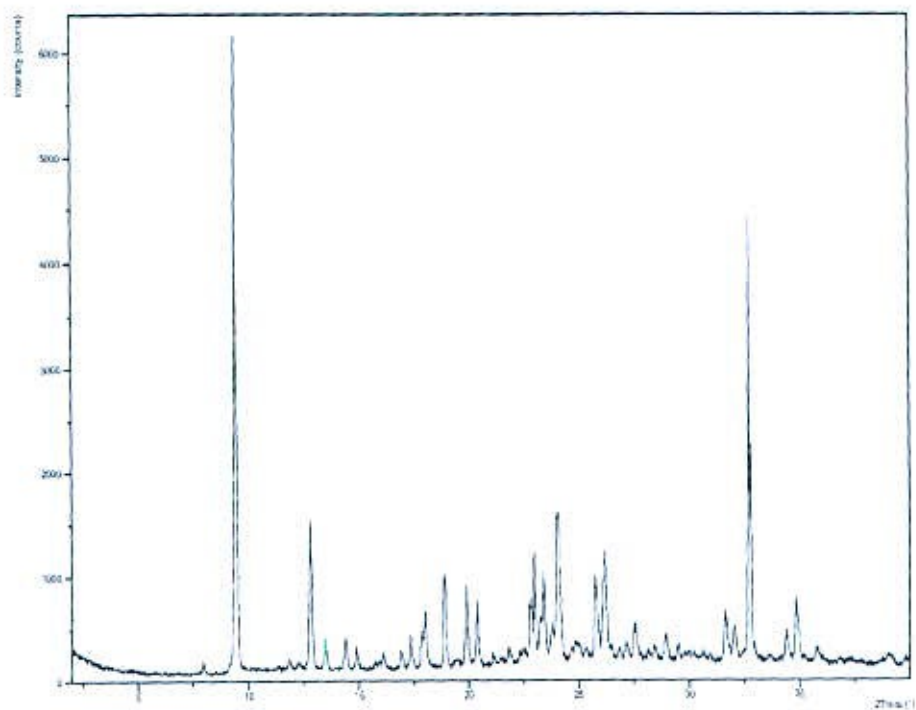


Figure 5

4-(8-METHOXY-1-((1-METHOXYPROPAN-2-YL)-2-(TETRAHYDRO-2H-PYRAN-4-YL)-1H-IMIDAZO[4,5-C]QUINOLIN-7-YL)-3,5-DIMETHYLISOXAZOLE AND ITS USE AS BROMODOMAIN INHIBITOR

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is filed pursuant to 35 USC 371 as a United States National Phase Application of International Patent Application Serial No. PCT/EP2012/065918 filed on Aug. 15, 2012, which claims priority from 1114103.3 filed on Aug. 17, 2011 in the United Kingdom.

FIELD OF THE INVENTION

The present invention relates to novel compounds, pharmaceutical compositions containing such compounds and to their use in therapy.

BACKGROUND OF THE INVENTION

The genomes of eukaryotic organisms are highly organised within the nucleus of the cell. The long strands of duplex DNA are wrapped around an octamer of histone proteins (most usually comprising two copies of histones H2A, H2B, H3 and H4) to form a nucleosome. This basic unit is then further compressed by the aggregation and folding of nucleosomes to form a highly condensed chromatin structure. A range of different states of condensation are possible, and the tightness of this structure varies during the cell cycle, being most compact during the process of cell division. Chromatin structure plays a critical role in regulating gene transcription, which cannot occur efficiently from highly condensed chromatin. The chromatin structure is controlled by a series of post translational modifications to histone proteins, notably histones H3 and H4, and most commonly within the histone tails which extend beyond the core nucleosome structure. These modifications include acetylation, methylation, phosphorylation, ubiquitinylation, SUMOylation. These epigenetic marks are written and erased by specific enzymes, which place the tags on specific residues within the histone tail, thereby forming an epigenetic code, which is then interpreted by the cell to allow gene specific regulation of chromatin structure and thereby transcription.

Histone acetylation is most usually associated with the activation of gene transcription, as the modification loosens the interaction of the DNA and the histone octamer by changing the electrostatics. In addition to this physical change, specific proteins bind to acetylated lysine residues within histones to read the epigenetic code. Bromodomains are small (~110 amino acid) distinct domains within proteins that bind to acetylated lysine residues commonly but not exclusively in the context of histones. There is a family of around 50 proteins known to contain bromodomains, and they have a range of functions within the cell.

The BET family of bromodomain containing proteins comprises 4 proteins (BRD2, BRD3, BRD4 and BRD-t) which contain tandem bromodomains capable of binding to two acetylated lysine residues in close proximity, increasing the specificity of the interaction. BRD2 and BRD3 are reported to associate with histones along actively transcribed genes and may be involved in facilitating transcriptional elongation (Leroy et al, Mol. Cell. 2008 30(1):51-60), while BRD4 appears to be involved in the recruitment of the pTEF-β complex to inducible genes, resulting in phosphory-

lation of RNA polymerase and increased transcriptional output (Hargreaves et al, Cell, 2009 138(1): 129-145). It has also been reported that BRD4 or BRD3 may fuse with NUT (nuclear protein in testis) forming novel fusion oncogenes, BRD4-NUT or BRD3-NUT, in a highly malignant form of epithelial neoplasia (French et al. Cancer Research, 2003, 63, 304-307 and French et al. Journal of Clinical Oncology, 2004, 22 (20), 4135-4139). Data suggests that BRD-NUT fusion proteins contribute to carcinogenesis (Oncogene, 2008, 27, 2237-2242). BRD-t is uniquely expressed in the testes and ovary. All family members have been reported to have some function in controlling or executing aspects of the cell cycle, and have been shown to remain in complex with chromosomes during cell division—suggesting a role in the maintenance of epigenetic memory. In addition some viruses make use of these proteins to tether their genomes to the host cell chromatin, as part of the process of viral replication (You et al Cell, 2004 117(3):349-60).

Japanese patent application JP2008-156311 discloses a benzimidazole derivative which is said to be a BRD2 bromodomain binding agent which has utility with respect to virus infection/proliferation.

Patent application WO2009084693A1 discloses a series of thienotriazolodiazepine derivatives that are said to inhibit the binding between an acetylated histone and a bromodomain containing protein which are said to be useful as anti-cancer agents.

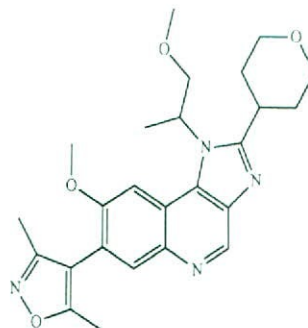
Patent application WO2011/054846 discloses a series of quinoline derivatives that inhibit the binding of BET family bromodomains with acetylated lysine residues.

Novel compounds have been found which inhibit the binding of bromodomains with its cognate acetylated proteins, more particularly a class of compounds that inhibit the binding of BET family bromodomains to acetylated lysine residues. Such compounds will hereafter be referred to as "bromodomain inhibitors".

SUMMARY OF THE INVENTION

In a first aspect of the present invention, there is provided a compound of formula (I) or a salt thereof, more particularly a compound of formula (I) or a pharmaceutically acceptable salt thereof

(I)



In a second aspect of the present invention, there is provided a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable carriers, diluents or excipients.

In a third aspect of the present invention, there is provided a compound of formula (I), or a pharmaceutically acceptable

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salt thereof for use in therapy, in particular in the treatment of diseases or conditions for which a bromodomain inhibitor is indicated.

In a fourth aspect of the present invention, there is provided a method of treating diseases or conditions for which a bromodomain inhibitor is indicated in a subject in need thereof which comprises administering a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In a fifth aspect of the present invention, there is provided the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of diseases or conditions for which a bromodomain inhibitor is indicated.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1: Shows an XRPD pattern of a crystalline form of 4-(8-methoxy-1-((R)-1-methoxypropan-2-yl)-2-(tetrahydro-2H-pyran-4-yl)-1H-imidazo[4,5-c]quinolin-7-yl)-3,5-dimethylisoxazole (anhydrous form 1).

FIG. 2: Shows an XRPD pattern of a crystalline form of 4-(8-methoxy-1-((R)-1-methoxypropan-2-yl)-2-(tetrahydro-2H-pyran-4-yl)-1H-imidazo[4,5-c]quinolin-7-yl)-3,5-dimethylisoxazole (anhydrous form 2).

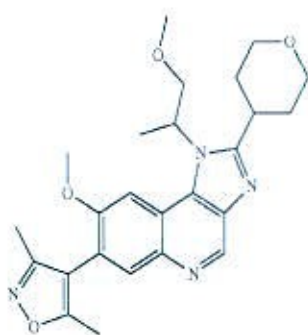
FIG. 3: Shows an XRPD pattern of a crystalline form of 4-(8-methoxy-1-((R)-1-methoxypropan-2-yl)-2-(tetrahydro-2H-pyran-4-yl)-1H-imidazo[4,5-c]quinolin-7-yl)-3,5-dimethylisoxazole (anhydrous form 3).

FIG. 4: Shows an XRPD pattern of a crystalline form of 4-(8-methoxy-1-((R)-1-methoxypropan-2-yl)-2-(tetrahydro-2H-pyran-4-yl)-1H-imidazo[4,5-c]quinolin-7-yl)-3,5-dimethylisoxazole (hydrate).

FIG. 5: Shows an XRPD pattern of a crystalline form of 4-(8-methoxy-1-((R)-1-methoxypropan-2-yl)-2-(tetrahydro-2H-pyran-4-yl)-1H-imidazo[4,5-c]quinolin-7-yl)-3,5-dimethylisoxazole hydrochloride (hydrochloride).

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a compound of formula (I) which is 4-(8-methoxy-1-((1-methoxypropan-2-yl)-2-(tetrahydro-2H-pyran-4-yl)-1H-imidazo[4,5-c]quinolin-7-yl)-3,5-dimethylisoxazole



or a salt thereof.

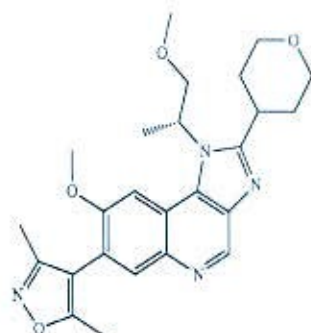
The compound of formula (I) contains a chiral atom such that optical isomers, e.g. enantiomers may be formed. Accordingly, the present invention encompasses all isomers of the compound of formula (I) whether as individual isomers isolated such as to be substantially free of the other isomer

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(i.e. pure) or as mixtures (i.e. racemates and racemic mixtures). An individual isomer isolated such as to be substantially free of the other isomer (i.e. pure) may be isolated such that less than 10%, particularly less than about 1%, for example less than about 0.1% of the other isomer is present.

Separation of isomers may be achieved by conventional techniques known to those skilled in the art, e.g. by fractional crystallisation, chromatography or HPLC.

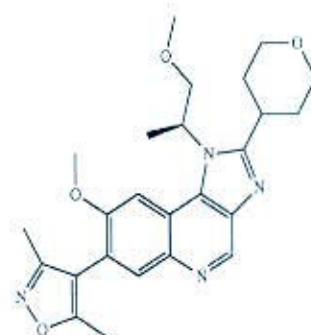
In one embodiment there is provided a compound of formula (IA) which is 4-(8-methoxy-1-((R)-1-methoxypropan-2-yl)-2-(tetrahydro-2H-pyran-4-yl)-1H-imidazo[4,5-c]quinolin-7-yl)-3,5-dimethylisoxazole



(IA)

or a salt thereof.

In a further embodiment there is provided a compound of formula (IB) which is 4-(8-methoxy-1-((S)-1-methoxypropan-2-yl)-2-(tetrahydro-2H-pyran-4-yl)-1H-imidazo[4,5-c]quinolin-7-yl)-3,5-dimethylisoxazole



(IB)

or a salt thereof.

It will be appreciated that the compounds of formula (IA) and formula (IB) are within the scope of the compound of formula (I). As used herein, unless otherwise stated, a reference to a compound of formula (I) also includes a reference to the compound of formula (IA) and a compound of formula (IB).

It will be appreciated that the present invention covers compounds of formula (I) as the free base and as salts thereof, for example as a pharmaceutically acceptable salt thereof. In one embodiment the invention relates to compounds of formula (I) in the form of a free base. In one embodiment the invention relates to compounds of formula (I) or a pharmaceutically acceptable salt thereof.

Because of their potential use in medicine, salts of the compounds of formula (I) are desirably pharmaceutically

acceptable. Suitable pharmaceutically acceptable salts can include acid addition salts. For a review of suitable pharmaceutically acceptable salts see Berge et al., *J. Pharm. Sci.*, 66:1-19, (1977). Typically, a pharmaceutically acceptable salt may be readily prepared by using a desired acid or base as appropriate. The resultant salt may precipitate from solution and be collected by filtration or may be recovered by evaporation of the solvent.

A pharmaceutically acceptable acid addition salt can be formed by reaction of a compound of formula (I) with a suitable inorganic or organic acid (such as hydrobromic, hydrochloric, sulphuric, nitric, phosphoric, succinic, maleic, acetic, propionic, fumaric, citric, tartaric, lactic, benzoic, salicylic, glutamic, aspartic, p-toluenesulfonic, benzenesulfonic, methanesulfonic, ethanesulfonic, naphthalenesulfonic such as 2-naphthalenesulfonic, or hexanoic acid), optionally in a suitable solvent such as an organic solvent, to give the salt which is usually isolated for example by crystallisation and filtration or by evaporation followed by trituration. A pharmaceutically acceptable acid addition salt of a compound of formula (I) can comprise or be for example a hydrobromide, hydrochloride, sulfate, nitrate, phosphate, succinate, maleate, acetate, propionate, fumarate, citrate, tartrate, lactate, benzoate, salicylate, glutamate, aspartate, p-toluenesulfonate, benzenesulfonate, methanesulfonate, ethanesulfonate, naphthalenesulfonate (e.g. 2-naphthalenesulfonate) or hexanoate salt. In one embodiment a pharmaceutically acceptable acid addition salt of a compound of formula (I) can comprise or be a hydrochloride, sulfate, maleate, fumarate, citrate, p-toluenesulfonate, benzenesulfonate or methanesulfonate salt. In a particular embodiment there is provided a compound of formula (IA) in the form of a hydrochloride salt.

Other non-pharmaceutically acceptable salts, e.g. formates, oxalates or trifluoroacetates, may be used, for example in the isolation of the compounds of formula (I), and are included within the scope of this invention.

The invention includes within its scope all possible stoichiometric and non-stoichiometric forms of the salts of the compounds of formula (I).

It will be appreciated that many organic compounds can form complexes with solvents in which they are reacted or from which they are precipitated or crystallized. These complexes are known as "solvates". For example, a complex with water is known as a "hydrate". Solvents with high boiling points and/or capable of forming hydrogen bonds such as water, xylene, N-methylpyrrolidinone, methanol and ethanol may be used to form solvates. Methods for identification of solvates include, but are not limited to, NMR and microanalysis. Solvates of the compounds of formula (I) are within the scope of the invention.

The invention includes within its scope all possible stoichiometric and non-stoichiometric forms of the solvates of the compounds of formula (I).

The invention encompasses all prodrugs, of the compound of formula (I) or a pharmaceutically acceptable salt thereof, which upon administration to the recipient is capable of providing (directly or indirectly) the compound of formula (I) or a pharmaceutically acceptable salt thereof, or an active metabolite or residue thereof. Such derivatives are recognizable to those skilled in the art, without undue experimentation. Nevertheless, reference is made to the teaching of Burger's *Medicinal Chemistry and Drug Discovery*, 5th Edition, Vol 1: Principles and Practice, which is incorporated herein by reference to the extent of teaching such derivatives.

The compounds of formula (I) may be in crystalline or amorphous form. Furthermore, some of the crystalline forms

of the compounds of formula (I) may exist as polymorphs, which are included within the scope of the present invention. Polymorphic forms of compounds of formula (I) may be characterized and differentiated using a number of conventional analytical techniques, including, but not limited to, X-ray powder diffraction (XRPD) patterns, infrared (IR) spectra, Raman spectra, differential scanning calorimetry (DSC), thermogravimetric analysis (TGA) and solid state nuclear magnetic resonance (SSNMR).

The compound of formula (IA), that is to say 4-(8-methoxy-1-((R)-1-methoxypropan-2-yl)-2-(tetrahydro-2H-pyran-4-yl)-1H-imidazo[4,5-c]quinolin-7-yl)-3,5-dimethylisoxazole, in the form of a free base has been found to exist in a number of different crystalline forms, namely, anhydrous forms 1, 2 and 3 and hydrated form 1. Such crystalline forms can be prepared by procedures described herein.

Thus in one embodiment, there is provided a crystalline form of 4-(8-methoxy-1-((R)-1-methoxypropan-2-yl)-2-(tetrahydro-2H-pyran-4-yl)-1H-imidazo[4,5-c]quinolin-7-yl)-3,5-dimethylisoxazole (anhydrous form 1) characterised by substantially the X-ray powder diffraction (XRPD) pattern as shown in FIG. 1, wherein the XRPD pattern is expressed in terms of 2 theta angles and obtained with a diffractometer using copper K α -radiation using procedures described herein. The XRPD pattern of anhydrous form 1 shows characteristic 2 theta angle peaks as listed in Example 9 Table 1.

In a further embodiment, there is provided a crystalline form of 4-(8-methoxy-1-((R)-1-methoxypropan-2-yl)-2-(tetrahydro-2H-pyran-4-yl)-1H-imidazo[4,5-c]quinolin-7-yl)-3,5-dimethylisoxazole (anhydrous form 2) characterised by substantially the X-ray powder diffraction (XRPD) pattern as shown in FIG. 2, wherein the XRPD pattern is expressed in terms of 2 theta angles and obtained with a diffractometer using copper K α -radiation using procedures described. The XRPD pattern of anhydrous form 2 shows characteristic 2 theta angle peaks as listed in Example 9 Table 1.

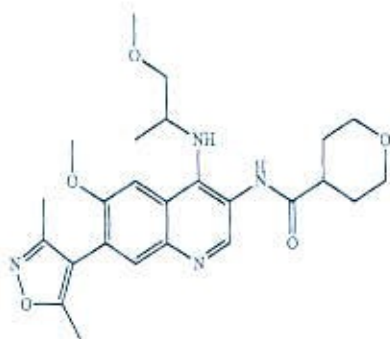
In a further embodiment, there is provided a crystalline form 4-(8-methoxy-1-((R)-1-methoxypropan-2-yl)-2-(tetrahydro-2H-pyran-4-yl)-1H-imidazo[4,5-c]quinolin-7-yl)-3,5-dimethylisoxazole (anhydrous form 3) characterised by substantially the X-ray powder diffraction (XRPD) pattern as shown in FIG. 3, wherein the XRPD pattern is expressed in terms of 2 theta angles and obtained with a diffractometer using copper K α -radiation using procedures described herein. The XRPD pattern of anhydrous form 3 shows characteristic 2 theta angle peaks as listed in Example 9 Table 1.

In a further embodiment, there is provided a crystalline form of 4-(8-methoxy-1-((R)-1-methoxypropan-2-yl)-2-(tetrahydro-2H-pyran-4-yl)-1H-imidazo[4,5-c]quinolin-7-yl)-3,5-dimethylisoxazole (hydrate) characterised by substantially the X-ray powder diffraction (XRPD) pattern as shown in FIG. 4, wherein the XRPD pattern is expressed in terms of 2 theta angles and obtained with a diffractometer using copper K α -radiation using procedures described herein. The XRPD pattern of the hydrate shows characteristic 2 theta angle peaks as listed in Example 9 Table 1.

The invention also provides for the compound of formula (IA) that is to say 4-(8-methoxy-1-((R)-1-methoxypropan-2-yl)-2-(tetrahydro-2H-pyran-4-yl)-1H-imidazo[4,5-c]quinolin-7-yl)-3,5-dimethylisoxazole hydrochloride in crystalline form. Such a crystalline form can be prepared by procedures described herein.

In a further embodiment, there is provided a crystalline form of 4-(8-methoxy-1-((R)-1-methoxypropan-2-yl)-2-(tetrahydro-2H-pyran-4-yl)-1H-imidazo[4,5-c]quinolin-7-yl)-3,5-dimethylisoxazole hydrochloride (hydrochloride form 1) characterised by substantially the X-ray powder diffraction

The compound of formula (I) can be prepared from the compound of formula (II) by, for example, heating the compound of formula (II) in acetic acid or p-toluenesulfonic acid in toluene.

COc1c2c(c3c1ncn3)cc(NC(C)CO)c(OC)c2OC(=O)C1CCOCC1

Where the compound of formula (I) is a mixture of isomers the compounds of formula (IA) and formula (IB) can be obtained from the compound of formula (I) using suitable separation techniques which are familiar to those skilled in the art, such as those described herein. Alternatively the compounds of formula (IA) and (IB) may be prepared by a chiral synthesis procedure. By way of illustration, the compound of formula (IA) may be prepared by the procedure set out in Scheme 1.

(II)

1. 2.5M BuLi
2. B(Oi-Pr)₃

HO OH

(III)

1

NO₂

Me(allyl)₂Cl₂

(IV)

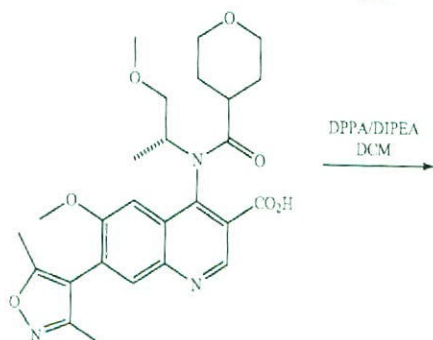
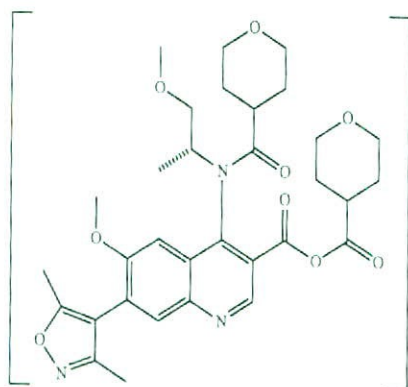
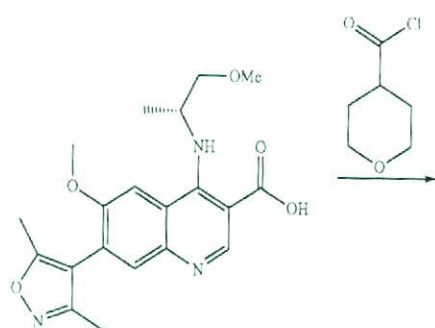
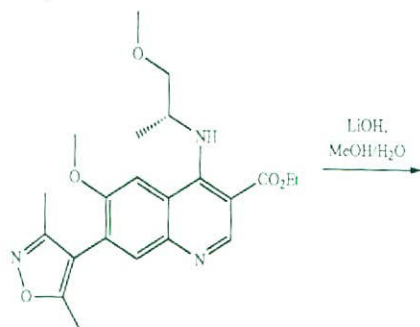
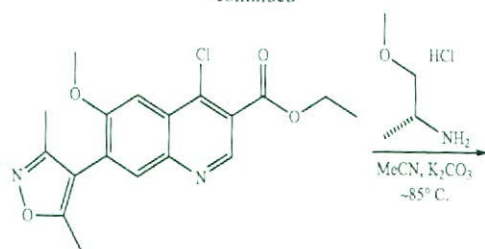
Me(allyl)₂Cl₂

POCl₃

-130°C.

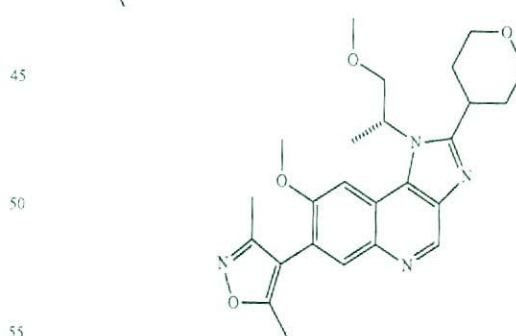
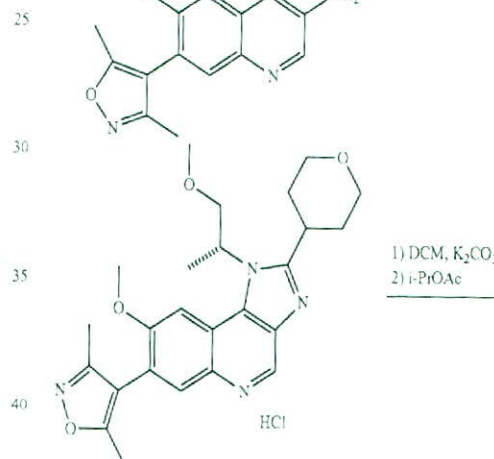
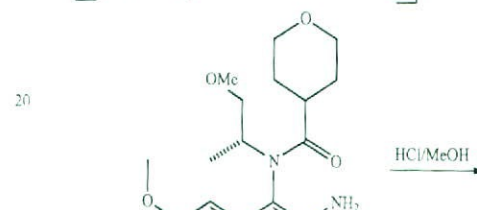
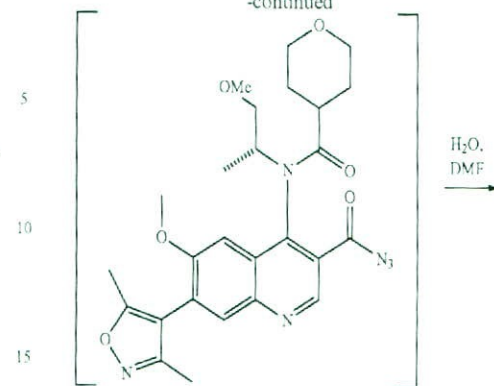
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It will be appreciated by those skilled in the art that it may be advantageous to protect one or more functional groups of the compounds described above. Examples of protecting groups and the means for their removal can be found in T. W. Greene 'Protective Groups in Organic Synthesis' (4th edition, J. Wiley and Sons, 2006). Suitable amine protecting groups include acyl (e.g. acetyl, carbamate (e.g. 2',2',2'-trichloroethoxycarbonyl, benzyloxycarbonyl or t-butoxycarbonyl) and arylalkyl (e.g. benzyl), which may be removed by hydrolysis (e.g. using an acid such as hydrochloric acid in dioxane or trifluoroacetic acid in dichloromethane) or reductively (e.g.

hydrogenolysis of a benzyl or benzyloxycarbonyl group or reductive removal of a 2',2',2'-trichloroethoxycarbonyl group using zinc in acetic acid) as appropriate. Other suitable amine protecting groups include trifluoroacetyl ($-\text{COCF}_3$) which may be removed by base catalysed hydrolysis.

It will be appreciated that in any of the routes described above, the precise order of the synthetic steps by which the various groups and moieties are introduced into the molecule may be varied. It will be within the skill of the practitioner in the art to ensure that groups or moieties introduced at one stage of the process will not be affected by subsequent transformations and reactions, and to select the order of synthetic steps accordingly.

Certain intermediate compounds described above form a yet further aspect of the invention.

The compounds of formula (I) and salts thereof are bromodomain inhibitors, and thus are believed to have potential utility in the treatment of diseases or conditions for which a bromodomain inhibitor is indicated. Further, compounds of formula (I) and pharmaceutically acceptable salts thereof (such as the compound of formula (IA) or a pharmaceutically acceptable salt thereof) may have one or more ADMET (absorption, distribution, metabolism, excretion and toxicity) property that makes it particularly suitable.

The present invention thus provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use in therapy. In one embodiment there is provided a compound of formula (IA) or a pharmaceutically acceptable salt thereof for use in therapy.

The compound of formula (I) or a pharmaceutically acceptable salt thereof can be used in the treatment of diseases or conditions for which a bromodomain inhibitor is indicated. The present invention thus provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use in the treatment of any diseases or conditions for which a bromodomain inhibitor is indicated. In one embodiment there is provided a compound of formula (IA) or a pharmaceutically acceptable salt thereof for use in the treatment of any diseases or conditions for which a bromodomain inhibitor is indicated. In another embodiment there is provided a compound of formula (I) (such as a compound of formula (IA)) or a pharmaceutically acceptable salt thereof for use in the treatment of chronic auto-immune and/or inflammatory conditions. In a further embodiment there is provided a compound of formula (I) (such as a compound of formula (IA)) or a pharmaceutically acceptable salt thereof for use in the treatment of cancer.

Also provided is the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of diseases or conditions for which a bromodomain inhibitor is indicated. In one embodiment there is provided the use of a compound of formula (IA) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of diseases or conditions for which a bromodomain inhibitor is indicated.

Also provided is a method of treating diseases or conditions for which a bromodomain inhibitor is indicated in a subject in need thereof which comprises administering a therapeutically effective amount of compound of formula (I) or a pharmaceutically acceptable salt thereof. In one embodiment there is provided a method of treating diseases or conditions for which a bromodomain inhibitor is indicated in a subject in need thereof which comprises administering a therapeutically effective amount of a compound of formula (IA) or a pharmaceutically acceptable salt thereof.

Suitably the subject in need thereof is a mammal, particularly a human.

As used herein, the term "effective amount" means that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, or subject (e.g. a human) that is being sought, for instance, by a researcher or clinician. Furthermore, the term "therapeutically effective amount" means any amount which, as compared to a corresponding subject who has not received such amount, results in improved treatment, healing, prevention, or amelioration of a disease, disorder, or side effect, or a decrease in the rate of advancement of a disease or disorder. The term also includes within its scope amounts effective to enhance normal physiological function.

Bromodomain inhibitors are believed to be useful in the treatment of a variety of diseases or conditions related to systemic or tissue inflammation, inflammatory responses to infection or hypoxia, cellular activation and proliferation, lipid metabolism, fibrosis and in the prevention and treatment of viral infections.

Bromodomain inhibitors may be useful in the treatment of a wide variety of chronic autoimmune and inflammatory conditions such as rheumatoid arthritis, osteoarthritis, acute gout, psoriasis, systemic lupus erythematosus, multiple sclerosis, inflammatory bowel disease (Crohn's disease and Ulcerative colitis), asthma, chronic obstructive airways disease, pneumonia, myocarditis, pericarditis, myositis, eczema, dermatitis (including atopic dermatitis), alopecia, vitiligo, bullous skin diseases, nephritis, vasculitis, atherosclerosis, Alzheimer's disease, depression, Sjögren's syndrome, sialoadenitis, central retinal vein occlusion, branched retinal vein occlusion, Irvine-Glass syndrome (post cataract and post-surgical), retinitis pigmentosa, pars planitis, birdshot retinochoroidopathy, epiretinal membrane, cystic macular edema, parafoveal telangiectasis, tractional maculopathies, vitreomacular traction syndromes, retinal detachment, neuroretinitis, idiopathic macular edema, retinitis, dry eye (keratoconjunctivitis Sicca), vernal keratoconjunctivitis, atopic keratoconjunctivitis, uveitis (such as anterior uveitis, pan uveitis, posterior uveitis, uveitis-associated macula edema), scleritis, diabetic retinopathy, diabetic macula edema, age-related macula dystrophy, hepatitis, pancreatitis, primary biliary cirrhosis, sclerosing cholangitis, Addison's disease, hypophysitis, thyroiditis, type I diabetes and acute rejection of transplanted organs.

Bromodomain inhibitors may be useful in the treatment of a wide variety of acute inflammatory conditions such as acute gout, giant cell arteritis, nephritis including lupus nephritis, vasculitis with organ involvement such as glomerulonephritis, vasculitis including giant cell arteritis, Wegener's granulomatosis, Polyarteritis nodosa, Behcet's disease, Kawasaki disease, Takayasu's Arteritis, pyoderma gangrenosum, vasculitis with organ involvement and acute rejection of transplanted organs.

Bromodomain inhibitors may be useful in the treatment of diseases or conditions which involve inflammatory responses to infections with bacteria, viruses, fungi, parasites or their toxins, such as sepsis, sepsis syndrome, septic shock, endotoxaemia, systemic inflammatory response syndrome (SIRS), multi-organ dysfunction syndrome, toxic shock syndrome, acute lung injury, ARDS (adult respiratory distress syndrome), acute renal failure, fulminant hepatitis, burns, acute pancreatitis, post-surgical syndromes, sarcoidosis, Herxheimer reactions, encephalitis, myelitis, meningitis, malaria and SIRS associated with viral infections such as influenza, herpes zoster, herpes simplex and coronavirus.

Bromodomain inhibitors may be useful in the treatment of conditions associated with ischaemia-reperfusion injury such as myocardial infarction, cerebro-vascular ischaemia (stroke), acute coronary syndromes, renal reperfusion injury,

organ transplantation, coronary artery bypass grafting, cardio-pulmonary bypass procedures, pulmonary, renal, hepatic, gastro-intestinal or peripheral limb embolism.

Bromodomain inhibitors may be useful in the treatment of disorders of lipid metabolism via the regulation of APO-A1 such as hypercholesterolemia, atherosclerosis and Alzheimer's disease.

Bromodomain inhibitors may be useful in the treatment of fibrotic conditions such as idiopathic pulmonary fibrosis, renal fibrosis, post-operative stricture, keloid scar formation, scleroderma (including morphea) and cardiac fibrosis.

Bromodomain inhibitors may be useful in the treatment of viral infections such as herpes virus, human papilloma virus, adenovirus and poxvirus and other DNA viruses.

Bromodomain inhibitors may be useful in the treatment of cancer, including hematological (such as leukaemia, lymphoma and multiple myeloma), epithelial including lung, breast and colon carcinomas, midline carcinomas, mesenchymal, hepatic, renal and neurological tumours.

Bromodomain inhibitors may be useful in the treatment of one or more cancers selected from brain cancer (gliomas), glioblastomas, Bannayan-Zonana syndrome, Cowden disease, Lhermitte-Duclos disease, breast cancer, inflammatory breast cancer, colorectal cancer, Wilm's tumor, Ewing's sarcoma, rhabdomyosarcoma, ependymoma, medulloblastoma, colon cancer, head and neck cancer, kidney cancer, lung cancer, liver cancer, melanoma, squamous cell carcinoma, ovarian cancer, pancreatic cancer, prostate cancer, sarcoma cancer, osteosarcoma, giant cell tumor of bone, thyroid cancer, lymphoblastic T-cell leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia, hairy-cell leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia, chronic neutrophilic leukemia, acute lymphoblastic T-cell leukemia, plasmacytoma, immunoblastic large cell leukemia, mantle cell leukemia, multiple myeloma, megakaryoblastic leukemia, acute megakaryocytic leukemia, promyelocytic leukemia, mixed lineage leukaemia, erythroleukemia, malignant lymphoma, Hodgkins lymphoma, non-Hodgkins lymphoma, lymphoblastic T-cell lymphoma, Burkitt's lymphoma, follicular lymphoma, neuroblastoma, bladder cancer, urothelial cancer, vulval cancer, cervical cancer, endometrial cancer, renal cancer, mesothelioma, esophageal cancer, salivary gland cancer, hepatocellular cancer, gastric cancer, nasopharyngeal cancer, buccal cancer, cancer of the mouth, GIST (gastrointestinal stromal tumor) and testicular cancer.

In one embodiment the cancer is a leukaemia, for example a leukaemia selected from acute monocytic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia and mixed lineage leukaemia (MLL). In another embodiment the cancer is NUT-midline carcinoma. In another embodiment the cancer is multiple myeloma. In another embodiment the cancer is a lung cancer such as small cell lung cancer (SCLC). In another embodiment the cancer is a neuroblastoma. In another embodiment the cancer is Burkitt's lymphoma. In another embodiment the cancer is cervical cancer. In another embodiment the cancer is esophageal cancer. In another embodiment the cancer is ovarian cancer. In another embodiment the cancer is colorectal cancer.

In one embodiment the disease or condition for which a bromodomain inhibitor is indicated is selected from diseases associated with systemic inflammatory response syndrome, such as sepsis, burns, pancreatitis, major trauma, haemorrhage and ischaemia. In this embodiment the bromodomain inhibitor would be administered at the point of diagnosis to reduce the incidence of: SIRS, the onset of shock, multi-organ dysfunction syndrome, which includes the onset of acute lung

injury, ARDS, acute renal, hepatic, cardiac or gastro-intestinal injury and mortality. In another embodiment the bromodomain inhibitor would be administered prior to surgical or other procedures associated with a high risk of sepsis, haemorrhage, extensive tissue damage, SIRS or MODS (multiple organ dysfunction syndrome). In a particular embodiment the disease or condition for which a bromodomain inhibitor is indicated is sepsis, sepsis syndrome, septic shock and endotoxaemia. In another embodiment, the bromodomain inhibitor is indicated for the treatment of acute or chronic pancreatitis. In another embodiment the bromodomain is indicated for the treatment of burns.

In one embodiment the disease or condition for which a bromodomain inhibitor is indicated is selected from herpes simplex infections and reactivations, cold sores, herpes zoster infections and reactivations, chickenpox, shingles, human papilloma virus, human immunodeficiency virus (HIV), cervical neoplasia, adenovirus infections, including acute respiratory disease, poxvirus infections such as cowpox and smallpox and African swine fever virus. In one particular embodiment a bromodomain inhibitor is indicated for the treatment of Human papilloma virus infections of skin or cervical epithelia. In one embodiment the bromodomain inhibitor is indicated for the treatment of latent HIV infection.

As used herein the reference to the "treatment" of a particular disease or condition includes the prevention or prophylaxis of such a disease or condition.

The term "diseases or conditions for which a bromodomain inhibitor is indicated", is intended to include each of or all of the above diseases or conditions.

The invention further provides for a method for inhibiting a bromodomain which comprises contacting the bromodomain with a compound of formula (I) or a pharmaceutically acceptable salt thereof.

While it is possible that for use in therapy, a compound of formula (I) as well as pharmaceutically acceptable salts thereof may be administered as the raw chemical, it is common to present the active ingredient as a pharmaceutical composition.

The present invention therefore provides in a further aspect a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt and one or more pharmaceutically acceptable carriers, diluents or excipients. In one embodiment there is provided a pharmaceutical composition comprising a compound of formula (IA) or a pharmaceutically acceptable salt and one or more pharmaceutically acceptable carriers, diluents or excipients. The compounds of formula (I) and pharmaceutically acceptable salts, are as described above. The carrier(s), diluent(s) or excipient(s) must be acceptable in the sense of being compatible with the other ingredients of the composition and not deleterious to the recipient thereof. In accordance with another aspect of the invention there is also provided a process for the preparation of a pharmaceutical composition including admixing a compound of formula (I), or a pharmaceutically acceptable salt thereof, with one or more pharmaceutically acceptable carriers, diluents or excipients. The pharmaceutical composition can be used in the treatment of any of the conditions described herein.

Since the compounds of formula (I) are intended for use in pharmaceutical compositions it will be readily understood that they are each preferably provided in substantially pure form, for example, at least 85% pure, especially at least 98% pure (% in a weight for weight basis).

Pharmaceutical compositions may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. Preferred unit dosage compositions

are those containing a daily dose or sub-dose, or an appropriate fraction thereof, of an active ingredient. Such unit doses may therefore be administered more than once a day. Preferred unit dosage compositions are those containing a daily dose or sub-dose (for administration more than once a day), as herein above recited, or an appropriate fraction thereof, of an active ingredient.

Pharmaceutical compositions may be adapted for administration by any appropriate route, for example by the oral (including buccal or sublingual), rectal, inhaled, intranasal, topical (including buccal, sublingual or transdermal), ocular (including topical, intraocular, subconjunctival, episcleral, sub-Tenon), vaginal or parenteral (including subcutaneous, intramuscular, intravenous or intradermal) route. Such compositions may be prepared by any method known in the art of pharmacy, for example by bringing into association the active ingredient with the carrier(s) or excipient(s).

In one embodiment the pharmaceutical composition is adapted for parenteral administration, particularly intravenous administration.

In one embodiment the pharmaceutical composition is adapted for oral administration.

In one embodiment the pharmaceutical composition is adapted for topical administration.

Pharmaceutical compositions adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the composition isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The compositions may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets.

Pharmaceutical compositions adapted for oral administration may be presented as discrete units such as capsules or tablets; powders or granules; solutions or suspensions in aqueous or non-aqueous liquids; edible foams or whips; or oil-in-water liquid emulsions or water-in-oil liquid emulsions.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Powders suitable for incorporating into tablets or capsules may be prepared by reducing the compound to a suitable fine size (e.g. by micronisation) and mixing with a similarly prepared pharmaceutical carrier such as an edible carbohydrate, for example, starch or mannitol. Flavoring, preservative, dispersing and coloring agent can also be present.

Capsules may be made by preparing a powder mixture, as described above, and filling formed gelatin sheaths. Glidants and lubricants such as colloidal silica, talc, magnesium stearate, calcium stearate or solid polyethylene glycol can be added to the powder mixture before the filling operation. A disintegrating or solubilizing agent such as agar-agar, calcium carbonate or sodium carbonate can also be added to improve the availability of the medicament when the capsule is ingested.

Moreover, when desired or necessary, suitable binders, glidants, lubricants, sweetening agents, flavours, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural

sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include starch, methyl cellulose, agar, bentonite, xanthan gum and the like. Tablets are formulated, for example, by preparing a powder mixture, granulating or slugging, adding a lubricant and disintegrant and pressing into tablets. A powder mixture is prepared by mixing the compound, suitably comminuted, with a diluent or base as described above, and optionally, with a binder such as carboxymethylcellulose, an algininate, gelatin, or polyvinyl pyrrolidone, a solution retardant such as paraffin, a resorption accelerator such as a quaternary salt and/or an absorption agent such as bentonite, kaolin or dicalcium phosphate. The powder mixture can be granulated by wetting with a binder such as syrup, starch paste, acacia mucilage or solutions of cellulosic or polymeric materials and forcing through a screen. As an alternative to granulating, the powder mixture can be run through the tablet machine and the result is imperfectly formed slugs broken into granules. The granules can be lubricated to prevent sticking to the tablet forming dies by means of the addition of stearic acid, a stearate salt, talc or mineral oil. The lubricated mixture is then compressed into tablets. The compounds of formula (I) and pharmaceutically acceptable salts thereof, can also be combined with a free flowing inert carrier and compressed into tablets directly without going through the granulating or slugging steps. A clear or opaque protective coating consisting of a sealing coat of shellac, a coating of sugar or polymeric material and a polish coating of wax can be provided. Dyestuffs can be added to these coatings to distinguish different unit dosages.

Oral fluids such as solution, syrups and elixirs can be prepared in dosage unit form so that a given quantity contains a predetermined amount of the compound. Syrups can be prepared by dissolving the compound in a suitably flavored aqueous solution, while elixirs are prepared through the use of a non-toxic alcoholic vehicle. Suspensions can be formulated by dispersing the compound in a non-toxic vehicle. Solubilizers and emulsifiers such as ethoxylated isostearyl alcohols and polyoxy ethylene sorbitol ethers, preservatives, flavor additive such as peppermint oil or natural sweeteners or saccharin or other artificial sweeteners, and the like can also be added.

Compositions for administration (e.g. oral administration) may be designed to provide a modified release profile so as to sustain or otherwise control the release of the therapeutically active agent. A modified release profile of the therapeutically active agent may be obtained through the design of polymeric matrices incorporating different choices and properties of biodegradable/bioerodable polymers (e.g. poly(ethylene vinyl) acetate (EVA), superhydrolyzed PVA), hydroxyalkyl cellulose (HPC), methylcellulose (MC), hydroxypropyl methyl cellulose (HPMC), polycaprolactone, poly(glycolic) acid, poly(lactic) acid, polyanhydride, of polymer molecular weights, polymer crystallinity, copolymer ratios, processing conditions, surface finish, geometry, excipient addition and polymeric coatings that will enhance drug diffusion, erosion, dissolution and osmosis.

Where appropriate, dosage unit compositions for oral administration can be microencapsulated. The composition may be prepared to prolong or sustain the release as for example by coating or embedding particulate material in polymers, wax or the like.

The compounds of formula (I) and pharmaceutically acceptable salts thereof, can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

Pharmaceutical compositions adapted for topical administration may be formulated as ointments, creams, suspensions, emulsions, lotions, powders, solutions, pastes, gels, foams, sprays, aerosols or oils. Such pharmaceutical compositions may include conventional additives which include, but are not limited to, preservatives, solvents to assist drug penetration, co-solvents, emollients, propellants, viscosity modifying agents (gelling agents), surfactants and carriers. In one embodiment there is provided a pharmaceutical composition adapted for topical administration which comprises between 0.01-10%, or between 0.01-1% of the compound of formula (I), or a pharmaceutically acceptable salt thereof, by weight of the composition.

For treatments of the eye or other external tissues, for example mouth and skin, the compositions are preferably applied as a topical ointment, cream, gel, spray or foam. When formulated in an ointment, the active ingredient may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredient may be formulated in a cream with an oil-in-water cream base or a water-in-oil base.

Pharmaceutical compositions adapted for topical administrations to the eye include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent. Compositions to be administered to the eye will have ophthalmically compatible pH and osmolality. One or more ophthalmically acceptable pH adjusting agents and/or buffering agents can be included in a composition of the invention, including acids such as acetic, boric, citric, lactic, phosphoric and hydrochloric acids; bases such as sodium hydroxide, sodium phosphate, sodium borate, sodium citrate, sodium acetate, and sodium lactate; and buffers such as citrate/dextrose, sodium bicarbonate and ammonium chloride. Such acids, bases, and buffers can be included in an amount required to maintain pH of the composition in an ophthalmically acceptable range. One or more ophthalmically acceptable salts can be included in the composition in an amount sufficient to bring osmolality of the composition into an ophthalmically acceptable range. Such salts include those having sodium, potassium or ammonium cations and chloride, citrate, ascorbate, borate, phosphate, bicarbonate, sulfate, thiosulfate or bisulfite anions.

The ocular delivery device may be designed for the controlled release of one or more therapeutic agents with multiple defined release rates and sustained dose kinetics and permeability.

Pharmaceutical compositions for ocular delivery also include in situ gellable aqueous composition. Such a composition comprises a gelling agent in a concentration effective to promote gelling upon contact with the eye or with lacrimal fluid. Suitable gelling agents include but are not limited to thermosetting polymers. The term "in situ gellable" as used herein includes not only liquids of low viscosity that form gels upon contact with the eye or with lacrimal fluid, but also includes more viscous liquids such as semi-fluid and thixotropic gels that exhibit substantially increased viscosity or gel stiffness upon administration to the eye. See, for example, Ludwig (2005) *Adv. Drug Deliv. Rev.* 3: 57:1595-639, herein incorporated by reference for purposes of its teachings of examples of polymers for use in ocular drug delivery.

Dosage forms for nasal or inhaled administration may conveniently be formulated as aerosols, solutions, suspensions, gels or dry powders.

For compositions suitable and/or adapted for inhaled administration, it is preferred that the compound of formula (I) or a pharmaceutically acceptable salt thereof, is in a particle-size-reduced form e.g. obtained by micronisation. The preferable particle size of the size-reduced (e.g. micronised) compound or salt is defined by a D50 value of about 0.5 to about 10 microns (for example as measured using laser diffraction).

Aerosol formulations, e.g. for inhaled administration, can comprise a solution or fine suspension of the active substance in a pharmaceutically acceptable aqueous or non-aqueous solvent. Aerosol formulations can be presented in single or multidose quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomising device or inhaler. Alternatively the sealed container may be a unitary dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve (metered dose inhaler) which is intended for disposal once the contents of the container have been exhausted.

Where the dosage form comprises an aerosol dispenser, it preferably contains a suitable propellant under pressure such as compressed air, carbon dioxide or an organic propellant such as a hydrofluorocarbon (HFC). Suitable HFC propellants include 1,1,1,2,3,3,3-heptafluoropropane and 1,1,1,2-tetrafluoroethane. The aerosol dosage forms can also take the form of a pump-atomiser. The pressurised aerosol may contain a solution or a suspension of the active compound. This may require the incorporation of additional excipients e.g. co-solvents and/or surfactants to improve the dispersion characteristics and homogeneity of suspension formulations. Solution formulations may also require the addition of co-solvents such as ethanol.

For pharmaceutical compositions suitable and/or adapted for inhaled administration, the pharmaceutical composition may be a dry powder inhalable composition. Such a composition can comprise a powder base such as lactose, glucose, trehalose, mannitol or starch, the compound of formula (I) or a pharmaceutically acceptable salt thereof (preferably in particle-size-reduced form, e.g. in micronised form), and optionally a performance modifier such as L-leucine or another amino acid and/or metal salt of stearic acid such as magnesium or calcium stearate. Preferably, the dry powder inhalable composition comprises a dry powder blend of lactose e.g. lactose monohydrate and the compound of formula (I) or salt thereof. Such compositions can be administered to the patient using a suitable device such as the DISKUS® device, marketed by GlaxoSmithKline which is for example described in GB 2242134 A.

The compounds of formula (I) and pharmaceutically acceptable salts thereof may be formulated as a fluid formulation for delivery from a fluid dispenser, for example a fluid dispenser having a dispensing nozzle or dispensing orifice through which a metered dose of the fluid formulation is dispensed upon the application of a user-applied force to a pump mechanism of the fluid dispenser. Such fluid dispensers are generally provided with a reservoir of multiple metered doses of the fluid formulation, the doses being dispensable upon sequential pump actuations. The dispensing nozzle or orifice may be configured for insertion into the nostrils of the user for spray dispensing of the fluid formulation into the nasal cavity. A fluid dispenser of the aforementioned type is described and illustrated in WO-A-2005/044354.

A therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof, will

depend upon a number of factors including, for example, the age and weight of the subject, the precise condition requiring treatment and its severity, the nature of the formulation, and the route of administration, and will ultimately be at the discretion of the attendant physician or veterinarian. In the pharmaceutical composition, each dosage unit for oral or parenteral administration preferably contains from 0.01 to 3000 mg, more preferably 0.5 to 1000 mg, of a compound of formula (I) or a pharmaceutically acceptable salt thereof, calculated as the free base. Each dosage unit for nasal or inhaled administration preferably contains from 0.001 to 50 mg, more preferably 0.01 to 5 mg, of a compound of the formula (I) or a pharmaceutically acceptable salt thereof, calculated as the free base.

The pharmaceutically acceptable compounds of formula (I) and pharmaceutically acceptable salts thereof, can be administered in a daily dose (for an adult patient) of, for example, an oral or parenteral dose of 0.01 mg to 3000 mg per day, 0.5 to 1000 mg per day or 100 mg to 2500 mg per day, or a nasal or inhaled dose of 0.001 to 50 mg per day or 0.01 to 5 mg per day, of the compound of the formula (I) or a pharmaceutically acceptable salt thereof, calculated as the free base. This amount may be given in a single dose per day or more usually in a number (such as two, three, four, five or six) of sub-doses per day such that the total daily dose is the same. An effective amount of a salt thereof, may be determined as a proportion of the effective amount of the compound of formula (I) per se.

The compounds of formula (I) and pharmaceutically acceptable salts thereof, and may be employed alone or in combination with other therapeutic agents. Combination therapies according to the present invention thus comprise the administration of at least one compound of formula (I) or a pharmaceutically acceptable salt thereof, and the use of at least one other therapeutically active agent. Preferably, combination therapies according to the present invention comprise the administration of at least one compound of formula (I) or a pharmaceutically acceptable salt thereof, and at least one other therapeutically active agent. The compound(s) of formula (I) and pharmaceutically acceptable salts thereof, and the other therapeutically active agent(s) may be administered together in a single pharmaceutical composition or separately and, when administered separately this may occur simultaneously or sequentially in any order. The amounts of the compound(s) of formula (I) and pharmaceutically acceptable salts thereof, and the other therapeutically active agent(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect. Thus in a further aspect, there is provided a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof, and at least one other therapeutically active agent.

Thus in one aspect, the compound of formula (I) or a pharmaceutically acceptable salt thereof, and pharmaceutical compositions comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof, according to the invention may be used in combination with or include one or more other therapeutic agents, for example selected from antibiotics, anti-virals, glucocorticosteroids, muscarinic antagonists beta-2 agonists and Vitamin D3 analogues. In a further embodiment a compound of formula (I) or a pharmaceutically acceptable salt thereof may be used in combination with a further therapeutic agent which is suitable for the treatment of cancer. Examples of such further therapeutic agents are described in *Cancer Principles and Practice of Oncology* by V. T. Devita and S. Hellman (editors), 6th edition (2001), Lippincott Williams & Wilkins Publishers. A person

of ordinary skill in the art would be able to discern which combinations of agents would be useful based on the particular characteristics of the drugs and the cancer involved. Further therapeutic agents to be used in combination with the compound of formula (I) or a pharmaceutically acceptable salt thereof include, but are not limited to, anti-microtubule agents (such as diterpenoids and vinca alkaloids); platinum coordination complexes; alkylating agents (such as nitrogen mustards, oxazaphosphorines, alkylsulfonates, nitrosoureas, and triazenes); antibiotic agents (such as anthracyclins, actinomycins and bleomycins); topoisomerase II inhibitors (such as epipodophyllotoxins); antimetabolites (such as purine and pyrimidine analogues and anti-folate compounds); topoisomerase I inhibitors (such as camptothecins); hormones and hormonal analogues; signal transduction pathway inhibitors (such as tyrosine receptor inhibitors); non-receptor tyrosine kinase angiogenesis inhibitors; immunotherapeutic agents; proapoptotic agents; epigenetic or transcriptional modulators (such as histone deacetylase inhibitors) and cell cycle signaling inhibitors.

It will be appreciated that when the compound of formula (I) or a pharmaceutically acceptable salt thereof, is administered in combination with other therapeutic agents normally administered by the inhaled, intravenous, oral or intranasal route, that the resultant pharmaceutical composition may be administered by the same routes. Alternatively the individual components of the composition may be administered by different routes.

One embodiment of the invention encompasses combinations comprising one or two other therapeutic agents.

It will be clear to a person skilled in the art that, where appropriate, the other therapeutic ingredient(s) may be used in the form of salts, for example as alkali metal or amine salts or as acid addition salts, or prodrugs, or as esters, for example lower alkyl esters, or as solvates, for example hydrates, to optimise the activity and/or stability and/or physical characteristics, such as solubility, of the therapeutic ingredient. It will be clear also that, where appropriate, the therapeutic ingredients may be used in optically pure form.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical composition and thus pharmaceutical compositions comprising a combination as defined above together with a pharmaceutically acceptable diluent or carrier represent a further aspect of the invention.

The compounds of formula (I) and pharmaceutically acceptable salts thereof, may be prepared by the methods described below or by similar methods. Thus the following Intermediates and Examples serve to illustrate the preparation of the compounds of formula (I) and pharmaceutically acceptable salts thereof, and are not to be considered as limiting the scope of the invention in any way.

General Experimental Details

All temperatures referred to are in °C.

The names of the following compounds have been obtained using the compound naming programme "ACD Name Pro 6.02" or Chem Draw Ultra 12.0.

Abbreviations

1,2-DCE 1,2-dichloroethane
AcOH acetic acid
CHCl₃ chloroform
D6-DMSO deuterated dimethylsulfoxide
DCM dichloromethane
DIPEA diisopropylamine
DMSO dimethylsulfoxide

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DPPA diphenylphosphoryl azide
 Et₃N triethylamine
 EtOAc ethyl acetate
 h hour(s)
 HATU O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethylu-
 ronium hexafluorophosphate
 HCl hydrochloric acid
 i-PrOAc isopropylacetate
 i-Pr₂O diisopropyl ether
 LCMS liquid chromatography-mass spectrometry
 LiOH lithium hydroxide
 M molar (concentration)
 MeCN acetonitrile
 MeOH methanol
 min minute(s)
 N normal (concentration)
 Na₂CO₃ sodium carbonate
 Na₂SO₄ sodium sulphate
 Pd/C palladium on carbon
 Rt retention time
 TBME tertiary butyl methyl ether
 TFA trifluoroacetic acid
 THF tetrahydrofuran
 UPLC Ultra performance liquid chromatography
 LCMS Methodology
 Method Formate
 LC Conditions
 The UPLC analysis was conducted on an Acquity UPLC BEH
 C18 column (50 mm×2.1 mm, i.d. 1.7 μm packing diameter)
 at 40° C.

The solvents employed were:

A=0.1% v/v solution of formic acid in water

B=0.1% v/v solution of formic acid in acetonitrile

The gradient employed was:

Time (min)	Flow rate (ml/min)	% A	% B
0	1	97	3
1.5	1	0	100
1.9	1	0	100
2.0	1	97	3

The UV detection was a summed signal from wavelength
 of 210 nm to 350 nm.

MS conditions

MS: Waters ZQ

Ionisation mode: Alternate-scan positive and negative elec-
 trospray

Scan range: 100 to 1000 AMU

Scan time: 0.27 sec

Inter scan: delay 0.10 sec

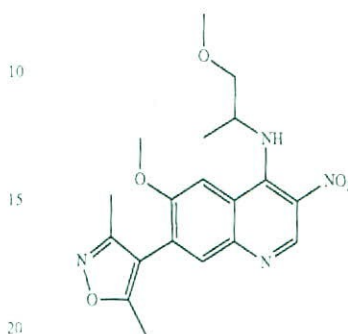
NMR

Spectra were run on a 400 MHz NMR machine at either 302
 K or for VT spectra at 392-393 K.

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Intermediate 1

7-(3,5-dimethylisoxazol-4-yl)-6-methoxy-N-(1-
 methoxypropan-2-yl)-3-nitroquinolin-4-amine



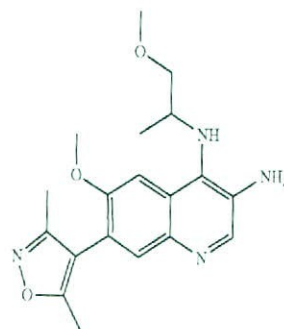
To a solution of 4-(4-chloro-6-methoxy-3-nitroquinolin-7-
 yl)-3,5-dimethylisoxazole (Manchester Organics) (20 g, 59.9
 mmol) in 1,4-dioxane (200 ml) was added 1-methoxypropan-
 2-amine (31.6 ml, 300 mmol) and the reaction mixture heated
 at 70° C. for 1.5 h. The solvent was removed under reduced
 pressure and the resulting solid partitioned between ethyl
 acetate (3×750 ml) and water (750 ml). The organic layers
 were combined, dried (hydrophobic frit) and evaporated
 under reduced pressure to give 7-(3,5-dimethylisoxazol-4-
 yl)-6-methoxy-N-(1-methoxypropan-2-yl)-3-nitroquinolin-
 4-amine (25.8 g), which was used without further purification
 in the subsequent step.

NMR (D₆-DMSO): OH 9.03 (s, 1H), 8.63 (d, 1H), 7.83 (s,
 1H), 7.81 (s, 1H), 4.39 (m, 1H), 3.97 (s, 3H), 3.54 (m, 2H),
 3.27 (s, 3H), 2.34 (s, 3H), 2.15 (s, 3H), 1.41 (d, 3H).

LCMS (formate): Rt=0.97 min, MH⁺387.

Intermediate 2

7-(3,5-dimethylisoxazol-4-yl)-6-methoxy-N4-(1-
 methoxypropan-2-yl)quinoline-3,4-diamine



7-(3,5-Dimethylisoxazol-4-yl)-6-methoxy-N-(1-methox-
 ypropan-2-yl)-3-nitroquinolin-4-amine (for a preparation see
 Intermediate 1)(25.8 g, 66.8 mmol) was dissolved in a mix-
 ture of ethyl acetate (1000 ml) and DMSO (50 ml) and the
 solution was hydrogenated using a flow-hydrogenation appa-
 ratus (H-cube™) (settings: 20° C., 1 bar, 1 ml/min flow rate)
 and a 10% Pd/C CatCart 70 catalyst cartridge. The catalyst

cartridge was changed whenever it became blocked. The reaction mixture was evaporated under reduced pressure and partitioned between ethyl acetate (750 ml) and water (3x750 ml). The aqueous layers were combined and extracted with ethyl acetate (750 ml). The organic layers were combined, dried (hydrophobic frit) and evaporated under reduced pressure. The residue was dissolved in DCM and applied to a silica cartridge (100 g). The cartridge was eluted with a 2M ammonia in methanol/DCM gradient (0-4%). The appropriate fractions were combined and evaporated under reduced pressure to give 7-(3,5-dimethylisoxazol-4-yl)-6-methoxy-N⁴-(1-methoxypropan-2-yl)quinoline-3,4-diamine and recovered 7-(3,5-dimethylisoxazol-4-yl)-6-methoxy-N-(1-methoxypropan-2-yl)-3-nitroquinolin-4-amine (6.5 g)

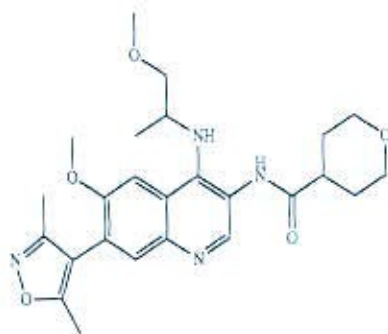
The recovered starting material was dissolved in ethyl acetate (250 ml) and the solution was hydrogenated using a flow-hydrogenation apparatus (H-cube™) (settings: 20°C, 1 bar, 1 ml/min flow rate) and 10% Pd/C CatCart 70 catalyst cartridge. The reaction mixture was evaporated under reduced pressure and the residue was dissolved in DCM and applied to a silica cartridge (100 g). The cartridge was eluted with a 2M ammonia in methanol/DCM gradient (0-4%). The appropriate fractions were combined and evaporated under reduced pressure to give 7-(3,5-dimethylisoxazol-4-yl)-6-methoxy-N⁴-(1-methoxypropan-2-yl)quinoline-3,4-diamine

The batches of product were combined to give 7-(3,5-dimethylisoxazol-4-yl)-6-methoxy-N⁴-(1-methoxypropan-2-yl)quinoline-3,4-diamine (15.6 g, 43.8 mmol, 65.6% yield) as a sticky dark brown gum.

NMR (D₂O-DMSO): δH 8.29 (s, 1H), 7.55 (s, 1H), 7.45 (s, 1H), 5.13 (s, 2H), 4.48 (d, 1H), 3.88 (s, 3H), 3.54 (m, 1H), 3.35 (m, 2H), 3.29 (s, 3H), 2.30 (s, 3H), 2.10 (s, 3H), 1.18 (d, 3H). LCMS (formate): Rt 0.73 min, MH⁺357

Intermediate 3

N-(7-(3,5-dimethylisoxazol-4-yl)-6-methoxy-4-((1-methoxypropan-2-yl)amino)quinolin-3-yl)tetrahydro-2H-pyran-4-carboxamide



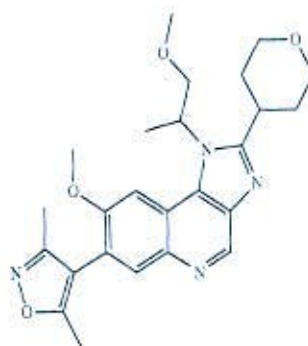
A solution of 7-(3,5-dimethylisoxazol-4-yl)-6-methoxy-N⁴-(1-methoxypropan-2-yl)quinoline-3,4-diamine (for a preparation see Intermediate 2) (9.1 g) in DCM (300 ml) was treated with pyridine (30 ml) and tetrahydro-2H-pyran-4-carbonyl chloride (5.0 ml) and the solution stirred under nitrogen at ambient temperature for 3.5 h and then left standing overnight (ambient temperature, under nitrogen). The volatiles were evaporated in vacuo and the residue partitioned between DCM and water. The organic phase was washed with

water x2 and the combined aqueous extracted with DCM. The combined organic phases were washed with brine, dried (hydrophobic frit) and reduced to dryness in vacuo. The combined aqueous including the brine wash (~pH4) was basified with solid sodium hydrogen carbonate and the aqueous extracted with DCM x2. The organic fractions were dried (hydrophobic frit), combined with the previous material and reduced to dryness in vacuo to give a brown foam. This foam was further dried in vacuo, triturated with diethyl ether, the suspension chilled (ice/water bath) and the solid isolated by filtration. The solid was washed with a little diethyl ether and air-dried to give N-(7-(3,5-dimethylisoxazol-4-yl)-6-methoxy-4-((1-methoxypropan-2-yl)amino)quinolin-3-yl)tetrahydro-2H-pyran-4-carboxamide as a beige solid (11.95 g, 100%).

NMR (D₂O-DMSO): δH 9.49 (s, 1H), 8.38 (s, 1H), 7.70 (s, 1H), 7.63 (s, 1H), 5.33 (d, 1H), 3.96-3.90 (m, 6H), 3.43-3.28 (m partially obscured by water, 7H), 2.69 (m, 1H), 2.32 (s, 3H), 2.12 (s, 3H), 1.81-1.67 (m, 4H), 1.19 (d, 3H). LCMS (formate): Rt 0.69 mins, MH⁺469.

Example 1

4-(8-methoxy-1-(1-methoxypropan-2-yl)-2-(tetrahydro-2H-pyran-4-yl)-1H-imidazo[4,5-c]quinolin-7-yl)-3,5-dimethylisoxazole



A suspension of N-(7-(3,5-dimethylisoxazol-4-yl)-6-methoxy-4-((1-methoxypropan-2-yl)amino)quinolin-3-yl)tetrahydro-2H-pyran-4-carboxamide (for a preparation see Intermediate 3) (29.4 g, 62.7 mmol) in acetic acid (250 ml, 62.7 mmol) was heated at 120°C for 2 h. 3 Å molecular sieves (20 g) were added and heating continued for 3.5 h. Further 3 Å molecular sieves (20 g, oven dried) were added and heating was continued overnight. Further 3 Å molecular sieves (20 g, oven dried) were added and heating continued for a further 24 h.

The reaction mixture was allowed to cool to room temperature, and the solid removed by filtration. The residue and filtrate were combined and evaporated under reduced pressure. Water (3 l) was added, and the resultant slurry was neutralised by the slow addition of solid sodium hydrogen carbonate. The aqueous slurry was extracted with DCM (3x1 l), and the organic phases were combined, dried (hydrophobic frit) and evaporated under reduced pressure to give a brown gum.

The gum was dissolved with warming and sonication in a minimal quantity of DCM. The solution was applied to a silica column (750 g) which had been pre-wetted with DCM. The column was eluted with a gradient of [2 M ammonia in

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methanol, methanol (3:1)/DCM (0–8%). The product fractions were combined and reduced to dryness under reduced pressure to give a cream foam/glass (13.027 g).

The mixed product fractions were combined and reduced to dryness under reduced pressure to give a deep yellow oil. This oil was dissolved in diethyl ether and the volatiles evaporated in vacuo to give a yellow solid. The solid was triturated with diethyl ether, the solid isolated by filtration and washed with diethyl ether (x2) to give 4-(8-methoxy-1-(1-methoxypropan-2-yl)-2-(tetrahydro-2H-pyran-4-yl)-1H-imidazo[4,5-c]quinolin-7-yl)-3,5-dimethylisoxazole.

The cream foam/glass was triturated with diethyl ether/ethyl acetate, the mixture reduced to dryness under reduced pressure and the trituration was repeated with diethyl ether. The previous product fraction was added to the suspension and the mixture aged overnight. The solid was isolated by filtration and washed with diethyl ether to give 4-(8-methoxy-1-(1-methoxypropan-2-yl)-2-(tetrahydro-2H-pyran-4-yl)-1H-imidazo[4,5-c]quinolin-7-yl)-3,5-dimethylisoxazole as a cream solid. The solid was dried in vacuo and retrituated with diethyl ether with stirring over ~30 min. The solid was isolated by filtration and washed with diethyl ether. The solid was dried in vacuo to give 4-(8-methoxy-1-(1-methoxypropan-2-yl)-2-(tetrahydro-2H-pyran-4-yl)-1H-imidazo[4,5-c]quinolin-7-yl)-3,5-dimethylisoxazole as a white solid (11.73 g).

¹H NMR (D₂O-DMSO): δH 9.04 (s, 1H), 7.99 (s, 1H), 7.74 (s, 1H), 5.45 (m, 1H), 4.14 (m, 1H), 4.06–4.01 (m, 6H), 3.62 (m, 2H), 3.47 (m, 1H), 3.28 (s, 3H), 2.35 (s, 3H), 2.17 (s, 3H), 2.09 (m, 2H), 1.92 (m, 2H), 1.83 (d, 3H). LCMS (formate): Rt 0.76 min, MH⁺451.

Example 1

Alternative Preparation 4-(8-methoxy-1-(1-methoxypropan-2-yl)-2-(tetrahydro-2H-pyran-4-yl)-1H-imidazo[4,5-c]quinolin-7-yl)-3,5-dimethylisoxazole

A mixture of N-(7-(3,5-dimethylisoxazol-4-yl)-6-methoxy-4-((1-methoxypropan-2-yl)amino)quinolin-3-yl)tetrahydro-2H-pyran-4-carboxamide (for a preparation see Intermediate 3) (11.95 g, 25.5 mmol) and p-toluenesulfonic acid (1.2 g, 25.5 mmol) in toluene (250 ml) was heated under nitrogen at reflux using a Dean-Stark apparatus for 3 days. Further p-toluenesulfonic acid (0.2 g, 4.3 mmol) was added and heating continued overnight. Water (750 ml) was added, and the mixture basified to pH 8 using saturated aqueous sodium hydrogen carbonate solution. The aqueous was extracted with ethyl acetate (3x750 ml), the organic layers combined, dried (hydrophobic frit) and evaporated under reduced pressure. The residual solid was triturated in ether (~200 ml), sonicated briefly. The majority of the solid appeared to be a fine powder. The fine powder suspended in the ether was decanted, the solid isolated by filtration, and dried in a vacuum oven to give crude 4-(8-methoxy-1-(1-methoxypropan-2-yl)-2-(tetrahydro-2H-pyran-4-yl)-1H-imidazo[4,5-c]quinolin-7-yl)-3,5-dimethylisoxazole (6.3 g). This material was triturated in ether (~100 ml), sonicated briefly, and stood overnight at room temperature. The solid was isolated by filtration and dried in a vacuum oven to give 4-(8-methoxy-1-(1-methoxypropan-2-yl)-2-(tetrahydro-2H-pyran-4-yl)-1H-imidazo[4,5-c]quinolin-7-yl)-3,5-dimethylisoxazole (4.9 g, 10.88 mmol, 42.6% yield). LCMS (formate): Rt 0.75 min, MH⁺451.

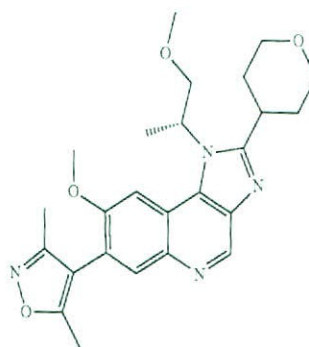
The clumped solid left over from the decanting was triturated in ether (100 ml), sonicated for 15 min, and stood at room temperature for 3 days. The solid was isolated by filtra-

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tion and dried in a vacuum oven to give 4-(8-methoxy-1-(1-methoxypropan-2-yl)-2-(tetrahydro-2H-pyran-4-yl)-1H-imidazo[4,5-c]quinolin-7-yl)-3,5-dimethylisoxazole (3.6 g, 7.99 mmol, 31.3% yield). LCMS (formate): Rt 0.76 min, MH⁺451.

Example 2

4-(8-methoxy-1-((R)-1-methoxypropan-2-yl)-2-(tetrahydro-2H-pyran-4-yl)-1H-imidazo[4,5-c]quinolin-7-yl)-3,5-dimethylisoxazole



Chiral resolution of 4-(8-methoxy-1-(1-methoxypropan-2-yl)-2-(tetrahydro-2H-pyran-4-yl)-1H-imidazo[4,5-c]quinolin-7-yl)-3,5-dimethylisoxazole was carried out using the following conditions:

Column: Chiralpak AD-H (250x30 mm, 5 micron) [ADH10029-01]

Flowrate: 45 ml/min

Detection: UV DAD (300 nm (bandwidth 180 nm, reference 550 nm (bandwidth 100 nm)).

Mobile Phase A: n-Hexane (10 ml of isopropylamine per Winchester (2.5 L))

Mobile Phase B: Ethanol (10 ml of isopropylamine per Winchester (2.5 L))

Isocratic system—85:15 mobile phase A:B

Run time—ca. 35 min

4-(8-methoxy-1-(1-methoxypropan-2-yl)-2-(tetrahydro-2H-pyran-4-yl)-1H-imidazo[4,5-c]quinolin-7-yl)-3,5-dimethylisoxazole (500 mg) was suspended in ethanol and ethylene glycol (10 ml:5 ml) and then sonicated and heated to aid solution. Isopropylamine (1 ml) was then added. This working solution was warmed on a hotplate (60° C.) whilst purification was ongoing to keep in solution. Injections (1.5 ml) were made using autosampler. Fractions collected on time basis using funnel bed fraction collector between 28 min and 35 min. The combined fraction solutions were evaporated to dryness using a rotary evaporator (30° C. bath temp) and the residue transferred to a tared 20 ml glass vial using ethanol (ca 12 ml). The ethanol was evaporated under a stream of nitrogen gas (room temp).

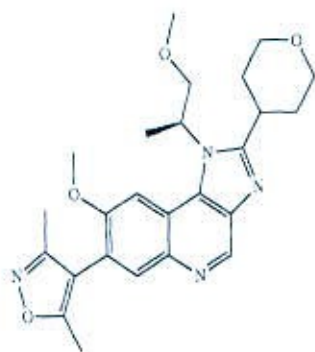
4-(8-methoxy-1-((R)-1-methoxypropan-2-yl)-2-(tetrahydro-2H-pyran-4-yl)-1H-imidazo[4,5-c]quinolin-7-yl)-3,5-dimethylisoxazole (1.16 g) isolated using the above process was triturated with diethyl ether (~3 ml) over ~4 h at ambient temperature. The solid was isolated by filtration, washed with diethyl ether and dried in vacuo to give 4-(8-methoxy-1-((R)-1-methoxypropan-2-yl)-2-(tetrahydro-2H-pyran-4-yl)-1H-imidazo[4,5-c]quinolin-7-yl)-3,5-dimethylisoxazole as a cream solid (0.96 g).

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VT NMR (D_2O -DMSO): δ H 9.03 (s, 1H), 7.98 (s, 1H), 7.74 (s, 1H), 5.43 (m, 1H), 4.13 (m, 1H), 4.04-4.00 (m, 6H), 3.61 (m, 2H), 3.46 (m, 1H), 3.28 (s, 3H), 2.35 (s, 3H), 2.16 (s, 3H), 2.08 (m, 2H), 1.92 (m, 2H), 1.82 (d, 3H). LCMS (formate): Rt 0.76 min, MH⁺451.

Example 3

4-(8-methoxy-1-((S)-1-methoxypropan-2-yl)-2-(tetrahydro-2H-pyran-4-yl)-1H-imidazo[4,5-c]quinolin-7-yl)-3,5-dimethylisoxazole



Chiral resolution of 4-(8-methoxy-1-((S)-1-methoxypropan-2-yl)-2-(tetrahydro-2H-pyran-4-yl)-1H-imidazo[4,5-c]quinolin-7-yl)-3,5-dimethylisoxazole was carried out using the following conditions:

Column: Chiralpak AD-H (250x30 mm, 5 micron) [ADH10029-01]

Flowrate: 45 ml/min

Detection: UV DAD (300 nm (bandwidth 180 nm, reference 550 nm (bandwidth 100 nm)).

Mobile Phase A: Heptane

Mobile Phase B: Ethanol

Isocratic system—85:15 mobile phase A:B

Run time—ca. 35 min

4-(8-methoxy-1-((S)-1-methoxypropan-2-yl)-2-(tetrahydro-2H-pyran-4-yl)-1H-imidazo[4,5-c]quinolin-7-yl)-3,5-dimethylisoxazole (85 mg) was dissolved in ethanol (ca. 4 ml) with heating and sonication. Injections (400 μ l) were then made via plastic syringe. The fractions between 24 min and 26.5 min were collected and the combined fraction solutions were evaporated to dryness using a rotary evaporator (30° C. bath temp). The residue was transferred to a tared glass vial using ethanol (ca 12 ml). The solvent was then removed by evaporation under a stream of nitrogen gas (room temp) to give 4-(8-methoxy-1-((S)-1-methoxypropan-2-yl)-2-(tetrahydro-2H-pyran-4-yl)-1H-imidazo[4,5-c]quinolin-7-yl)-3,5-dimethylisoxazole (38 mg).

VT NMR (D_2O -DMSO): δ H 9.00 (s, 1H), 7.95 (s, 1H), 7.72 (s, 1H), 5.41 (m, 1H), 4.10 (m, 1H), 4.03-3.97 (m, 6H), 3.59 (m, 2H), 3.45 (m, 1H), 3.26 (s, 3H), 2.32 (s, 3H), 2.13 (s, 3H), 2.07 (m, 2H), 1.90 (m, 2H), 1.80 (d, 3H). LCMS (formate): Rt 0.73 min, MH⁺451.

Example 4

Preparation of a crystalline form of 4-(8-methoxy-1-((R)-1-methoxypropan-2-yl)-2-(tetrahydro-2H-pyran-4-yl)-1H-imidazo[4,5-c]quinolin-7-yl)-3,5-dimethylisoxazole (anhydrous form 1)

4-(8-methoxy-1-((R)-1-methoxypropan-2-yl)-2-(tetrahydro-2H-pyran-4-yl)-1H-imidazo[4,5-c]quinolin-7-yl)-3,5-

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dimethylisoxazole (for a preparation see Example 2 or reaction scheme 1, 18.87 g) was dissolved in isopropyl acetate (95 mL) at reflux and then allowed to cool to 20° C. over 1 hr. Cyclohexane (190 mL) was then added over 1 hr and the resultant slurry was aged for 1 hr. The slurry was then filtered and washed with 2:1 cyclohexane:isopropylacetate (30 mL) and then cyclohexane (30 mL) before being pulled dry. The cake was then oven dried overnight at 40° C. under vacuum. An XRPD was recorded on this material (see Example 9).

Example 5

Preparation of a crystalline form of 4-(8-methoxy-1-((R)-1-methoxypropan-2-yl)-2-(tetrahydro-2H-pyran-4-yl)-1H-imidazo[4,5-c]quinolin-7-yl)-3,5-dimethylisoxazole (anhydrous form 2)

A pre-mixed solution of isopropyl acetate (211 mL) and cyclohexane (422 mL) was added to 4-(8-methoxy-1-((R)-1-methoxypropan-2-yl)-2-(tetrahydro-2H-pyran-4-yl)-1H-imidazo[4,5-c]quinolin-7-yl)-3,5-dimethylisoxazole (for a preparation see Example 2 or reaction scheme 1, 42.19 g, 94 mmol). The resulting suspension was stirred for 24 hours, filtered, the resulting solid washed (1x cyclohexane:isopropyl acetate (2:1, 180 mL), 1x cyclohexane (180 mL), 1x TBME (180 mL)), pulled to dryness and dried in vacuo at 40° C. to constant weight giving an almost white solid (90% yield). An XRPD was recorded on this material (see Example 9).

Example 6

Preparation of a crystalline form of 4-(8-methoxy-1-((R)-1-methoxypropan-2-yl)-2-(tetrahydro-2H-pyran-4-yl)-1H-imidazo[4,5-c]quinolin-7-yl)-3,5-dimethylisoxazole (hydrate)

A pre-mixed solution of ethanol (2,000 mL) and water (8.00 mL) was added to 4-(8-methoxy-1-((R)-1-methoxypropan-2-yl)-2-(tetrahydro-2H-pyran-4-yl)-1H-imidazo[4,5-c]quinolin-7-yl)-3,5-dimethylisoxazole (for a preparation see Example 2 or reaction scheme 1, 1.00 g, 2.220 mmol) and the resulting suspension stirred overnight. The suspension was filtered, washed (2x water, 2x TBME), pulled to dryness under vacuum and dried in vacuo at 40° C. to give a white powder. An XRPD was recorded on this material (see Example 9).

Example 7

Preparation of a crystalline form of 4-(8-methoxy-1-((R)-1-methoxypropan-2-yl)-2-(tetrahydro-2H-pyran-4-yl)-1H-imidazo[4,5-c]quinolin-7-yl)-3,5-dimethylisoxazole (anhydrous form 3)

4-(8-methoxy-1-((R)-1-methoxypropan-2-yl)-2-(tetrahydro-2H-pyran-4-yl)-1H-imidazo[4,5-c]quinolin-7-yl)-3,5-dimethylisoxazole hydrate (for a preparation see Example 6, 860 mg, 1.835 mmol) was heated at 135° C. at 9 mbar overnight. An XRPD was recorded on this material (see Example 9).

Example 8

Preparation of 4-(8-methoxy-1-((R)-1-methoxypropan-2-yl)-2-(tetrahydro-2H-pyran-4-yl)-1H-imidazo[4,5-c]quinolin-7-yl)-3,5-dimethylisoxazole hydrochloride (hydrochloride)

In a first reactor a solution of 7-(3,5-dimethylisoxazol-4-yl)-6-methoxy-4-(N-((R)-1-methoxypropan-2-yl)tetrahy-

dro-2H-pyran-4-carboxamido)quinoline-3-carboxylic acid (for a preparation see Scheme 1, 23.3 kg) in DCM (113 kg) and DIPEA (3.8 kg) was combined with acetonitrile (61.6 kg) and di-iso-propylamine (12.8 kg) the mixture was cooled to between -10 and -3° C. Diphenylphosphoryl azide (19.0 kg) was added maintaining the temperature between -10 and -3° C. and the reaction stirred at this temperature. Further diphenylphosphoryl azide (2.4 kg) was added maintaining the temperature between -10 and -3° C. and the reaction stirred at this temperature to form a first solution.

In a second reactor dimethyl formamide (144 kg) and water (72 kg) were heated to 90-100° C. The first solution was added maintaining the temperature between 85-100° C., reactor 1 was rinsed with acetonitrile (7 kg) and the rinse added to the second reactor maintaining the temperature between 85-100° C. The mixture was stirred at this temperature and then cooled to 20-30° C. The pH was adjusted to pH=10 with 30% wt aqueous sodium hydroxide solution (10.4 kg) maintaining the temperature between 20-30° C. Dichloromethane (315 kg) and water (351 kg) were charged, the layers were separated and the aqueous layer extracted with dichloromethane (315 kg). The combined organic layers were washed with water (234 kg). Water (234 kg) was charged to the organic layer, the mixture stirred, sodium chloride (80 kg) added and the layers separated. The organic layer was concentrated under reduced pressure below 30° C., methanol (201 kg) was charged and the solution concentrated under

washed with acetonitrile (9 kg) to give the title compound (33.40 kg, 99.3% purity) as a wet cake.

Example 9

X-ray Powder Diffraction (XRPD) Studies on Crystalline Forms of 4-(8-methoxy-1-((R)-1-methoxypropan-2-yl)-2-(tetrahydro-2H-pyran-4-yl)-1H-imidazo[4,5-c]quinolin-7-yl)-3,5-dimethylisoxazole as a free base and as a hydrochloride salt

The data were acquired on a PANalytical X'Pert Pro powder diffractometer, model PW3040/60 using an X'Celerator detector. The acquisition conditions were: radiation: Cu K α , generator tension: 40 kV, generator current: 45 mA, start angle: 2.0° 2 θ , end angle: 40.0° 2 θ , step size: 0.0167° 2 θ , time per step: 31.75 seconds. The sample was prepared by mounting a few milligrams of sample on a silicon wafer (zero background) plate, resulting in a thin layer of powder.

Peak positions were measured using Highscore software. The margin of error is approximately $\pm 0.1^\circ 2\theta$ for each of the peak assignments. Peak intensities may vary from sample to sample due to preferred orientation.

Table 1 shows characteristic XRPD peak positions and d-spacings for crystalline form of the compound 4-(8-methoxy-1-((R)-1-methoxypropan-2-yl)-2-(tetrahydro-2H-pyran-4-yl)-1H-imidazo[4,5-c]quinolin-7-yl)-3,5-dimethylisoxazole as a free base and as a hydrochloride salt.

TABLE 1

Free base anhydrous form 1		Free base anhydrous form 2		Free base anhydrous form 3		Free base Hydrate		hydrochloride	
2 θ ^o	d-spacing/Å	2 θ ^o	d-spacing/Å	2 θ ^o	d-spacing/Å	2 θ ^o	d-spacing/Å	2 θ ^o	d-spacing/Å
7.9	11.1	6.5	13.6	8.8	10.0	8.1	10.9	9.4	9.4
8.5	10.4	10.8	8.2	11.2	7.9	10.2	8.7	12.8	6.9
10.7	8.3	13.0	6.8	11.7	7.5	12.0	7.4	13.5	6.6
12.1	7.3	14.0	6.3	16.1	5.5	14.8	6.0	14.4	6.1
12.7	7.0	15.3	5.8	16.5	5.4	16.6	5.3	14.9	5.9
13.9	6.4	17.7	5.0	18.2	4.9	17.5	5.1	17.4	5.1
15.9	5.6	19.3	4.6	20.6	4.3	18.2	4.9	18.9	4.7
16.7	5.3	20.8	4.3	21.5	4.1	18.8	4.7	19.9	4.5
18.8	4.7	21.6	4.1	23.0	3.9	19.7	4.5	20.4	4.4
21.0	4.2	22.6	3.9			20.5	4.3	24.0	3.7
22.7	3.9	25.3	3.5			23.3	3.8	25.7	3.5
24.3	3.7	27.2	3.3			24.1	3.7	26.2	3.4
29.1	3.1					26.6	3.4	32.7	2.7
29.8	3.0								

reduced pressure below 50° C. Further methanol (199 kg) and 4M hydrochloric acid in methanol (68.5 kg) were charged maintaining the temperature 20-30° C. and the reaction was stirred at this temperature. The mixture was concentrated under reduced pressure below 50° C. and acetonitrile (104 kg) charged. The mixture was concentrated under reduced pressure below 50° C. and further acetonitrile (97 kg) charged. The mixture was concentrated under reduced pressure below 50° C. and further acetonitrile (116 kg) charged. The mixture was evaporated under reduced pressure below 50° C. and further acetonitrile (103.0 kg) was charged. The mixture was cooled to between -5-0° C. and stirred at this temperature. The slurry was centrifuged in two portions, each portion was

Biological Test Methods

The compounds of formula (I) may be tested in one or more of the following assays.

Time Resolved Fluorescence Resonance Energy Transfer (TR-FRET) Assay

The binding of the compounds of formula (I) to Bromodomains BRD2, BRD3 and BRD4 was assessed using a time resolved fluorescent resonance energy transfer binding assay, that measures the binding of an acetylated histone peptide to the bromodomain protein.

The bromodomain protein, histone peptide and a variable concentration of test compound are incubated together to

reach thermodynamic equilibrium. The assay is configured such that in the absence of test compound the bromodomain and peptide are significantly bound (~30%) and in the presence of a sufficient concentration of a potent inhibitor this interaction is disrupted leading to a measurable drop in fluorescent resonance energy transfer.

Histone Peptide:

H-Ser-Gly-Arg-Gly-Lys(Ac)-Gly-Gly-Lys(Ac)-Gly-Leu-Gly-Lys(Ac)-Gly-Gly-Ala-Lys(Ac)-Arg-His-Gly-Ser-Gly-Ser-Lys(Biotin)-OH. 3TPA

The protected peptide was assembled on a solid-phase synthesizer using preloaded Wang resin and utilising standard Fmoc synthesis protocols. The C-terminal lysine was protected by a hyper acid-labile group allowing for its selective removal at the end of the assembly and attachment of the biotin. The crude peptide was obtained after cleavage from the resin with a mixture of trifluoroacetic acid (TFA), triisopropylsilane and water (95:2.5:2.5) for 3 h at room temperature and was then purified using a C18 reverse-phase column utilising a 0.1% TFA-buffered water/acetonitrile gradient. The resulting fractions were analysed and fractions which were >95% pure by analytical HPLC and giving the correct mw (by MALDI-TOF mass spectroscopy) were pooled and freeze dried. The final material was analysed by HPLC to confirm purity.

Protein Production:

Recombinant Human Bromodomains (BRD2 (1-473), BRD3 (1-435) and BRD4 (1-477)) were expressed in *E. coli* cells (in pET15b vector) with a six-His tag at the N-terminal. The His-tagged Bromodomain was extracted from *E. coli* cells using sonication and purified using a nickel sepharose 6FF column, the proteins were washed and then eluted with 50 mM Tris-HCl pH8.0, 300 mM NaCl, 1 mM 6-mercaptoethanol and 20 mM imidazole. Further purification was performed by affinity chromatography on a HiTrap HP column, eluting with a linear 0-500 mM sodium chloride gradient, over 20 column volumes. Final purification was completed by Superdex 200 prep grade size exclusion column. Purified protein was stored at -80 C in 20 mM HEPES pH 7.5 and 100 mM NaCl. Protein identity was confirmed by peptide mass fingerprinting and predicted molecular weight confirmed by mass spectrometry.

Protocol for Bromodomain BRD 2, 3 and 4 Assays:

All assay components were dissolved in buffer composition of 50 mM HEPES pH7.4, 50 mM NaCl and 0.5 mM CHAPS. The final concentration of bromodomain proteins were 100 nM and the histone peptide was 300 nM, these components are premixed and allowed to equilibrate for 1 hour in the dark. 8 µl of this reaction mixture was added to all wells containing 50 nM of various concentrations of test compound or DMSO vehicle (0.5% final) in Greiner 384 well black low volume microtitre plates and incubated in dark for 60 mins at room temperature. 2 µl of detection mixture containing anti-6His XL665 labeled antibody and streptavidin labeled with europium cryptate was added to all wells and a further dark incubation of at least 30 mins was performed. Plates were then read on the Envision plate reader, (λ_{exc}=317 nm, donor λ_{EM}=615 nm; acceptor λ_{EM}=665 nm; Dichroic LANCE dual). Time resolved fluorescent intensity measurements were made at both emission wavelengths and the ratio of acceptor/donor was calculated and used for data analysis. All data was normalized to the mean of 16 high and 16 low control wells on each plate. A four parameter curve fit of the following form was then applied:

$$y = a + (b - a) / (1 + (10^{(x - c)/d})^2)$$

Where 'a' is the minimum, 'b' is the Hill slope, 'c' is the pI50 and 'd' is the maximum.

Examples 1-3 were tested in all of the BRD2, BRD3 and BRD4 assays described above and were found to have a pIC₅₀ in the range 6.5-7.5 in each assay.

Measurement of LPS induced IL-6 Secretion from Whole Blood

Activation of monocytic cells by agonists of toll-like receptors such as bacterial lipopolysaccharide (LPS) results in production of key inflammatory mediators including IL-6. Such pathways are widely considered to be central to the pathophysiology of a range of auto-immune and inflammatory disorders.

Compounds to be tested are diluted to give a range of appropriate concentrations of which 1 µl of the diluted stocks is added to a 96 well plate. Following addition of whole blood (130 µl) the plates are incubated at 37 degrees (5% CO₂) for 30 min before the addition of 10 µl of 2.8 µg/ml LPS, diluted in complete RPMI 1640 (final concentration=200 ng/ml), to give a total volume of 140 µl per well. After further incubation for 24 hours at 37 degrees, 140 µl of PBS are added to each well. The plates are sealed, shaken for 10 minutes and then centrifuged (2500 rpm x 10 min). 100 µl of the supernatant are removed and IL-6 levels assayed by immunoassay (typically by MesoScale Discovery technology) either immediately or following storage at -20 degrees. Concentration response curves for each compound was generated from the data and an IC₅₀ value was calculated.

Examples 1 and 2 were tested in this assay and were found to have a IC₅₀ in the range 6.0-7.0.

These data demonstrate that bromodomain inhibitors tested in the above whole blood assay inhibited the production of key inflammatory mediator IL-6.

In Vivo Mouse Model to Demonstrate Modulation of Pro-Inflammatory Response

Male CD1 mice (25-30 g, n=4 per group) received a single i.v. bolus injection of LPS (100 µg/kg) via the tail vein 1 h after pre-treatment with a single oral administration of either vehicle (1% (w/v) methylcellulose in sterile water) or the test compound (3, 10 and 30 mg/kg). Serial blood samples were obtained from the tail vein by direct venepuncture at various time points up to 5 h post-LPS administration for analysis of IL-6 and the test compound concentrations by Meso Scale Discovery (MSD) analysis and LC-MS/MS respectively.

In vehicle control mice, i.v. LPS induced a time-dependent increase in serum IL-6 concentrations, while mice pre-treated orally with the compound of Example 2 (3, 10 and 30 mg/kg) had reduced maximum (C_{max}) IL-6 levels by 46%, 79%, 73% respectively, and reduced total exposures (AUC) of IL-6 by 35%, 70%, 63% respectively. This reduction in IL-6 is comparable to the maximal reduction observed with the positive control dexamethasone, i.e.: 73% and 70% reduction in IL-6 C_{max} and AUC, respectively.

These data demonstrate that the compound of Example 2 tested in the above assay reduced LPS-induced systemic IL-6 levels in the mouse following a single oral administration and consequently may have utility as an anti-inflammatory agent.

Oncology Cell Growth Assay

Human cell lines (n=80 comprising cell lines described in Table 2 below) were cultured in RPMI-1640 containing 10% fetal bovine serum, 1000 viable cells per well were plated in 384-well black flat bottom polystyrene plates (Greiner #781086) in 48 µl of culture media. All plates were placed at 5% CO₂, 37° C. overnight. The following day one plate was harvested with CellTiter-Glo (CTG, Promega #G7573) for a time equal to 0 (T0) measurement and compound (20 point titration from 14.7 µM to 7 µM) was added to the remaining

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plates. The final concentration of DMSO in all wells was 0.15%. Cells were incubated for 72 hours or the indicated time and each plate was developed with CellTiter-Glo reagent using a volume equivalent to the cell culture volume in the wells. Plates were shaken for approximately 2 minutes and chemiluminescent signal was read on the Analyst GT (Molecular Devices) or EnVision Plate Reader (Perkin Elmer).

Results are expressed as a percent of the T0 and plotted against the compound concentration. The T0 value was normalized to 100% and represents the number of cells at time of compound addition and the concentration response data were fit with a 4 parameter curve fit using XLfit software (model 205). The concentration that inhibited cell growth by 50% (gIC₅₀) is the midpoint of the 'growth window' (between the T0 and DMSO control). The Ymin-T0 value is determined by subtracting the T0 value (100%) from the Ymin value (%) determined from the fit of the concentration response curve. Values from the wells with no cells were subtracted from all samples for background correction.

The compound of Example 2 was tested in accordance with the above procedure and found to have the gIC₅₀ as shown in Table 2.

TABLE 2

Cell line type	n (number of lines)	gIC ₅₀
Multiple myeloma	16	1.1 to >29326 nM (median 414 nM), with 15 out of 16 cell lines in the range 1.1 to 2000 nM
Small cell lung cancer (SCLC)	38	76 to >29326 nM (median 538 nM), with 35 of the 38 cell lines in the range 76 to 2500 nM
Cervical cancer	4	266-847 nM
NLT-midline carcinoma	2	59-66 nM
Neuroblastoma	12	25-435 nM (median 193 nM)
Esophageal	8	208-1544 nM (median 759 nM)

The compound of Example 2 was also tested in accordance with an analogous procedure using 96 well plates along with appropriate modifications to volumes and concentrations that would be apparent to those skilled in the art. The compound of Example 2 was tested and found to have the gIC₅₀ as shown in Table 3.

TABLE 3

Cell line type	n (number of lines)	gIC ₅₀
Acute monocytic leukemia	1	123 nM
Acute promyelocytic leukemia	1	141 nM
Cutaneous T cell lymphoma	1	162 nM
Burkitt's lymphoma	3	181-807 nM
Chronic myeloid leukemia	1	776 nM
Breast cancer (ductal)	1	537 nM
Ovarian carcinoma	1	707 nM

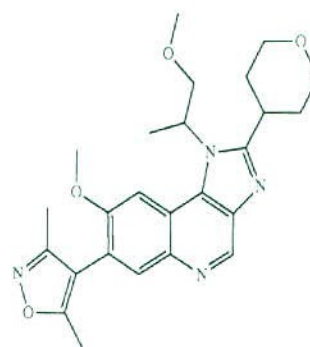
These data demonstrate that the compound of Example 2 tested in the above assay inhibited cell growth in a panel of oncology cell lines and may therefore have utility in the treatment of one or more cancers.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

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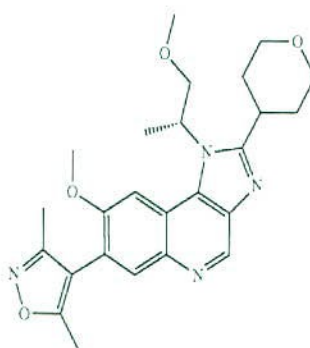
What is claimed is:

1. A compound of formula (I) which is 4-(8-methoxy-1-(1-methoxypropan-2-yl)-2-(tetrahydro-2H-pyran-4-yl)-1H-imidazo[4,5-c]quinolin-7-yl)-3,5-dimethylisoxazole



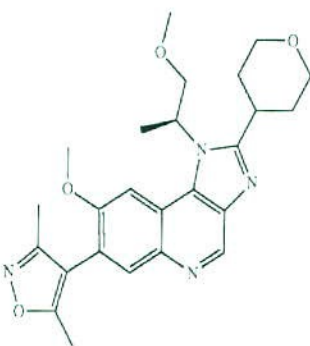
or a salt thereof.

2. A compound of formula (IA) which is 4-(8-methoxy-1-((R)-1-methoxypropan-2-yl)-2-(tetrahydro-2H-pyran-4-yl)-1H-imidazo[4,5-c]quinolin-7-yl)-3,5-dimethylisoxazole



or a salt thereof.

3. A compound of formula (IB) which is 4-(8-methoxy-1-((S)-1-methoxypropan-2-yl)-2-(tetrahydro-2H-pyran-4-yl)-1H-imidazo[4,5-c]quinolin-7-yl)-3,5-dimethylisoxazole



or a salt thereof.

4. A compound according to claim 2 or a pharmaceutically acceptable salt thereof.

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5. A pharmaceutical composition which comprises a compound or a pharmaceutically acceptable salt thereof as defined in claim 4 and one or more pharmaceutically acceptable carriers, diluents or excipients.

6. A combination pharmaceutical product comprising a compound or a pharmaceutically acceptable salt thereof as defined in claim 4 together with one or more other therapeutically active agents.

7. A method of treating a chronic autoimmune and/or inflammatory condition which comprises administering, to a human subject in need thereof, a therapeutically effective amount of a compound or a pharmaceutically acceptable salt thereof as defined in claim 4.

8. A method of treating cancer which comprises administering, to a human subject in need thereof, a therapeutically effective amount of a compound or a pharmaceutically acceptable salt thereof as defined in claim 4.

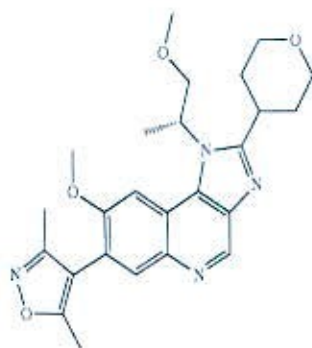
9. A method according to claim 8 wherein said cancer is a leukaemia, a NUT-midline carcinoma, multiple myeloma, lung cancer, a neuroblastoma, Burkitt's lymphoma, cervical cancer, esophageal cancer, ovarian cancer, breast cancer, or colorectal cancer.

10. A salt of a compound of Formula (IA) according to claim 2 wherein said salt is selected from the group consisting of hydrochloride, sulfate, maleate, fumarate, citrate, p-toluenesulfonate, benzenesulfonate, and methanesulfonate salt.

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11. A salt according to claim 10 wherein said salt is a methanesulfonate salt.

12. A compound of formula (IA) which is 4-(8-methoxy-1-((R)-1-methoxypropan-2-yl)-2-(tetrahydro-2H-pyran-4-yl)-1H-imidazo[4,5-c]quinolin-7-yl)-3,5-dimethylisoxazole.



(IA)

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Application No. 12 748 028.3 - 1452	Ref. ADS/PB64734	Date 30.03.2015
Applicant GlaxoSmithKline LLC		

Communication under Rule 71(3) EPC

1. Intention to grant

You are informed that the Examining Division intends to grant a European patent on the basis of the above application with the text and drawings and the related bibliographic data as indicated below.

A copy of the relevant documents is enclosed.

1.1 In the text for the Contracting States:

AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT
RO RS SE SI SK SM TR

Description, Pages

1-33 as published

Claims, Numbers

1-10 filed with entry into the regional phase before the EPO

Drawings, Sheets

1/5-5/5 as published

With the following amendments to the above-mentioned documents proposed by the division

Description, Pages 2, 5, 13, 33

Claims, Numbers 2, 3, 9, 10

Comments

DESCRIPTION

Page 5: Inconsistency between claim and description removed (Art. 84 EPC)

Page 13: Article 53(c) EPC

Page 33: Article 84 EPC

CLAIMS

Page 1, Claim 2: Inconsistency between claims removed (Art. 84 EPC)

Page 1, Claim 3: Inconsistency between claims removed (Art. 84 EPC)

Page 2, Claim 9: Inconsistency between claims removed (Art. 84 EPC)

Page 2, Claim 10: Inconsistency between claims removed (Art. 84 EPC)

1.2 Bibliographic data

The title of the invention in the three official languages of the European Patent Office, the international patent classification, the designated Contracting States, the registered name(s) of the applicant(s) and the other bibliographic data are shown on the **enclosed EPO Form 2056**.

2. Invitation

You are invited, **within a non-extendable period of four months** of notification of this communication,

2.1 to EITHER approve the text communicated above and verify the bibliographic data (R. 71(5) EPC)

(1) by filing a translation of the claim(s) in the other two official languages of the EPO

	Fee code	EUR
(2a) by paying the fee for grant including the fee for publication: minus any amount already paid (R. 71a(5) EPC):	007	915.00 0.00

Total amount: 915.00

(3) by paying additional claims fees under Rule 71(4) EPC;
number of claims fees payable: 0
minus any amount already paid (R. 71a(5) EPC):

016 0.00
0.00

Total amount: 0.00

Important: If the translations of the claims and fees have already been filed and paid respectively in reply to a previous communication under Rule 71(3) EPC, e.g. in the case of resumption of examination after approval (see Guidelines C-V, 6), **agreement as to the text to be granted** (R. 71a(1) EPC) must be expressed within the same time limit (e.g. by approving the text and verifying the bibliographic data, by confirming that grant proceedings can go ahead with the documents on file and/or by stating which translations of the claims already on file are to be used).

Note 1: See "Important notes concerning fee payments" below.

Note 2: Any overpaid "minus" amounts will be refunded when the decision to grant (EPO Form 2006A) has been issued.

Note 3: For the calculation of the grant fee under Art. 2(2), No. 7, RFees (old fee structure), the number of pages is determined on the basis of a clean copy of the application documents, in which text deleted as a result of any amendments by the Examining Division is not shown. Such clean copy is made available via on-line file inspection only.

- 2.2 OR, in the case of disapproval, to request **reasoned** amendments or corrections to the **text** communicated above or keep to the latest text submitted by you (R. 71(6) EPC).

In this case the translations of the claims and fee payments mentioned under point 2.1 above are NOT due.

The terms "amendment(s)" and "correction(s)" refer only to amendments or corrections of the application documents and not of other documents (e.g. bibliographic data, the designation of the inventor, etc.).

If filing amendments, you must identify them and indicate the basis for them in the application as filed. Failure to meet either requirement may lead to a communication from the Examining Division requesting that you correct this deficiency (R. 137(4) EPC).

2.3 Bibliographic data

Where you request a change or correction of bibliographic data in response to the Rule 71(3) communication, this will **not** cause the sending of a second communication under Rule 71(3) EPC. You will still have to pay the fees and file translations in reply to the Rule 71(3) communication in the case of 2.1 above, unless you also file a reasoned request for amendments or corrections in response to the Rule 71(3) communication (see case 2.2 above).

3. Loss of rights

If neither of the two possible actions above (see points 2.1 or 2.2) is performed in due time, the European patent application will be deemed to be withdrawn (R. 71(7) EPC).

4. Further procedure

4.1 In the case of point 2.1 above

- 4.1.1 The decision to grant the European patent will be issued, and the **mention of the grant** of the patent will be published in the European Patent Bulletin, if the requirements concerning the translation of the claims and the payment of all fees are fulfilled and there is agreement as to the text to be granted (R. 71a(1) EPC).

Note on payment of the renewal fee:

If a renewal fee becomes due before the next possible date for publication of the mention of the grant of the European patent, publication will be effected only after the renewal fee and any additional fee have been paid (R. 71a(4) EPC).

Under Article 86(2) EPC, the obligation to pay renewal fees to the European Patent Office terminates with the payment of the renewal fee due in respect of the year in which the mention of the grant of the European patent is published.

Note on payment of the designation fee(s):

If the designation fee(s) become(s) due after the communication under Rule 71(3) EPC, the mention of the grant of the European patent will not be published until the designation fee(s) has/have been paid (R. 71a(3) EPC).

- 4.1.2 After publication, the **European patent specification** can be downloaded free of charge from the EPO publication server <https://data.epo.org/publication-server> or ordered from the Vienna sub-office upon payment of a fee (OJ EPO 2005, 126).

Until 31 December 2013, each proprietor may request in writing to receive the certificate for the European patent together with one copy of the new patent specification only if the request is filed within three-month or the additional two-month period (R. 95(3) and (4) EPC). If such request has been previously filed, it has to be confirmed within the same period. The requested copy is free of charge. Any request or confirmation of a request filed after 31 December 2013 or after expiry of these periods will not be dealt with and the certificate

will be delivered without a copy of the new European patent specification (cf. Notice from the European Patent Office dated 16 July 2013 concerning communication of the certificate for a European patent, OJ 2013, 418).

4.1.3 Filing of translations in the Contracting States

As regards translation requirements prescribed by the Contracting States under Article 65(1) EPC, please consult the website of the European Patent Office

www.epo.org → Law & practice → Legal texts, National law relating to the EPC

www.epo.org → Law & practice → All Legal texts → London Agreement

In the case of a valid extension or validation

As regards translation requirements prescribed by the Extension or or Validation States, please consult the website of the European Patent Office

www.epo.org → Law & practice → Legal texts, National law relating to the EPC

Failure to supply a prescribed translation in a Contracting State, or in an Extension or Validation State may result in the patent being deemed to be void *ab initio* in the State concerned (Art. 65(3) EPC).

4.2 In case of 2.2 above

If the present communication under Rule 71(3) EPC is based on an auxiliary request and, within the time limit, you maintain the main request or a higher ranking request which is not allowable, the application will be refused (Art. 97(2) EPC).

If the Examining Division gives its consent to the requested amendments or corrections, it will issue a new communication under Rule 71(3) EPC; otherwise, it shall resume the examination proceedings (R. 71(6) EPC).

5. Filing of a divisional application

Any divisional application relating to this European patent application must be filed directly with the European Patent Office in Munich, The Hague or Berlin and will be in the language of the proceedings for the present application, or if the latter was not in an official language of the EPO, the divisional application may be filed in the language of the present application as filed (see Article 76(1) and Rule 36(2) EPC). Any such divisional application must be filed while the present application is still pending and the time limit for filing divisional applications must be observed (R. 36(1) EPC; Guidelines A-IV, 1.1.1).

6. Important notes concerning fee payments

6.1 For all payments, please refer to the relevant fee code(s).

6.2 Automatic debiting procedure

The fee for grant, including the fee for publication, and any additional claims fees due under Rule 71(4) EPC will be debited automatically on the date of filing of the translations of the claims, or on the last day of the period of this communication. However, if the designation fee(s) become(s) due as set out in Rule 71a(3) EPC and/or a renewal fee becomes due as set out in Rule 71a(4) EPC, these should be paid separately by another permitted way of payment in order not to delay the publication of the mention of the grant. The same applies in these circumstances to the payment of extension fees. For further details see the Arrangements for the automatic debiting procedure (AAD) and accompanying information from the EPO concerning the automatic debiting procedure (Annexes A.1 and A.2 to the Arrangements for deposit accounts (ADA) Supplementary publication 4 - OJ EPO 2014).

6.3 Important information relating to fee amounts

Following any amendment to the Rules relating to Fees, the amount(s) mentioned in this communication may be different from the amount(s) **actually due on the date of payment**. The latest version of the Schedule of

fees and expenses, published as a Supplement to the Official Journal of the EPO, is also available on the EPO website (www.epo.org) and can be found under www.epo.org/schedule-of-fees, which allows the viewing, downloading and searching for individual fee amounts, both current and previous.

Please note that procedural fees are usually adjusted every two years, on even years, with effect from 1 April.

Examining Division:

Chairman:	Sahagún Krause, H
2nd Examiner:	Gettins, Marc
1st Examiner:	Von Daacke, Axel



Benitez Sierra, O
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Tel. No.: +49 89 2399 - 5715

Enclosure(s): Text intended for grant

EPO Form 2056