

JOSE LLORED CAMACHO & CO.

ABOGADOS

Calle 72 No. 5-83 Piso 5, Bogotá, D.C. Tel: 6069700 Fax 6069701

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 10-131479- -00011-0000

Fecha: 2013-07-31 16:38:07 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 412 REPOSPRESRECU Folios: 19

Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

DIVISIÓN DE NUEVAS CREACIONES

E. S. D.

Re: PI.-GILEAD SCIENCES, INC.-Solicitud de Patente de Invención en Fase Nacional PCT para "NUCLEÓSIDOS DE IMIDAZOL[1,5-F][1,2,4]TRIAZINIL, IMIDAZOL[1,2-F][1,2,4]TRIAZINIL Y [1,2,4]TRIAZOLO[4,3-F][1,2,4] TRIAZINIL PARA TRATAMIENTO ANTIVIRAL".-Clase C07D 487/04.-Expediente número 10-131.479.-

Yo, **ALICIA LLORED RICAURTE**, mayor de edad, vecina de ésta ciudad, abogada titulada e identificada con la cédula de ciudadanía número 39.690.713 de Usaquén, Representante Legal en Bogotá para todos los asuntos relativos a la Propiedad Industrial de la sociedad **GILEAD SCIENCES, INC.**, atentamente manifiesto a usted que interpongo **RECURSO DE REPOSICIÓN** contra la Resolución Número **36960** dictada por el señor Superintendente de Industria y Comercio, el 20 de Junio de 2013, por medio del cual se niega el privilegio de patente para la invención contenida en el expediente de la referencia, con base en los siguientes:

I. FUNDAMENTOS DE DERECHO

Como fundamento de mi Recurso me permito manifestar ante ese Despacho que el contenido de la Resolución Número **36960** evidencia que durante el examen técnico realizado a la solicitud denegada de ninguna manera se consideraron de manera correcta las características, el objeto e importancia de la invención allí reclamada en su verdadera dimensión.

Es así que, a pesar de las modificaciones y argumentos proporcionados por el solicitante en mi memorial de fecha 28 de Enero de 2013 que se presentó como respuesta al Oficio Número 19681, en la Resolución impugnada ese Despacho mantiene las objeciones frente al Nivel Inventivo de la solicitud.

En vista de lo anterior, a continuación me permito brindar argumentos técnicos que no sólo demostrarán a ese Despacho que la presente invención sí cumple con el requisito de Nivel Inventivo exigido por el Artículo 18 de la Decisión 486 de 2000, sino que además establecerán que el análisis realizado es incorrecto, toda vez que se interpreta de manera errónea tanto la invención como el arte previo; constituyéndose por lo tanto la negación de la solicitud en una clara violación al mencionado Artículo 18 de la Decisión Andina 486 de 2000.

1. Argumentos que demuestran el nivel inventivo de la invención denegada de acuerdo con lo establecido en el Artículo 18 de la Decisión Andina 486 de 2000

En relación con el nivel inventivo de la presente solicitud me permito manifestar que esa Oficina no repara en los argumentos que fueron presentados en mi memorial de 28 de Enero de 2013, los cuales establecen de forma incontrovertible el nivel inventivo que conlleva la solicitud denegada frente al estado del arte más próximo, y por lo tanto ese Despacho afirma en la Resolución impugnada que los compuestos de la reivindicación 1 de la solicitud resultarían obvios a la luz de la combinación de las enseñanzas de los documentos Dunfield P. J. et. al., "*Synthesis of C-ribosyl imidazo[2,1-f][1,2,4]triazines as inhibitors of adenosine and AMP deaminases*", **J. Chem. Soc., Perkin Trans. 1, 1999, pp. 2929-2936 (D1)** y **US 20040067901 (D2)**.

Con relación al documento D1 el señor Examinador manifiesta que es el documento del estado del arte más cercano a la invención, el cual se diferencia de esta última en que en la reivindicación 1 de la solicitud denegada los compuestos tienen en la posición 5 del anillo [2,1-f][1,2,4] triazina un grupo de sustituyentes que incluyen: halógeno, amino, ciano, entre otros, mientras que el documento D1 divulga un sustituyente hidrógeno para dicha posición.

Por otro lado, ese Despacho sostiene que la diferencia entre la invención definida en la reivindicación 1 y el compuesto (I) del documento D2 corresponde a que en la reivindicación 1 de la invención denegada se define como sustituyente en la posición 2 de anillo tetrahidrofurano una base nitrogenada seleccionada entre imidazo [2,1-f][1,2,4]triazina y [1,2,4]triazolo [3,4-f][1,2,4] triazina y el documento D2 tiene como sustituyente un grupo de bases nitrogenadas que incluyen: 9-H-purina, 3H-pirazolo[4,3-d] pirimidina, 1H-pirazolo[3,4-d] pirimidina y 7H-pirrolo [3,2-d] pirimidina.

Así las cosas, esa Oficina manifiesta que el problema técnico objeto que pretende resolver esta invención se puede formular como "*cómo modificar los*

compuestos del documento D1 para así obtener nuevos compuesto antivirales útiles para el tratamiento de infecciones por virus de la familia Flaviviridae."

A lo anterior añade que *"Sin embargo, el documento D1 refiere que el 3-β-D-ribofuranósido de una nueva imidazo [2,1-f][1,2,4] triazina (Compuesto 6) es isomérico e isoelectrónico con el nucleósido deaminoformicina (compuesto 1), por lo cual una persona versada en la materia entendería que el anillo imidazo[2,1-f][1,2,4] triazina es isomérico e isoelectrónico al anillo 3H-pirazolo[4,3-d]pirimidina en el caso de los ribufuranósidos antivirales y dado que el documento D2 divulga que los derivados nucleósidos del anillo 3H-pirazolo [4,3-d] pirimidina son inhibidores de la RNA-polimerasa viral dependiente de RNA útiles como inhibidores de la replicación del virus de la hepatitis C." (sic)*

Así las cosas, el señor Examinador concluye que *"En consecuencia, existía suficiente sugerencia o motivación para remplazar los sustituyentes del compuesto 6 divulgado en el documento D1 por los sustituyentes específicos divulgados en el documento D2 dado que los anillo imidazo [2,1-f][1,2,4] triazina y 3H-pirazolo[4,3-d]pirimidina son isoméricos e isoelectrónicos y por lo tanto, resultan equivalentes biológicos, por lo que permite obtener una nueva serie de compuestos inhibidores de la RNA-polimerasa viral dependientes de RNA, por lo cual la reivindicación 1 se considera obvia."*

Además manifiesta que las reivindicaciones dependientes 2 a 10 no mencionan características inventivas adicionales y por lo tanto no se pueden considerar tampoco inventivas.

Sumado a lo anterior, el señor Examinador sostiene que las reivindicaciones de composición 11 a 13 tampoco son inventivas pues los compuestos de la solicitud son bioisómeros de los compuestos divulgados en el documento D2 y se espera un comportamiento similar dentro de composiciones farmacéuticas, a lo que se suma el hecho que el documento D2 también revela composiciones farmacéuticas con las demás características técnicas de las reivindicaciones 11 a 13.

Finalmente, frente a los argumentos presentados en mi memorial de fecha 28 de Enero de 2013 esa Oficina argumenta que *"el documento D1 revela los compuestos 1 y 3 correspondientes a la deaminoformicina y el β-D-ribofuranósido de la 7H-purina, los cuales son inhibidores de adenosina y AMP desaminasas (Fl. 1, columna 1) y puesto que forman parte del alcance del documento D2, una persona del oficio normalmente versada en la materia concluiría sin dificultad que los compuestos señalados son tanto inhibidores de adenosina y AMP desaminasas como de la replicación de la RNA-polimerasa viral dependiente de RNA del virus de la hepatitis C de acuerdo con las enseñanzas del documento D2. Lo anterior porque*

el documento D2 menciona dentro de los posibles sustituyentes del anillo tetrahidrofurano un grupo extenso de bases nitrogenadas incluyendo entre otros el anillo 3H-pirazolo[4,3-d]pirimidina y además reporta actividad como inhibidores de VCH y porque el documento D1 da a conocer que los anillos 3H-pirazolo[4,3-d]pirimidina y imidazo [2,1-f][1,2,4] triazina son serie isomérica e isoelectrónica."

Con base en lo anterior el señor Examinador concluye que "una persona del oficio normalmente versada en la materia enfrentada al problema de obtener antivirales alternativos con acción específica sobre la replicación de la RNA-polimerasa viral dependiente de RNA del virus de la hepatitis C o cualquier otro virus de la familia flaviviridae estaría motivada a utilizar o remplazar los sustituyentes específicos de los compuestos divulgados en el documento D2 en el compuesto 6 divulgado en el documento D1, para así generar una serie de compuestos alternativos útiles como inhibidores de la replicación de la RNA-polimerasa viral dependiente de RNA del virus de la hepatitis C (HCV) y otros virus de la familia flaviviridae, por lo anterior, este Despacho concluye que la serie reclamada no presenta nivel inventivo."

Visto lo anterior y con el ánimo de demostrar que el capítulo reivindicatorio de la solicitud denegada presenta un inequívoco carácter inventivo frente a la combinación de las enseñanzas de los documentos D1 y D2, atentamente me permito presentar los siguientes argumentos y consideraciones técnicas:

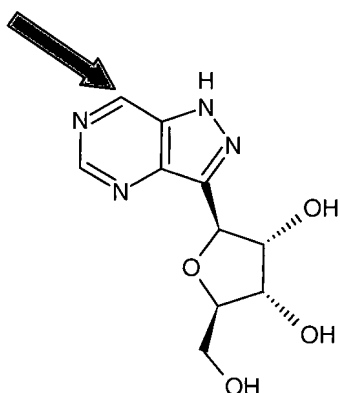
- En primer lugar me permito manifestar que el señor Examinador considera que el documento D1 es el documento del estado del arte más cercano a la presente invención debido a los compuestos 1 y 6 allí revelados.

No obstante, es necesario señalar que el compuesto 1 de D1 tiene en su estructura central una base nitrogenada diferente al anillo de imidazo [2,1-f][1,2,4] triazina o de [1,2,4] triazolo [3,4-f][1,2,4] triazina que tienen los compuestos de la formula I de la invención.

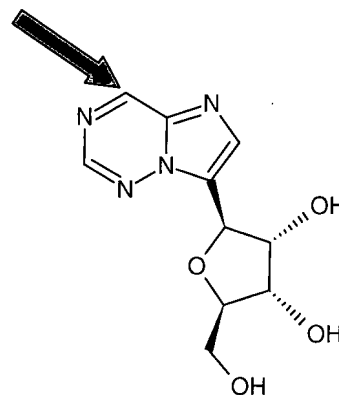
Por otro lado, considero importante dirigir la atención de ese Despacho al hecho que **tanto el compuesto 1 como el compuesto 6 del documento D1 fallan en enseñar el sustituyente que tienen todos los compuestos de la invención sobre la posición 5 del anillo de imidazo [2,1-f][1,2,4] triazina o de [1,2,4] triazolo [3,4-f][1,2,4] triazina, toda vez que en la solicitud denegada R⁸ se selecciona de sustituyentes que incluyen halógeno, amino y ciano entre otros, mientras que en los compuestos de D1 en la posición de este sustituyente se encuentra un hidrógeno.**

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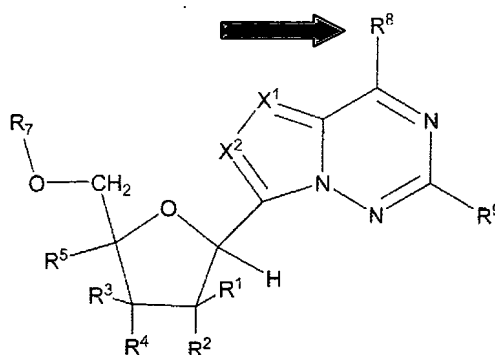
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Compuesto 1 de D1



Compuesto 6 de D1

Compuestos de Formula I
de la solicitud

Adicionalmente, me permito resaltar que a partir de la lectura del documento D1 salta a la vista que **dicha referencia enseña el uso de los compuestos identificados como inhibidores de adenosina y AMP desaminasas pero falla en enseñar o sugerir que los compuestos allí divulgados puedan ser útiles para tratamiento antiviral, como lo son los compuestos revelados por la presente solicitud.**

Así las cosas, **a la luz de las enseñanzas de D1 salta a la vista que una persona medianamente versada en la materia no podría tener una expectativa o sugerencia de que un compuesto para utilizarse como inhibidor de adenosina y AMP desaminasas podría ser efectivo para el tratamiento de infecciones virales causadas por *Flaviviridae*.**

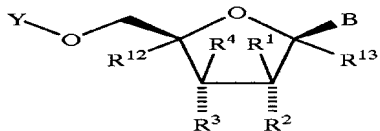
Sumado a lo anterior, me permito manifestar que D1 cita el artículo de Glazer¹ (que se adjunta a este escrito) para referirse a que los inhibidores de la enzima adenosina desaminasa son de interés en "**Quimioterapia viral**", como se señala en las líneas 5 y 6 de la columna izquierda de la primera página de D1. De

¹ Glazer R. I., "Adenosine Deaminase Inhibitors: Their Role in Chemotherapy and Immunosuppression", Cancer Chemother. Pharmacol., 1980, 4, pp. 227-235.

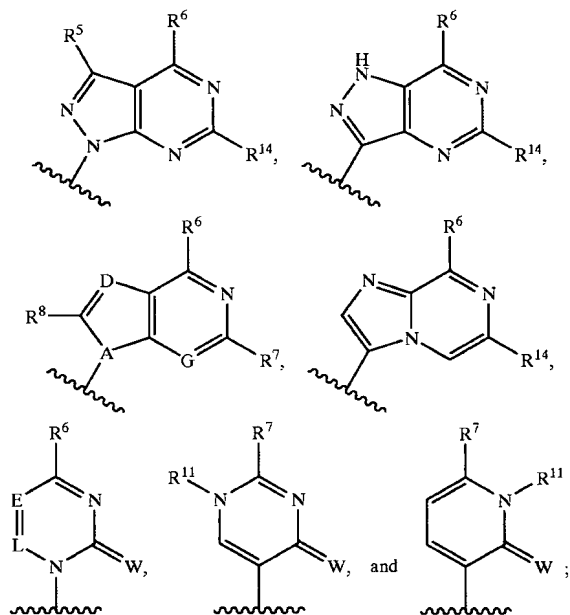
manera más particular, me permito señalar que la única mención que hace el documento de Glazer a una inhibición antiviral específica concierne a la inhibición de "herpes simplex I y II", así como también de virus de RNA que producen estomatitis y sarampión" (véase los primeros dos párrafos de la columna izquierda de la página 231).

Consecuentemente, queda una vez más expuesto el hecho que el documento D1 no enseña ni sugiere que los compuestos revelados en tal referencia del estado del arte tengan actividad antiviral contra *Flaviviridae*.

Por otro lado, me permito señalar que el documento D2 enseña derivados de nucleósidos para su uso como inhibidores de la RNA polimerasa viral dependiente de RNA. Sin embargo, de la lectura de D2 es claro que tal referencia falla en enseñar compuestos con el anillo central de imidazo [2,1-f][1,2,4] triazina o [1,2,4] triazolo [3,4-f][1,2,4] triazina que tienen los compuestos objeto de la presente invención, tal como se muestra a continuación:

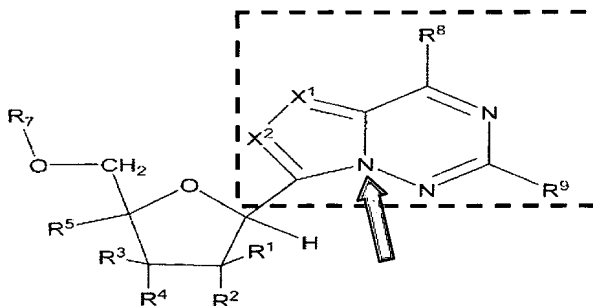


Compuestos de fórmula I de D2



Significados de la variable B de de la fórmula I de D2

(en donde A, D, L, E y G pueden ser CH o N)



Compuestos de fórmula I de la solicitud

▪ A la luz de lo anterior, la persona versada en la materia también reconocerá que **el compuesto 6 de D1 tampoco se encuentra cubierto por el alcance de D2 toda vez que dicho compuesto 6 de D1 tiene el mismo núcleo central de imidazo [2,1-f][1,2,4] triazina que pueden tener los compuestos de la presente invención y que no se encuentra cubierto por la formula I de D2.**

Por lo tanto, **a partir de las enseñanzas de los documentos D1 y D2 la persona medianamente versada en la materia no se vería motivada a sustituir específicamente la posición 5 del anillo de [2,1-f][1,2,4] triazina del compuesto 6 de D1 con los sustituyentes enseñados en D2 y esto básicamente porque a partir de las enseñanzas de los documentos D1 y D2 dicha persona medianamente versada en la materia no tendría una motivación para ello y mucho menos una expectativa razonable de éxito de que los compuestos así obtenidos fueran efectivos para el tratamiento de infecciones virales causadas por *Flaviviridae*, máxime cuando el compuesto 6 de D1 no hace parte del alcance del documento D2 tal como se expuso anteriormente.**

▪ Con relación a lo anterior me permito manifestar que el señor Examinador fundamenta sus argumentos de falta de nivel inventivo de los compuestos de la solicitud denegada con base en la supuesta existencia de equivalencia biológica (bioisosterismo) entre el anillo imidazo [2,1-f][1,2,4] triazina del compuesto 6 de D1 y los compuestos de la presente invención y el anillo 3H-pirazolo[4,3-d]pirimidina del compuesto 1 de D1 y los compuestos de D2, lo cual salta a la vista cuando ese Despacho afirma que:

"Sin embargo, el documento D1 refiere que el 3-β-D-ribofuranósido de una nueva imidazo [2,1-f][1,2,4] triazina (Compuesto 6) es isomérico e isoelectrónico con el nucleósido deaminoformicina (compuesto 1), por lo cual una persona versada en la materia entendería que el anillo imidazo[2,1-f][1,2,4] triazina es isomérico e isoelectrónico al anillo 3H-pirazolo[4,3-d]pirimidina en el caso de los ribufuranósidos antivirales y dado que el documento D2 divulga que los derivados nucleósidos del anillo 3H-pirazolo [4,3-d] pirimidina son inhibidores de la RNA-polimerasa viral dependiente de RNA útiles como inhibidores de la replicación del virus de la hepatitis C."

En consecuencia, existía suficiente sugerencia o motivación para remplazar los sustituyentes del compuesto 6 divulgado en el documento D1 por los sustituyentes específicos divulgados en el documento D2 dado que los anillos imidazo [2,1-f][1,2,4] triazina y 3H-pirazolo[4,3-d]pirimidina son isoméricos e isoelectrónicos y por lo tanto, resultan equivalentes biológicos, por lo que permite

obtener una nueva serie de compuestos inhibidores de la RNA-polimerasa viral dependientes de RNA, por lo cual la reivindicación 1 se considera obvia."

"Dado que los compuestos de la solicitud son bioisómeros de los compuestos divulgados en el documento D2, se espera un comportamiento similar dentro de composiciones farmacéuticas..."

Contrario a lo afirmado por el señor Examinador, me permito dirigir la atención de ese Despacho al Reporte de Búsqueda Internacional y la Opinión Escrita de la Autoridad de Búsqueda Internacional que fueron emitidos para la correspondiente solicitud internacional, documentos que se anexan al presente escrito. En la Opinión Escrita de la Autoridad de Búsqueda Internacional, dicha Autoridad afirma que con relación a los compuestos objeto de la solicitud en cuestión:

"el bioisosterismo en este campo específico no ha sido demostrado" (numeral 3. Nivel Inventivo)

Sumado a esto, me permito señalar las revelaciones del documento de Cheeseright T.² el cual discute la incertidumbre del bioisosterismo y señala que:

"La esperanza del bioisosterismo es que las propiedades de un compuesto puedan ser ajustadas sin afectar su actividad biológica subyacente. Sin embargo esta esperanza no está exenta de desafíos. La aplicación exitosa del bioisosterismo para conseguir el resultado molecular adecuado es difícil por el problema fundamental que la estructura química es indicador poco fiable de la actividad biológica. Pequeños cambios en una molécula pueden tener un profundo impacto sobre la actividad, especificidad y toxicidad de un compuesto, mientras que quimotipos completamente diferentes pueden tener perfiles de actividad biológica casi idénticos." (Resaltado fuera de texto)

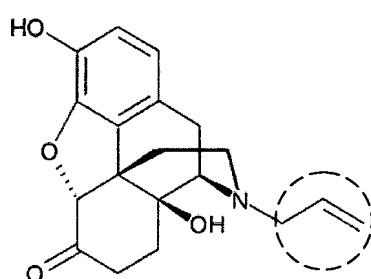
En este punto vale la pena resaltar que para la persona versada en la materia sería un hecho claro que aún cambios pequeños en la estructura de un compuesto pueden llegar a tener efectos significativos sobre su actividad biológica, especialmente si dichos cambios estructurales afectan el sitio en el cual ocurre la interacción con la molécula biológica objetivo.

Tan es así, que reemplazos isostéricos pueden proporcionar compuestos con actividad antagonista del compuesto original, *"estas sustituciones conducen no únicamente a productos cuya acción es idéntica a la de los compuestos tomados*

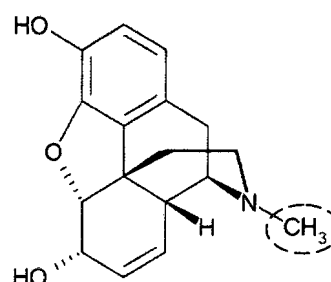
² Cheeseright T., "The Identification of Bioisosteres as Drug Development Candidates", Innovations in Pharmaceutical Technology, 2009, Issue 28, pp. 22-26.

como modelo, sino a antagonistas también. Muchos ejemplos pueden ser citados de equivalentes de productos naturales, parametabolitos, paravitaminas, parahormonas y miméticos, así como sus antagonistas específicos, antimetabolitos, antivitaminas, antihormonas y líticos.³

Un ejemplo de esto lo constituye la naloxona, un fármaco antagonista de los receptores opioides, muy usado en el tratamiento de la intoxicación aguda por opiáceos. Tal como se aprecia en la figura, la diferencia estructural entre la naloxona y la morfina (un conocido fármaco opioide) es únicamente el remplazo del grupo metilo por un propileno.



Naloxona
(Fármaco antagonista de los receptores opioides)



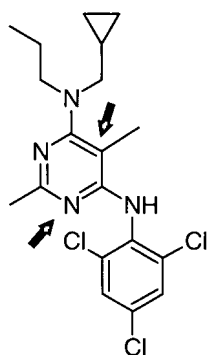
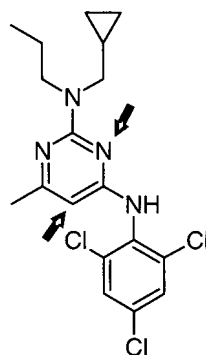
Morfina
(Fármaco opioide)

Es entonces evidente que un reemplazo de un sustituyente por otro en un anillo central, por pequeña que fuere la diferencia entre los sustituyentes, puede cambiar la actividad biológica y el efecto terapéutico de un compuesto toda vez que dependerá claramente del papel que desempeñe esa sección estructural en la interacción del compuesto con su molécula biológica objetivo.

En este mismo sentido, la persona versada en la materia reconocería que el sólo cambio de posición de un heteroátomo dentro del anillo central de un compuesto puede ser significativo dentro de su actividad, tal como se ha encontrado para ciertos Antagonistas del factor₁ de liberación de corticotropina⁴. Así, como es evidente de la siguiente figura, en este tipo de compuestos si el anillo de pirimidina central está sustituido en las posiciones 4 y 6 por los grupos amino el compuesto tiene una alta actividad inhibitoria, sin embargo si el patrón de sustitución se cambia a las posiciones 2 y 4 el compuesto disminuye 5 mil veces su actividad:

³ Korolkovas, Adrejus "Essential of Medicinal Chemistry" 2nd edition, Jhon Wiley & Sons, New York, 1988, página 82.

⁴ Chen, Chen, et al J. Med. Chem. 1996, 39, 4358-4360


 $K_i = 2 \text{ nM}$

 $K_i = >10\,000 \text{ nM}$

Así las cosas, para la persona versada en la materia resultará evidente que aun cuando (i) el documento D2 divulgue que los derivados nucleósidos del anillo 3H-pirazolo [4,3-d] pirimidina son inhibidores de la RNA-polimerasa viral dependiente de RNA útiles como inhibidores de la replicación del virus de la hepatitis C y que (ii) el documento D1 muestre que el anillo de imidazo [2,1-f][1,2,4] triazina es isomérico e isoelectrónico con el anillo 3H-pirazolo[4,3-d]pirimidina, esto no puede conducir de manera evidente a la persona medianamente versada en la materia a que los derivados de nucleósidos del anillo imidazo [2,1-f][1,2,4] triazina del compuesto 6 de D1 sean un equivalente biológico de los derivados de nucleósidos del anillo 3H-pirazolo[4,3-d]pirimidina y que por lo tanto los derivados nucleósidos de imidazo [2,1-f][1,2,4] triazina (como el compuesto 6 de D1 aun cuando se incluyeran en la posición 5 del anillo imidazo [2,1-f][1,2,4] triazina los sustituyentes mostrados en D2) también serían inhibidores de la RNA-polimerasa viral dependiente de RNA como los derivados nucleósidos del anillo 3H-pirazolo [4,3-d] pirimidina revelados por D2 **y esto básicamente porque, tal como ha quedado demostrado anteriormente, si el sólo cambio de posición de un heteroátomo dentro del anillo central de un compuesto o un reemplazo isostérico de un sustituyente o átomo en la estructura de una molécula puede cambiar la actividad biológica y el efecto terapéutico de dicha molécula entonces los efectos de sustituir un átomo de carbono en el anillo de 3H-pirazolo [4,3-d] pirimidina por un átomo de nitrógeno para obtener el anillo imidazo [2,1-f][1,2,4] triazina puede tener las mismas repercusiones sobre la actividad biológica y el efecto terapéutico de la molécula en cuestión.**

A la luz de lo anterior, me permito muy respetuosamente llamar la atención a ese Despacho al hecho que el análisis presentado en el referenciado Concepto Técnico estaría enmarcado dentro de lo que en el ámbito de las patentes se conoce como análisis "hindsight", o análisis "Ex post facto", toda vez que conociendo de antemano la invención el señor Examinador está seleccionado partes específicas de las enseñanzas contenidas dentro de los documentos D1 y D2 y las agrupa de

manera particular a fin de construir la materia reclamada por la presente solicitud sin una motivación en el estado del arte de para qué hacer tales agrupaciones, lo cual de ninguna manera podría ser evidente para la persona versada en la materia y mucho menos en el momento en el cual se desarrolló la invención.

En este sentido vale la pena resaltar que al tener conocimiento de la invención es de esperarse que parezcan obvias dichas selecciones particulares de los sustituyentes de D2 y su inclusión específicamente en la posición 5 del anillo de [2,1-f][1,2,4] triazina del compuesto 6 de D1 y que pareciera evidente que por el hecho que los anillos de imidazo [2,1-f][1,2,4] triazina y 3H-pirazolo[4,3-d]pirimidina sean isoméricos e isoeléctricos entonces dichos anillos también podrían ser equivalente biológicos, toda vez que ya se sabe de antemano que efectivamente los compuestos así obtenidos tienen el efecto conseguido por los compuestos de la solicitud denegada y resuelven un problema técnico (el cual vale la pena resaltar no se identifica ni se sugiere por ninguno de D1 o D2 o su combinación); sin embargo, esta información no era conocida por el inventor en el momento de desarrollar la invención, por lo que no podría tener certeza de la utilidad de realizar esta selección particular de sustituyentes de D2 y su presencia sobre una posición particular (posición 5) del anillo de [2,1-f][1,2,4] triazina, ni de que el anillo de imidazo [2,1-f][1,2,4] triazina pudiera generar derivados de nucleósidos efectivos para el tratamiento de infecciones virales causadas por *Flaviviridae*.

Teniendo en cuenta los anteriores argumentos, me permito señalar que dentro del ámbito de las patentes es bien conocido que para la evaluación de nivel inventivo de una solicitud de patente no se evalúa el hecho de si la persona medianamente versada en la materia podría intentar una o más alternativas y llegar a la materia de la solicitud en estudio por adaptación o modificación de las enseñanzas de los documentos del estado del arte, sino si dicha persona en realidad hubiera tenido una motivación a partir de las enseñanzas de tales documentos para hacer las adaptaciones o modificaciones en los compuestos allí revelados para obtener otros (los de la presente solicitud) **con la expectativa de resolver el problema técnico objetivo o la expectativa de alguna mejora o ventaja técnica.**

Tomando en consideración los argumentos anteriores, salta a la vista que **los compuestos de formula I reclamados por la reivindicación 1 de la presente solicitud son inventivos frente a las enseñanzas de los documentos D1 y**

D2 toda vez que a partir de estos documentos la persona medianamente versada en la materia no encontraría ninguna motivación que lo condujera de manera obvia a realizar la selección particular del compuesto 6 de D1 que es un derivado de nucleósido que tiene un anillo de imidazo [2,1-f][1,2,4] triazina y poner en dicho nucleósido determinados sustituyentes particulares de los derivados de nucleósidos revelados por D2 (de manera que correspondan a los compuestos de la presente invención) pues a partir de los documentos D1 y D2 la persona versada en la materia no podría tener una exceptiva de la utilidad de tales cambios y esto toda vez que partir de D1 y D2 la persona medianamente versada en la materia no podría esperar de manera evidente que los compuestos así obtenidos fueran efectivos para el tratamiento de infecciones virales causadas por *Flaviviridae* como lo son los compuestos objeto de la solicitud denegada, ya que aun cuando D1 revele que el anillo de imidazo [2,1-f][1,2,4] triazina es isomérico e isoelectrónico con el anillo 3H-pirazolo[4,3-d]pirimidina esto de ninguna manera puede ser considerado como un indicio de equivalencia biológica entre tales estructuras químicas ya que, como se expuso anteriormente, si el sólo cambio de posición de un heteroátomo dentro del anillo central de un compuesto o un reemplazo isostérico de un sustituyente o átomo en la estructura de una molécula puede cambiar la actividad biológica y el efecto terapéutico de dicha molécula entonces los efectos de sustituir un átomo de carbono en el anillo de 3H-pirazolo [4,3-d] pirimidina por un átomo de nitrógeno para obtener el anillo imidazo [2,1-f][1,2,4] triazina puede tener las mismas repercusiones de cambio en la actividad biológica y/o en el efecto terapéutico de la molécula en cuestión.

Dentro de este marco de ideas me permito referirme al señalamiento que hace el Tribunal de Justicia de la Comunidad Andina con respecto a las definiciones de "obvio" y "evidente" en la evaluación del Nivel Inventivo de una solicitud de patente⁵:

"Resulta pertinente, a los efectos del artículo 4 de la Decisión 344, definir qué se entiende por "obvio" y por "evidente" a fin de determinar qué se debe entender por nivel inventivo.

Lo obvio es aquello que salta a la vista de manera clara y directa; lo "que se encuentra o pone delante de los ojos, muy claro o que no tiene dificultad". Mientras que lo evidente consiste en la "certeza clara y manifiesta de la que no se puede dudar; cierto, claro, patente y sin la menor duda". De forma que algo que

⁵ Tribunal de Justicia de la Comunidad Andina, PROCESO 192-IP-2005

resulte obvio no es necesariamente evidente; empero lo que es evidente, es también obvio.

En este orden de ideas, se puede concluir que una invención goza de nivel inventivo cuando a los ojos de un experto medio en el asunto de que se trate, se necesita algo más que la simple aplicación de los conocimientos técnicos en la materia para llegar a ella, es decir, que de conformidad con el estado de la técnica el invento no sea consecuencia clara y directa de dicho estado."

Así, dado que a partir de los documentos D1 y D2 no "salta a la vista de manera clara y directa" compuestos con cada una de las características estructurales de los compuestos reclamados por la reivindicación 1 de la presente solicitud; y que de las enseñanzas de dichas referencias no se tiene ninguna "certeza clara y manifiesta" de que tales selecciones de sustituyentes y sus posiciones particulares sobre los anillos de los compuestos de D1 y D2 darían lugar a otro compuestos, los de la presente invención, que serían efectivos para el tratamiento de infecciones virales causadas por *Flaviviridae*, queda de manifiesto que la materia reclamada por la reivindicación 1 de la solicitud denegada conlleva nivel inventivo frente a la combinación de las enseñanzas del estado del arte comprendido en D1 y D2, cumpliendo de esta manera la materia reclamada por la presente solicitud con las disposiciones de patentabilidad establecidas en el Artículo 18 de la Decisión 486 de 2000.

De la misma manera, las reivindicaciones 2 a 13 del capítulo reivindicatorio de la solicitud también gozan de altura inventiva frente a las enseñanzas de los documentos D1 y D2 toda vez que son reivindicaciones dependientes de la reivindicación 1 cuya materia es inventiva frente a tales documentos del estado del arte.

2. Concesión de la Patente en otros países

Finalmente y aparte de lo anteriormente mencionado, me permito señalar que la solicitud de patente en cuestión ya ha sido aceptada por otras Oficinas de patentes como por ejemplo la Oficina de Propiedad Industrial de la Unión Europea y la Oficina de Patentes y Marcas de los Estados Unidos de América, las cuales han concedido respectivamente las patentes **EP 2280973 B1 y US 8,012,941 B2**.

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.

Sin embargo, sí considero de gran importancia resaltar el hecho de que la materia técnica revelada en la solicitud de patente en cuestión ha sido catalogada como novedosa, inventiva e industrialmente aplicable por los Examinadores de otra Oficina de Propiedad Intelectual, 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 486 de 2000.

II. CONCLUSIÓN

En conclusión me permito señalar a ese Despacho que a la luz de los argumentos discutidos con respecto a los documentos citados D1 y D2, se estableció de manera incontrovertible que a partir de sus enseñanzas la persona versada en la materia no podría obtener de manera obvia los compuestos derivados que son objeto de la solicitud denegada, ni a partir de tales documentos del estado del arte sería evidente que los compuestos de la invención serían efectivos para el tratamiento de infecciones virales causadas por *Flaviviridae*.

Por lo tanto es irrefutable el Nivel Inventivo que conlleva el capítulo reivindicatorio actualmente presentado para la solicitud, ajustándose así la presente invención a lo preceptuado por el Artículo 18 de la Decisión 486.

Consecuentemente, la presente solicitud sí goza del requisito de Nivel Inventivo frente al estado del arte más próximo citado en la Resolución Número **36960** ahora impugnada.

III. PETICIÓN

En vista de todo lo anterior, ruego a usted proceder a estudiar nuevamente la solicitud a la luz de las modificaciones y argumentaciones presentadas y proceder a revocar la Resolución Número **36960**, con el fin de que se conceda el privilegio de patente a la presente invención.

IV. PODER

Finalmente me permito recordarle a este Despacho que el documento que acredita mi calidad de representante legal en Bogotá para asuntos relativos a la Propiedad Industrial de las sociedades peticionarias, fue presentado ante dicha entidad junto con mi petitorio de fecha 22 de Octubre de 2010.

V. ANEXOS

Anexo me permito presentar:

- (a) Copia del Reporte de Búsqueda internacional emitido para la correspondiente solicitud internacional;
- (b) Copia de la Opinión Escrita de la Autoridad de Búsqueda Internacional emitido para la correspondiente solicitud internacional;
- (c) Copia del documento de Cheeseright T., "*The Identification of Bioisosteres as Drug Development Candidates*", *Innovations in Pharmaceutical Technology*, 2009, Issue 28, pp. 22-26;
- (d) Copia del documento de Korolkovas, Adrejus "*Essential of Medicinal Chemistry*" 2nd edition, Jhon Wiley & Sons, New York, 1988, página 82;
y
- (e) Copia del document de Chen, Chen, et al *J. Med. Chem.* 1996, 39, 4358-4360.

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

Dirección para Notificaciones: **notificacionespatentes@lloredacamacho.com**

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 777.PF	FOR FURTHER ACTION		See item 4 below
International application No. PCT/US2009/041432	International filing date (day/month/year) 22 April 2009 (22.04.2009)	Priority date (day/month/year) 23 April 2008 (23.04.2008)	
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237			
Applicant GILEAD SCIENCES, INC.			

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 7 sheets, including this cover sheet.

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

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

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

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

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland		Date of issuance of this report 26 October 2010 (26.10.2010)
Facsimile No. +41 22 338 82 70		Authorized officer Agnes Wittmann-Regis
Form PCT/IB/373 (January 2004)		e-mail: pt06.pct@wipo.int

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/US2009/041432

International filing date (day/month/year)
22.04.2009

Priority date (day/month/year)
23.04.2008

International Patent Classification (IPC) or both national classification and IPC
INV. C07D487/04 A61K31/395 A61K31/41 A61K31/4188 C07H19/23 A61K31/7052 A61P31/12

Applicant
GILEAD SCIENCES, INC

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

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

2. **FURTHER ACTION**

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

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

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

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

Name and mailing address of the ISA:



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

Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

Klein, Didier

Telephone No. +49 89 2399-7896



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2009/041432

Box No. I Basis of the opinion

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

Box No. II Priority

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

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2009/041432

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>1-27</u>
	No: Claims	<u>28</u>
Inventive step (IS)	Yes: Claims	<u>---</u>
	No: Claims	<u>1-28</u>
Industrial applicability (IA)	Yes: Claims	<u>1-28</u>
	No: Claims	<u>---</u>

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43bis.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43bis.1 and 70.9)

see form 210

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/US2009/041432

Re Item V

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

Reference is made to the following documents:

- D1: WO 2008/005542 A (GILEAD SCIENCES INC [US]; BOOJAMRA CONSTANTINE G [US]; CHEN JAMES M [U] 10 January 2008 (2008-01-10)
- D2: WO 02/057287 A (MERCK & CO INC [US]; ISIS PHARMACEUTICALS INC [US]; CARROLL STEVEN S [] 25 July 2002 (2002-07-25)
- D3: WO 00/56734 A (AVENTIS CROPSOURCE GMBH [DE]) 28 September 2000 (2000-09-28)
- D4: WO 2008/141079 A (BIOCRYST PHARM INC [US]; BABU YARLAGADDA S [US]; CHAND POORAN [US]) 20 November 2008 (2008-11-20)
- D5: WO 2008/089105 A (BIOCRYST PHARM INC [US]; BABU YARLAGADDA S [US]; CHAND POORAN [US]; KU) 24 July 2008 (2008-07-24)

1. Claims 21-26 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 use in a medical treatment.

2. Novelty (art. 33(2) PCT) :

- a. The subject-matter of claims 1-27 concern antiviral nucleoside derivatives having modified nucleobases.

D1 and D2 do not seem to disclose the specific nucleobases depicted in formula (I) of claim 1, the subject-matter of claims 1-27 is considered new with regard to said documents.

D3 discloses identical nucleobases but fails to disclose the modification on the ribose part of the molecule (which basically requires that at least one of the substituents R1-R5 of Formula (I) is not -H or -O-R. The subject-matter of claims 1-27 is thus also considered new with regard to said document.

- b. Claim 28 is not considered new as hundreds of compounds as "...described herein" (see for ex. on page 91 of the description) are already known.

3. Inventive step (Art. 33(3) PCT) :

D1 which is considered to represent the closest prior art discloses many antiviral compounds bearing different modified nucleobases.

The claimed nucleobase of formula (I) does not seem to be disclosed or even suggested in D1 or D2 (D3 not relating to the same technical field and therefore being irrelevant). Thus, as bioisosterism in this specific field has not been demonstrated, the subject-matter of the present application could be considered inventive.

Nevertheless, it appears that the applicant has not made credible yet (has not demonstrated yet) that the claimed compounds possess the claimed activities. Indeed, at the end of the description, there are several procedures disclosed concerning how to test the antiviral activities of the claimed compounds, but no examples, that seriously demonstrate an activity, are given.

Remark :

- a. Table 30 on p. 140 is not considered relevant by this Authority as, first of all, it is not clear to exactly which compounds, examples No 1,5,6,7,11,17 refer (an example not being necessarily numbered according to the corresponding compound), and secondly, under **specific** conditions, a **specific** result must be obtained, not an broad range like "B represents IC₅₀ from 10 to 200 µM" (which scientifically has not much value)
- b. The same remark also applies for the determination of the HCV EC₅₀'s which according to the description on p. 140 are : " **Preferably** compounds described herein had EC₅₀'s **below** 1000 µM, **more preferably below**.....,...compound... had EC₅₀'s of **less than**..."

Thus, until the applicant has provided **rigorous and exact** data that render the tests relevant, no inventive step will be acknowledged.

Re Item VI

Certain documents cited

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/US2009/041432

Certain published documents

Application No Patent No	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
D4	20.11.2008	08.05.2008	10.05.2007
			25.05.2007
D5	24.07.2008	11.01.2008	12.01.2007

D4/D5 which are an intermediate documents, are not prior art according to the Chap II PCT proceedings. Further, their content will not affect the novelty of the regional European proceeding to come.

Nevertheless, the extensive examination of that document, on the question whether they constitute prior art or not, will depend essentially on the analysis of the claimed priority rights of the present application and will only be performed in the regional European proceedings to come.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/041432

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D487/04 A61K31/395 A61K31/41 A61K31/4188 C07H19/23
A61K31/7052 A61P31/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07H C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2008/005542 A (GILEAD SCIENCES INC [US]; BOOJAMRA CONSTANTINE G [US]; CHEN JAMES M [U] 10 January 2008 (2008-01-10) the whole document	1-28
Y	WO 02/057287 A (MERCK & CO INC [US]; ISIS PHARMACEUTICALS INC [US]; CARROLL STEVEN S [] 25 July 2002 (2002-07-25) the whole document	1-28
A	WO 00/56734 A (AVENTIS CROPSOURCE GMBH [DE]) 28 September 2000 (2000-09-28)	1-28
P,Y	WO 2008/141079 A (BIOCRYST PHARM INC [US]; BABU YARLAGADDA S [US]; CHAND POORAN [US]) 20 November 2008 (2008-11-20) the whole document	1-28
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☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- * & * document member of the same patent family

Date of the actual completion of the international search

30 July 2009

Date of mailing of the international search report

11/08/2009

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Klein, Didier

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2009/041432

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, Y	WO 2008/089105 A (BIOCRYST PHARM INC [US]; BABU YARLAGADDA S [US]; CHAND POORAN [US]; KU) 24 July 2008 (2008-07-24) the whole document -----	1-28

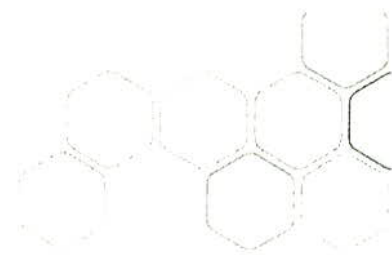
INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2009/041432

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 2008005542	A	10-01-2008	US 2008107628 A1	08-05-2008
WO 02057287	A	25-07-2002	AU 2002243600 B2	28-09-2006
			AU 2002243791 B2	29-06-2006
			BG 108000 A	31-08-2004
			BR 0206614 A	17-02-2004
			CA 2433878 A1	25-07-2002
			CA 2434386 A1	25-08-2002
			CN 1498221 A	19-05-2004
			CZ 20032005 A3	14-04-2004
			DE 60217465 T2	18-10-2007
			DK 1355916 T3	07-05-2007
			EE 200300338 A	15-10-2003
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The Identification of Bioisosteres as Drug Development Candidates

By Tim Cheesenght
at Cresset BioMolecular
Discovery

Molecular fields give a richer, more intuitive view of active molecules. Application of this technology to the search for bioisosteres results in relevant, non-obvious suggestions that make a significant impact on the drug development process.

Bioisosterism has played a central role in the development of drug molecules almost from the outset of the pharmaceutical industry. The promise of bioisosterism is that the properties of a compound can be fine-tuned without affecting its underlying biological activity. This promise is not however without its challenges. Successfully applying bioisosterism to achieve the desired molecular outcome is difficult because of the fundamental problem that chemical structure is an unreliable indicator of biological activity. Small changes in a molecule can have a profound impact on a compound's activity, specificity and toxicity, whilst completely different chemotypes may have near identical biological activity profiles. More rigorous and reproducible methods for suggesting relevant,

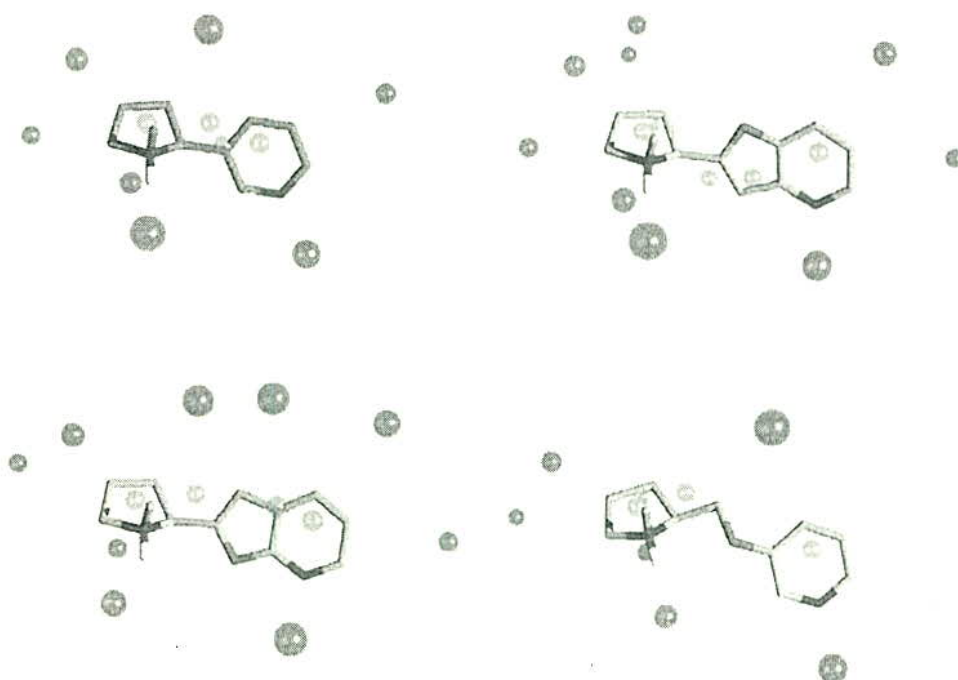
non-obvious and yet synthetically intuitive bioisosteres would have wide applicability.

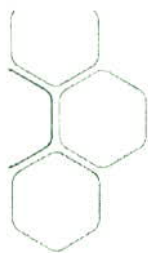
BIOISOSTERES IN DRUG DISCOVERY

Bioisosteres are used by researchers throughout the pharmaceutical industry to find new hits and leads by modifying known actives or substrates, to develop leads by modifying physicochemical properties and protecting their knowledge using patents.

Traditional drug discovery had bioisosterism at the core of its strategy for finding hits and leads. Having identified an interesting target, researchers often had little choice in finding an active inhibitor or antagonist, except through bioisosteric modification of the natural

Figure 1: Nicotine (shown in green) bioisosteres (3) shown using 'field points'. The field point patterns for these single digit nanomolar actives at $\alpha 4 \beta 2$ neuronal nicotinic receptor are clearly highly similar





ligand in a systematic and thoughtful manner. The modern HTS era has provided plenty of potential leads, but the need for bioisosteres remains. Actives found through HTS can have undesirable properties (either physical or biological) and often lack novelty.

Once hits are found, the principle of bioisosterism is central to converting the hit into a more useful lead or drug. Medicinal chemists make biologically relevant changes to the active structure that result in better physicochemical properties or that move the hits into desirable intellectual property (IP) space, facilitating their move from hits to leads. During lead optimisation, the lead molecule may be 'tweaked' to introduce the correct activity/selectivity profile combined with good physicochemical properties. More radically, replacement of core groups in the lead series with new scaffolds that introduce better selectivity or physical properties can rescue what would otherwise be a failed project.

Having successfully negotiated the maze of drug discovery, companies often need to find a backup series that uses all the knowledge gained in a successful project but has unique IP and/or better off-target effects. The challenge is to introduce significant structural diversity whilst at the same time retaining as much of the information gained as possible. Bioisostere substitution is an obvious route to achieving this.

The requirement to protect research positions through patent applications is critical for the development of new medicines. In this respect, IP protection is probably the most important use of bioisosteres in the modern drug discovery project. Chemical structures derived from a common scaffold are often used as surrogates for true bioisosteres to define a range of chemical space that is deemed to have a common biological activity. However, due in large part to the inadequacy of structure to describe biological activity, there are numerous examples where the definitions in a patent are not sufficient to prevent competitors from finding closely related drug development candidates. This has led on many occasions to significant reductions in the value of the original application. Clearly, more automated methods for identifying biologically relevant bioisosteres would be of significant value in the definition of IP space.

EXISTING APPROACHES TO FINDING NOVEL BIOISOSTERES

The application of bioisosterism in the current drug development process is widespread but also somewhat *ad hoc*, relying on the experience of medicinal chemists

to invent new molecules. It is consequently firmly grounded in the chemical structure descriptions of active molecules, resulting in only small evolutionary jumps in the underlying chemistry. This limits the tested chemical space to closely related structures, potentially synthesising and testing inactive structures and, more importantly, missing a range of interesting candidates whose structures are not closely related to the lead.

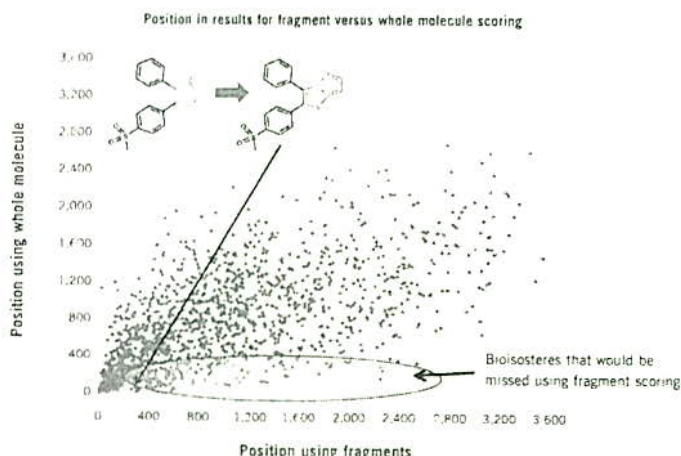
A method for describing molecules in a manner more related to their biological activity would have the potential to explore much broader sets of chemical space, suggest a wider range of modifications and enable research projects to progress faster. There has been increasing interest in methods that can suggest relevant, non-obvious, accurate bioisosteres to project teams. These methods broadly fall into two categories: knowledge-based approaches and computational techniques.

Knowledge-based approaches tend to use data mining techniques to find moieties that have previously been substituted for each other without a significant change in the activity under study. Thus the replacement of arginine by benzamidine in the Thrombin and Factor Xa projects of the 1990s would register benzamidine and arginine as bioisosteric. This approach has broad appeal; it can highlight changes that are known to be successful together with detailed examples. However, many replacements are specific to a particular protein and take no account of which parts of the moiety to be replaced are most important for activity. Equally, if the moiety to be replaced is not present in the literature then no suggestions are possible.

The variety and availability of computer algorithms to suggest bioisosteric replacements has increased significantly in recent years. Most methods attempt to excise a chosen moiety from a molecule and replace it with a fragment from a fragment database. These fragments are typically scored against the moiety to be replaced using shape or electrostatic measures of similarity, or by using the presence or absence of pharmacophore points.

All of these methods seem to suffer the same problem: they rarely suggest truly novel scaffolds to the experienced medicinal chemist. The reason for this is not clear but the one commonality is that these computational methods, like the literature methods, rely on fragment-to-fragment comparison. In this method, the replacement fragment is scored as an isolated molecule in itself, and not in the context of the final molecule. This is a subtle but critical problem, which means that there is no possibility for the properties of the

Figure 2: Comparison of fragment and whole molecule scoring. Each axis shows the position in the respective results file for 3,600 possible bioisosteres for the lactone group in rofecoxib (top left, red). The highlighted region shows bioisosteres that score well using whole molecules but poorly when compared at the fragment level. For example, the known COX2 active series containing the thiazolotriazole replacement for the lactone (top middle, green) appears some 250 places lower in the results using fragment only scoring compared with whole molecule scoring.



fragment to influence the properties of the final molecule. Moreover, as the final molecular context of the fragment is not considered, fragments that might represent only a small change to the final molecule in its entirety may be scored poorly because they represent a large change when scored at the fragment level.

NEW APPROACHES

In this journal in 2007, we outlined the Field Point approach to describing molecules (1). We showed how, by encoding the electrostatic environment surrounding a ligand, it could be viewed in a more insightful and informative way. We showed how distilling the full field down to a series of 'hot spots' around the molecule – termed 'Field Points' – provided both a powerful insight into the behaviour of molecules and a mechanism by which molecules could be compared in a computationally efficient and therefore rapid manner.

Field Point descriptions of molecules have been used widely to provide richer, more informative views of the way in which ligands interact with proteins, to inter-relate compounds from different chemical series that act at the same protein site, to find novel chemical series through virtual screening, and to decode Structure Activity Relationships (SAR) by comparing molecules as proteins 'see' them (2). Field Point technology can also provide a much more accurate basis on which to identify novel, chemically relevant bioisosteres.

Application of Molecular Fields to Bioisostere Finding

The principle behind fragment replacement methods to identify bioisosteres is simple: remove a portion of an active molecule, search a fragment database for a replacement moiety that will physically fit into the vacated space, and score the replacement for similarity to the original. In practice, a number of factors contribute to the effectiveness of the method. Primary amongst these are the accurate scoring of potential replacements, the relevance of the fragment database, and the originality and synthesisability of the suggested bioisosteres.

In scoring replacement fragments, it is essential to remember that the molecular fields around them are a property of the whole molecule and not of the isolated fragment. Replacement fragments cannot be assessed accurately in isolation from the whole molecule as they can have a significant effect on the retained portions of the molecule. Not only will fragments that are strongly electron donating have different effects from ones that are electron withdrawing, but the context of the molecule into which they are placed will determine the extent and character of those effects.

To this end, we chose to join replacement fragments into the retained portions of the target, minimising the energy of the result to ensure sensible geometry, before scoring the whole of the proposed new molecule against the original molecule using Field Points. This approach, using the fields of the whole molecule, is only tractable because of the significant computational advantages provided by Field Point representation.

Because the score is based on the whole molecule, any effects that the new fragment may have on the original molecule are automatically considered. This process gives a results list that is significantly richer in non-obvious bioisosteres than would be the case had we only considered the isolated fragment (see Figure 2). Using the whole molecule has an additional benefit in that the medicinal chemist is presented with a list of potentially active molecules rather than partial fragments. This allows them to select molecules for synthesis more easily without mentally having to construct and retrosynthesise the final molecule.

Choosing Fragments

Commercial screening collections provide molecules with good physicochemical properties, a high degree of synthetic accessibility and reasonable diversity.

Figure 3: The results of a FieldStere experiment to find bioisosteres for the lactone portion of rofecoxib (left, red). They include 'obvious' bioisosteres (Parecoxib and Valdecoxib analogues, dark blue, top), 'less obvious' bioisosteres (Etoricoxib and Celecoxib analogues, middle), and non-obvious bioisosteres such as the 12nM inhibitor triazolotriazole (green, bottom)

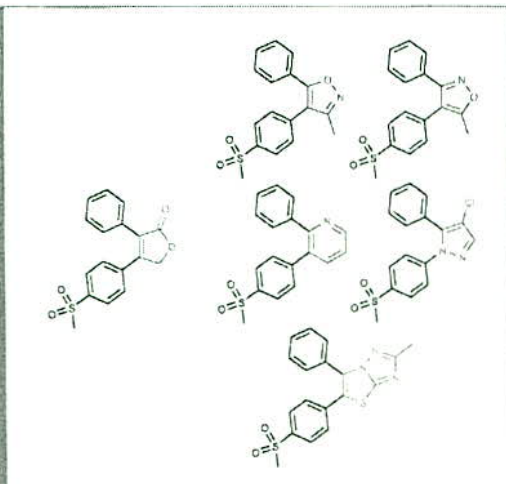
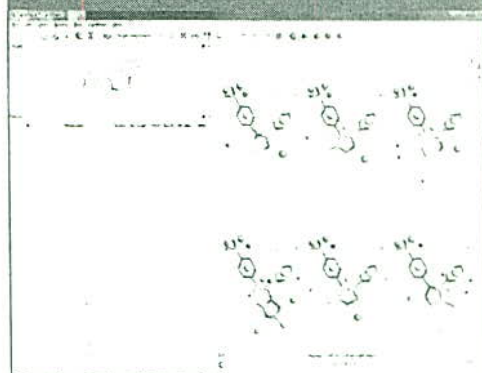


Figure 4: FieldStere screenshot showing the COX-2 results. Each bioisostere is presented as a 3D alignment to the original target and also in a table as a 2D picture together with calculated LogP and TPSA values



Fragmenting 2 million molecules by breaking bonds to heteroatoms and rings resulted in a database of 700,000 fragments. To aid the medicinal chemist further, we subdivided the database according to the frequency with which fragments are observed, arguing that more frequently occurring fragments were more synthetically accessible. Since Field Point patterns around fragments are dependent on the exact conformation of the fragment, each fragment is stored as a set of conformations, and the angles and distances between connection points in a fragment are recorded for each conformation that is stored.

It is important to have control over the nature of the connection points in the replacement fragment to reflect the types of chemistry that can be performed on the target molecules. To this end, each fragment is annotated with the nature of the connection points available. The user can simply specify that the connection point is, for example, an aromatic carbon to significantly restrict the search and chemistry space.

The originality and synthesizability of compounds produced using the Field Point method is best demonstrated through an example. Using rofecoxib as a starting point, we requested bioisosteres for the lactone moiety. We limited the chemistry space that was searched by specifying the replacement contain an aromatic carbon attached to the remaining phenyl group. The results (see Figure 3) contain an impressive range of bioisosteres from the 'obvious' – such as Valdecoxib and Parecoxib – to more interesting actives, such as an analogue of Etoricoxib. However, the results also contain 'non-obvious' bioisosteres such as the 12nM thiazolotriazole compound shown.

CONCLUSION

The use of Field Points represents a major advance in the computational methods available for finding novel bioisosteres. Unlike previous methods, it scores the suggested bioisosteres in the context of the final molecule rather than as an isolated fragment. The results are significantly more diverse than previous methods with both known bioisosteres and novel replacements being suggested in most cases. Application of Field Point based bioisostere technology to drug discovery projects has already been shown to shorten development time and increase novelty.

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Tim Cheeseright is currently Director, Products, at Cresset BioMolecular Discovery Ltd. He trained as a synthetic chemist at the University of Oxford, and then undertook post-doctoral studies at the University of Manchester and the Institute of Cancer Research before joining the Combinatorial Chemistry Group of Peptide Therapeutics Ltd (later Acambis plc). Tim moved into computational chemistry following the acquisition of Peptide's small molecule business by Medivir AB. He joined Cresset as Chief Application Scientist in 2002. Email: tim@cresset-bmd.com

Essentials of medicinal chemistry
 Andrius Korkalkovs, segunda edicija

Ed. John Wiley and Sons

NY 1988

2

DEVELOPMENT OF DRUGS

I. Sources of Drugs

Health, "the state of complete physical, mental and social well-being—and not just the absence of discomfort or disease," is one of the basic human necessities and has been a constant human worry. To preserve health or to restore it, human beings have, since primeval time, made use of a wide variety of resources to avoid and fight disease, principal among these being drugs and related chemicals.

The enormous progress observed in the area of synthetic drugs in the last 40 years tends to obscure the extraordinary role that drugs of natural origin have played, are still playing, and will continue to play in therapeutics. For centuries before people were pondering how to prepare by chemical means compounds useful for the treatment and prophylaxis of a variety of diseases, innumerable biological products were under extensive use. Others were introduced in the nineteenth century and the present one, contemporaneously with the notable development of biological sciences such as medicine and, principally, chemistry, especially in the field of synthesis of organic substances. It may be presumed that with progress in research, dozens and hundreds of active principles extracted from micro-organisms, plants, and animals will enrich the therapeutic arsenal and, in their turn, stimulate chemists to synthesize equal or analogous compounds, especially in consideration of the fact that up to now fewer than 10% of terrestrial plants have been investigated from a phytochemical point of view, and the marine flora and fauna have only recently received the attention they deserve as regards chemical aspects.

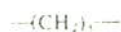
A. Ancient Sources

Analogous to what is occurring at present when an enlightened elite coexists with profoundly ignorant masses, the uncultured classes of some of the ancient peoples had extravagant and absurd opinions regarding the etiology of disease. They believed, for example, that disease was caused by evil spirits or devils, and that the only means of getting rid of a disease was to submit the dwelling of the evil spirit—the patient's body—to all sorts of discomfort and suffering, the thought being that the demon would not put up with the horrible treatment, thus abandoning the body of the diseased, who would then recover. Thus they used to anoint the patient with substances of repugnant odor and appearance, such like urine, feces, and stinking plants, or they resorted to nauseating fumigations.

Despite these and other therapeutic measures rooted in mysticism, in which amulets and enchantments, exorcisms, and ceremonial dances all had a part, the basis for the treatment of diseases consisted of drugs of vegetable and animal origin. In view of their ignorance regarding the cause of the disease and the way by which these natural drugs made the symptoms disappear, and trying to establish a relationship between them, some scholars—among them the famous Paracelsus, who lived from 1493 to 1541 and who became the

Table 2.10 (continued)

Spacer Groups



Annular Structures

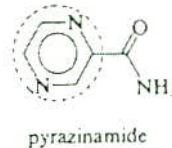
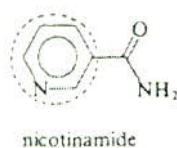
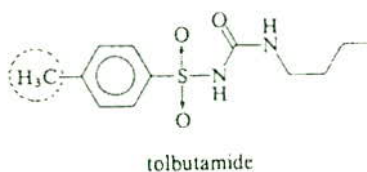
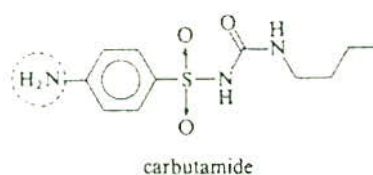
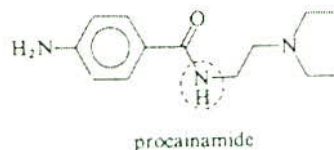
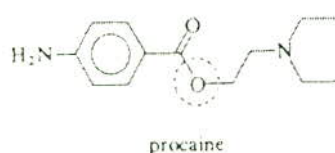


Open Structures



Source: C. W. Thornber, *Q. Rev. Chem. Soc.*, 8, 563 (1979). Reprinted with permission. Copyright (1979) by The Royal Society of Chemistry.

Although it is not possible to achieve pure isosterism, the principles of isosterism and bioisosterism are extensively used to modify the structure of biologically active compounds. Thornber pointed out that "in making a bioisosteric replacement the following parameters of the group being changed could be considered: size, shape (bond angles, hybridization), electronic distribution (polarizability, inductive effects, charge, dipoles), lipid solubility, water solubility, pK_a , chemical reactivity (including likelihood of metabolism), hydrogen bonding capacity." It is "unlikely that any bioisosteric replacement will leave all these parameters undisturbed." This substitution yields not only products whose action is identical to that of compounds taken as models but antagonists as well. Several examples may be cited of natural product equivalents, parametabolites, paravitamins, parahormones, and mimetics, as well as their specific antagonists, antimetabolites, antivitamins, antihormones, and lytics developed by applying the concept of isosterism:



In recent years, the interchange of Si for C in certain drugs is being studied. The results have been interesting in several cases, such as in derivatives of choline, barbiturates, penicillin, chloramphenicol, meprobamate, and insecticides.

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Letter

**Design and Synthesis of a Series of Non-Peptide High-Affinity
Human Corticotropin-Releasing Factor Receptor Antagonists**

Chen, Raymond Dagnino, Errol B. De Souza, Dimitri E. Grigoriadis, Charles Q. Huang, Kyung-II Kim, Zhengyu Liu, Terry Moran, Thomas R. Webb, Jeffrey P. Whitten, Yun Feng Xie, and James R. McCarthy

J. Med. Chem., **1996**, 39 (22), 4358-4360 • DOI: 10.1021/jm960149e • Publication Date (Web): 25 October 1996

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Design and Synthesis of a Series of Non-Peptide High-Affinity Human Corticotropin-Releasing Factor₁ Receptor Antagonists

Chen Chen,* Raymond Dagnino, Jr.,
Errol B. De Souza, Dimitri E. Grigoriadis,
Charles Q. Huang, Kyung-Il Kim, Zhengyu Liu,
Terry Moran, Thomas R. Webb, Jeffrey P. Whitten,
Yun Feng Xie, and James R. McCarthy*

Neurocrine Biosciences, 3050 Science Park Road,
San Diego, California 92121

Received May 20, 1996

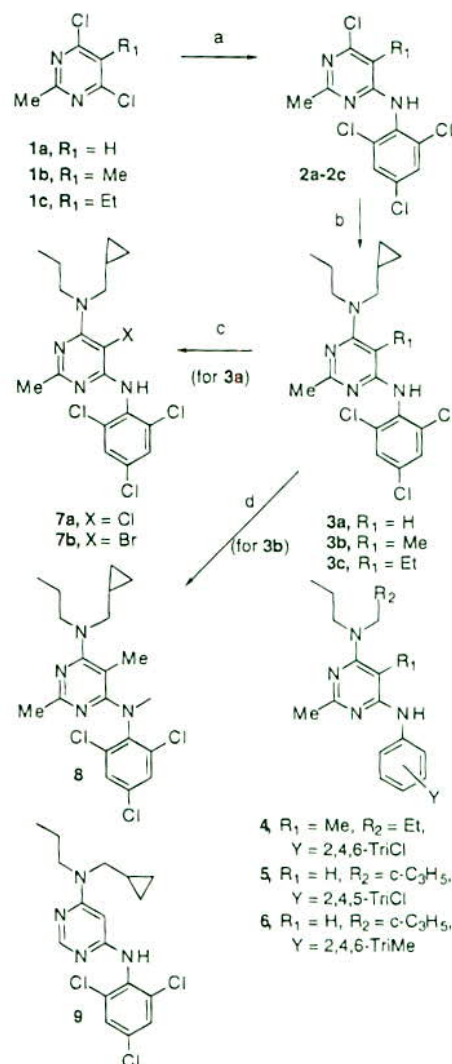
Corticotropin-releasing factor (CRF), a 41 amino acid peptide of hypothalamic origin, plays a major role in coordinating the endocrine, behavioral, and autonomic responses to stressful stimuli.^{1–3} The actions of CRF are mediated through high-affinity receptors which are part of the superfamily of G-protein-coupled seven transmembrane proteins.⁴ Recently two members of the CRF receptor family have been cloned expressed and characterized. These receptors demonstrate a different sequence, pharmacology, and regional distribution within the central nervous system and the periphery. The CRF₁ receptor demonstrates high affinity for CRF and its related mammalian analogs,^{4–7} as well as for non-mammalian related peptides including sauvagine (frog) and urotensin I (sucker fish).⁸ The CRF₂ family of receptors, while sharing sequence homology with the CRF₁ receptor subtype, demonstrates low affinity for CRF itself but retains its high affinity for the nonmammalian forms of the peptide.^{8,9}

While there is very little known about the physiology and function of the CRF₂ subfamily of receptors, a substantial amount of preclinical and clinical data exists that suggests that CRF and its high-affinity receptor play a major role in mediating various neurological and psychological disorders, including major depression, anxiety, and a variety of stress-related disorders (for reviews, see refs 2, 3, and 10). Treatments for these disorders have been hampered by the fact that ligands for these receptors have thus far been large peptides.¹¹ We report the design and synthesis of high affinity and selective non-peptide CRF₁ receptor antagonists, 4-anilino-6-aminopyrimidines (illustrated by **3b**), targeted for the treatment of CRF-mediated disorders.

The reaction sequence for the synthesis of **3a–c**, **4**, **5**, **6**, and **9** is illustrated with **3a–c** in Scheme 1. N-Methylation of the anilino nitrogen on **3b** with excess methyl iodide and 1 equiv of sodium hydride in THF gave **8**. Pyrimidines **11** and **12** (see Chart 1 and Supporting Information for Scheme 2 with synthesis) were prepared by a similar sequence as that used for the synthesis of **3a–c** starting with commercially available 2,6-dichloro-6-methylpyrimidine (**10**) and separating the anilino pyrimidines **11** and **12** by flash chromatography.

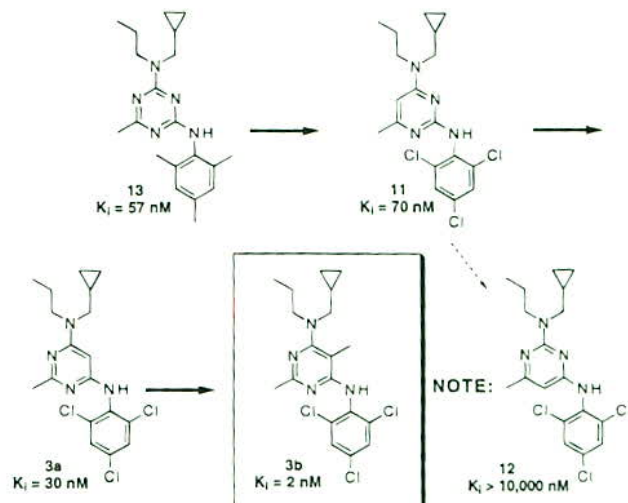
The inhibition of [¹²⁵I]CRF binding to cells expressing the human CRF₁ receptor was used to identify specific receptor antagonists in a radioligand binding assay.¹² The CRF receptors expressed in these cell lines demonstrated reversible, saturable, high-affinity binding to CRF with the pharmacological and functional charac-

Scheme 1^a



^a (a) 2,4,6-Cl₃C₆H₂NH₂, NaH, THF, RT or reflux; (b) *n*-C₃H₇NHCH₂CH₂CH₂CH₃, 100–190 °C; (c) NBS or NCS, CHCl₃, reflux; (d) NaH, MeI, THF, room temperature.

Chart 1. Sequence Followed in the Design of CRF₁ Receptor Antagonists



teristics comparable to those found in a variety of animal or human tissues.¹² CRF receptor binding assays were carried out essentially as previously described.¹³

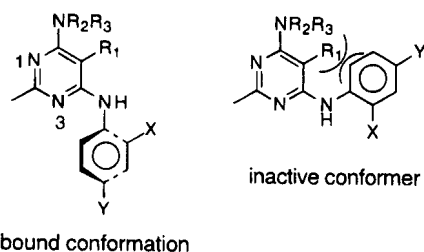


Figure 1. Proposed conformation for anilinopyrimidines to bind to the CRF₁ receptor and comparison with an inactive conformer.

Table 1. Inhibition (K_i) Values for Receptor Antagonists in Cells Stably Transfected with Human CRF₁ Receptors^a

compd	K_i (nM)	compd	K_i (nM)
3a	30	7a	1.7
3b	2.3	7b	2.0
3c	3.8	8	150
4	2.5	9	> 10000
5	253	D-PheCRF(12–41)	20
6	1390		

^a Compounds were tested at 6–12 doses for their ability to inhibit [¹²⁵I]CRF binding as described in text. Data are representative of duplicate determinations with the experiments repeated two or three times.

The design of **3b** starting from triazine **13**¹⁴ and the structure–activity relationship of related pyrimidines **11**, **3a**, and **12** with regard to CRF₁ receptor binding activity is outlined in Chart 1. Removal of the 1- or 5-nitrogen from triazine **13** (K_i = 57 nM), optimized by rapid microscale synthesis (RMS),¹⁴ gave pyrimidine **11** (K_i = 70 nM) or **3a** (K_i = 30 nM), respectively. However, changing the position of the 3-nitrogen (i.e. **12**) resulted in complete loss of activity. This CRF₁ receptor binding data led to a proposed pharmacophore model for binding to the CRF₁ receptor illustrated in Figure 1. In this model the bound conformation of the molecule requires the anilino group to be orthogonal to and below the pyrimidine (or triazine) ring. In addition, the nitrogen at the 3-position of **3a**, **3b**, **11**, and **13**, but absent in **12**, provides a critical hydrogen-bonding site. Consistent with the model, addition of a substituent at the 5-position of the pyrimidine ring resulted in a 30–50-fold increase in activity. Thus, addition of a methyl group (**3b**) or halogen (chloro, **7a**, or bromo, **7b**) provided compounds with K_i values in the 2 nM range (see Table 1). 2,4,6-Trichloroanilinopyrimidines were synthesized (**3a–c**, **4**, **6**, **8**, and **9**) on the basis of the 2,4,6-trisubstituted aryl group required for optimal activity for triazine **13** (Chart 1), the preference for trichloro over other substituents in related series (see Chart 1 and **3a** vs **6**), and the preference for an orthogonal relationship between the phenyl and pyrimidine rings with this substitution pattern. 2,4,5-Trisubstituted aryl compound **5** was over 10-fold less active than the corresponding 2,4,6-trisubstituted aryl compound **3a**. Interestingly, addition of a methyl group on the anilino nitrogen (**8**) resulted in over 100-fold loss in activity. As in the triazine **13**,¹⁴ *N*-propyl-*N*-cyclopropylmethyl was optimal for the N6 amino group, but unlike the triazine series *N,N*-dipropyl was equally active (**4**).

While direct inhibition of binding activity gives a valid measure of the potency of a compound at a specific receptor, functional tests must be employed in order to determine whether the compounds can act as agonists or antagonists at these receptors. Using membrane

preparations of the stable cell lines transfected with the CRF₁ receptor, the CRF₁ antagonist activity of the series was demonstrated by inhibition of CRF-stimulated cAMP production with **3a**, **4**, and **7a** using D-PheCRF-(12–41) as the standard (IC_{50} = 3700, 250, 100, and 200 nM, respectively). Inhibition of CRF-stimulated adenylate cyclase activity was performed as previously described.¹⁵ None of the compounds demonstrated any effects on basal cAMP production (that is in the absence of CRF or other stimulator), indicating that these compounds are devoid of agonist activity at this receptor subtype. In addition, these compounds could inhibit CRF-stimulated ACTH release from primary rat anterior pituitary cell cultures (data not shown), further demonstrating antagonist activity at CRF₁ receptors. In order to test for CRF receptor selectivity, the compounds synthesized in this series (Table 1) were assessed for inhibition of cAMP production in cells transfected with the human CRF_{2a} receptor and were completely devoid of activity (data not shown).

In conclusion, we have demonstrated the design and synthesis of selective, high-affinity non-peptide CRF₁ receptor antagonists **3b**, **3c**, **4**, **7a**, and **7b** with K_i values in the low nanomolar range. In addition, these compounds demonstrate *in vitro* inhibition of CRF-stimulated cAMP production in stable lines transfected with the human CRF₁ subtype. These compounds, and further modifications, will be of particular significance in establishing the utility and potential of CRF₁ receptor antagonists in the treatment of depression and anxiety-related disorders.

Supporting Information Available: A brief description of the biological assays, synthetic procedures for new compounds, and analytical data (8 pages). Ordering information is given on any current masthead page.

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JM960149E