

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO	
RAD: 14-65677- -7	FECHA: 2015-08-11 18:06:21
DEP: 2020 DIRECCION DE NUEVAS CREACIONES	EVE: 378 FASE NACIONAL INCLUIDO CAPITULO I
TRA: 11 PCT-PATENTE DE INVENCION CAPITULOS I Y II	FOLIOS: 14
ACT: 430 REQUERSOLICITA	

DIRECCIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogado(a)/Señor(a)
LUZ CLEMENCIA DE PÁEZ

Asunto: Radicación: 14-65677- -7
Trámite: 11
Evento: 378
Actuación: 430
Oficio: 9574
Folios: 14

Patente de Invención	X			Patente de Modelo de Utilidad	
Vía Nacional					
Vía PCT (Fase Nacional)	X	Capítulo I	X	Capítulo II	
No. Solicitud Internacional	PCT/US2012/052882				
Fecha de Presentación Internacional	29/08/2012				

Como resultado del examen de fondo realizado, con fundamento en el Artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se comunica:

1. Documentos estudiados

Descripción:	Radicado N° 14-065677-00000-0000	27/Marzo/2014
Reivindicaciones:	Radicado N° 14-065677-00000-0000	28/Febrero/2014
	Radicado N° 14-065677-00006-0000	19/Enero/2015
Oposición:	Radicado N° 14-065677-00001-0000	Lafrancol S.A.S 10/Julio/2014
Respuesta de la solicitante:	Radicado N° 14-065677-00006-0000	19/Enero/2015
Prioridad:	US 61/528,609	29/Agosto/2011

2. Análisis de la Prioridad

Se acepta la reivindicación de prioridad porque ésta solicitud fue presentada dentro del plazo establecido (Art. 9 D 486) y su contenido técnico corresponde con el de la prioridad reivindicada.

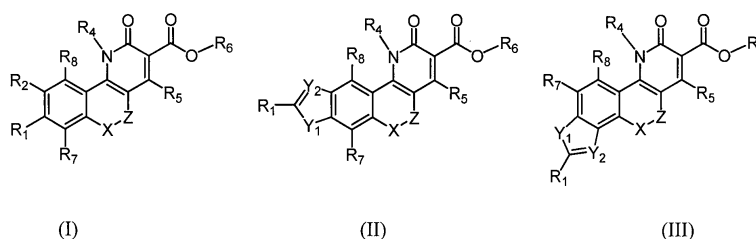
3. Objeto de la invención

De acuerdo con lo establecido en el numeral 1.2.2.2 del capítulo primero del Título 10 de la Circular Única para efectos del examen de patentabilidad, se tendrá en cuenta la tasa pagada por la solicitante al momento de comenzar el examen para las reivindicaciones adicionales; esto es que cuando la solicitud contenga más de diez (10) reivindicaciones y no se haya pagado la tasa complementaria, sólo se estudiarán las cubiertas por la tasa pagada. En el presente caso se estudiarán las reivindicaciones 1 a 11 del capítulo reivindicatorio (Radicado N°. 14-065677-00006-0000).

Título de la solicitud: “COMPUESTOS ANTIBACTERIANOS Y MÉTODOS PARA SU USO”

El problema planteado en esta solicitud consiste en la necesidad de proporcionar nuevos agentes antibióticos y antibacterianos.

Para resolver este problema técnico la solicitud en estudio proporciona compuestos, formas y composiciones farmacéuticas de los mismos y métodos de uso de tales compuestos, formas o composiciones de los mismos para tratar o mejorar una infección bacteriana resistente a múltiples fármacos. La solicitud se refiere a un compuesto de fórmula (I), fórmula (II) o fórmula (III).



El objeto de la presente solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): A61K31/473.

4. De la solicitud de patente

Título

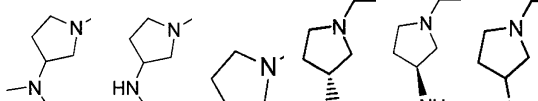
El título no corresponde al objeto de la solicitud, puesto que hace referencia al uso como agentes antibacterianos de compuestos en general, sin mencionar las características estructurales de los compuestos que se reclaman. Se sugiere incluirlas, con el fin de hacer el título un poco más concreto y pertinente.

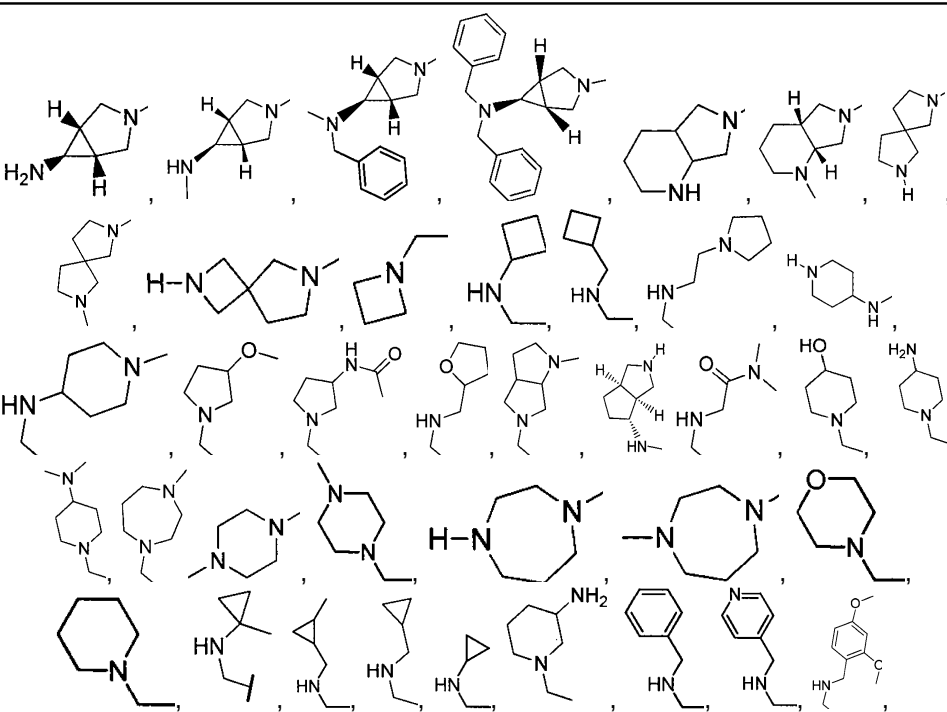
Reivindicaciones (Art 30 D 486, Art 22 PCT)

Errores de traducción

1. La reivindicación 1 no es clara porque:

- Las fórmulas estructurales presentadas en la reivindicación 1 no corresponden con las encontradas en el capítulo descriptivo (Pág. 9), puesto que el sustituyente presente en el anillo de piridona es $-C(=O)-CH_3$ en las fórmulas I, II y III de la reivindicación, y un grupo $-C(=O)-CR^6$ en las fórmulas I, II y III del capítulo descriptivo. Dado que la reivindicación indica la presencia del sustituyente R^6 , esta Oficina considera que esta inconsistencia resulta de un error material, y realizará el estudio teniendo en cuenta las características estructurales de las fórmulas encontradas en el capítulo descriptivo. Se sugiere a la solicitante realizar la corrección correspondiente en las estructuras presentadas.

Sustituciones	Soporte de los ejemplos presentados
X	-CH ₂ -, -CH ₂ CH ₂ -, -CH ₂ CH ₂ CH ₂ -, -CH(OH)CH ₂ -, -CH=CH-, -C(CH ₃)=CH-, -CH(OH)CH(OH)-, -O-, -O-CH ₂ -, -N(CH ₃)-CH ₂ -, -NH-CH ₂ -, -NH-CH ₂ CH ₂ -, -S-CH ₂ -, enlace.
Z	-CH ₂ -, -CH(CH ₃)-,
Y ₁	-N(CH ₃)-
Y ₂	-CH-
R ₁	-H, -Cl, -CH ₂ NH ₂ , -CH ₂ NHCH ₃ , -CH ₂ NHCH ₂ CH ₃ , -CH ₂ N(CH ₂ CH ₃) ₂ , -CH ₂ NH(CH ₂) ₂ CH ₃ , -CH ₂ NHCH ₂ C≡CH, -CH ₂ NHC(CH ₃) ₃ , -CH ₂ NHCH(CH ₃) ₂ , -CH ₂ N(CH ₃) ₂ , -CH ₂ NH(CH ₂) ₂ CH ₃ , -CH ₂ NH(CH ₂) ₃ CH ₃ , -CH ₂ NH(CH ₂) ₄ CH ₃ , -CH ₂ NH(CH ₂) ₅ CH ₃ , -CH ₂ NH(CH ₂) ₆ CH ₃ , -CH ₂ NH(CH ₂) ₇ CH ₃ , -CH ₂ NH(CH ₂) ₈ CH ₃ , - (CH ₂) ₂ NHCH ₂ CH ₃ , -N(CH ₃) ₂ , -NH(CH ₂) ₂ N(CH ₃) ₂ , -CH ₂ NH(CH ₂) ₂ NHCH ₃ , -CH ₂ NH(CH ₂) ₂ NH ₂ , -CH ₂ N(CH ₃)(CH ₂) ₂ N(CH ₃) ₂ , -CH ₂ NHC(CH ₃)CH ₂ CH ₃ , -CH ₂ NHCH ₂ CH ₂ OH, -CH ₂ NH(CH ₂) ₂ OCH ₃ , -CH ₂ N(CH ₃)(CH ₂) ₂ OH, -CH ₂ NHCH(CH ₃)CH ₂ OCH ₃ , -CH ₂ NHCH(CH ₃)CH ₂ OH, -CH ₂ NHCH ₂ CH=CH ₂ , -CH ₂ NHCH ₂ C(CH ₃) ₃ , -CH ₂ NHCH ₂ CH(CH ₃) ₂ , -CH ₂ NHCH(CH ₃)CH ₂ N(CH ₃) ₂ ,  -CH ₂ NHCH(CH ₃)CH ₂ CH ₃ .

Sustituciones	Soporte de los ejemplos presentados
	
R ₂ /R ₇ /R ₈	-H, -F
R ₄	-H, -CH ₃ , -CH ₂ CH ₃ -CH ₂ C ₆ H ₅
R ₅	H, -OH
R ₆	-H

La reivindicación 9 no se encuentra soportada en la descripción, puesto que en ella no se demuestra desarrollo de hidratos, solvatos, clatratos, isotopologos, polimorfos o tautómeros de los compuestos allí reclamados, por lo que se sugiere a la solicitante eliminar dichos términos de la reivindicación.

Se sugiere a la solicitante hacer las aclaraciones necesarias.

Descripción (Art 28 D 486)

La descripción no soporta adecuadamente el alcance dado por el capítulo reivindicatorio, dado que los 186 ejemplos de compuestos mostrados resultan ser insuficientes para la gran cantidad de compuestos reclamados bajo las formulas I, II y III.

Compuestos en los que R⁶ es diferente a hidrógeno, Z es diferente a -CH₂- o -CH(CH₃)-, Y₁ es diferente de -N(CH₃)-, Y₂ es diferente a -CH-, R₅ es diferentes de -OH o H, y donde R₂, R₇, R₈, son diferentes de H, no se encuentran ejemplificados. De esta forma no existe evidencia de su actividad farmacológica, por lo que se desconoce si comparten o no la actividad de los compuestos que sí fueron evaluados. Es imposible atribuir la actividad de los compuestos ensayados a la gran variedad de compuestos que se encuentran al alcance de la reivindicación 1, por lo que se considera que no existe una divulgación suficiente de la materia allí reclamada.

Dado que las características mencionadas anteriormente son comunes en los 186 ejemplos presentados por la solicitante, es evidente que estos sustituyentes son esenciales para la actividad biológica de los compuestos reclamados, por lo que se sugiere a la solicitante que lo plantee de esa forma.

Se sugiere a la solicitante hacer las aclaraciones necesarias.

5. Análisis de las Oposiciones

Argumentaciones de Lafrancol S.A.S

La opositora manifiesta que “(...) *composiciones y combinaciones farmacéuticas que comprenden una cantidad eficaz de un agente antibiótico o antibacteriano tales como Cefixima, Linezolid, entre muchos otros, útiles en el tratamiento o mejora de infecciones bacterianas causadas por patógenos Gram-negativos y Gram-positivos de tipo salvaje, son prácticas y eventos totalmente conocidos en la industria farmacéutica*”, por lo que manifiesta que carecen de los requisitos de novedad y nivel inventivo. Igualmente, indica que la solicitud pretende obtener patente de composiciones farmacéuticas que involucren agentes tales como Cefixime y Linezolid, entre muchos otros, señalando que no puede la solicitante acceder a beneficios patentarios sobre composiciones y combinaciones farmacéuticas que comprenden moléculas que se encuentran descubiertas y plenamente identificadas en el sector químico-farmacéutico, manifestando que en documentos como “The Index Merck” se evidencia que el principio activo Cefixime se encuentra bajo el conocimiento público desde un tiempo considerable, y que el mismo ostenta beneficios patentarios bajo los documentos EP 30630 y US 4409214 (Años 1981 y 1983) respectivamente y que por su parte la molécula Linezolid ostenta beneficios patentarios bajo los documentos WO 9507271 y US 5688792 (Años 1995 y 1997) respectivamente.

Asimismo la opositora señala que la solicitud pretende proteger objetos que no son considerados invenciones, tales como métodos de tratamiento y las combinaciones de productos conocidos.

Por último la opositora manifiesta que la solicitud carece de los requisitos de Novedad y Nivel inventivo, fundamentales para otorgársele el privilegio de patente de invención, si se tiene cuenta la materia revelada en documentos como:

- US 2008/0312292 A1 (Yasui et al).
- US 2010/0069380 A1 (Choi et al).
- US 2010/0261706 A1 (Jagtap et al).
- US 4,474,786 A (Smith et al).
- US 2007/0249583 A1 (Stein et al).

Respuestas de la Solicitante

Con respecto a la oposición presentada por la sociedad Lafrancol S.A.S la solicitante responde presentando un nuevo capítulo reivindicatorio conformado por 11 reivindicaciones e indica que en dicho capítulo se eliminaron las reivindicaciones referidas a métodos de tratamiento y aquellas que mencionaban la combinación de Cefixime y Linezolid con otras sustancias.

Por otra parte, la solicitante llama la atención sobre la poca argumentación del opositor y la ausencia de un estudio al objeto de la solicitud en el escrito de oposición, resaltando que la opositora se limita a reproducir una copia de los documentos citados en el informe de búsqueda internacional sin tener siquiera en cuenta la clasificación dada a los mismos, concluyendo que la oposición carece de argumentos sobre la falta de novedad o nivel inventivo de la solicitud.

Frente a la afirmación de la opositora sobre el incumplimiento de los requisitos de novedad, nivel inventivo y aplicación industrial, la solicitante se refiere al hallazgo por

parte de la autoridad internacional, la cual encontró que las reivindicaciones 2, 4 y 7-10 cumplen con dichos requisitos.

Finalmente, con respecto a los argumentos referidos a que la solicitud reclama métodos de tratamiento y a combinaciones que comprenden Cefixime y Linezolid, la solicitante reitera que dichas reivindicaciones han sido eliminadas del nuevo capítulo reivindicatorio.

Respuesta del Examinador Técnico

En primer lugar, sobre el nuevo capítulo reivindicatorio presentado junto con los argumentos de respuesta a la oposición, esta Oficina acepta las modificaciones realizadas puesto que no se considera una ampliación de la materia inicialmente divulgada.

En segundo lugar, con respecto al argumento de la opositora según el cual la actual solicitud reclama métodos de tratamiento y combinaciones, esta Oficina encuentra que dicha afirmación no es pertinente, puesto que tal como lo señala la solicitante en su respuesta, el capítulo reivindicatorio en estudio, radicado bajo el No. 14-065677-00006-00000, no contiene materia que pueda ser considerada como no patentable.

Por otra parte, frente al documento “*The Merck Index*” citado en el escrito de oposición de la Lafrancol S.A.S esta Oficina aclara que no hace referencia a compuestos con las características estructurales de las formulas (I), (II) y (II) reclamados en la actual solicitud, es decir no divulga las características técnicas esenciales de la materia reclamada, por lo que no se considera relevante para el análisis de patentabilidad de la solicitud.

Con respecto a los documentos citados en el escrito de oposición esta oficina considera que:

- El documento US 2008/0312292 A1 (Yasui et al), proporciona compuestos con acción antipruritica, los cuales son agonistas de los receptores de cannabinoides. Dentro de los compuestos revelados en este documento, se encuentran compuestos tricíclicos que comparten características estructurales con los compuestos reclamados, particularmente los compuestos 4-507 y 4-508 (Pág. 113) presentan características estructurales de acuerdo a lo reclamado por la solicitud, por lo que esta Oficina considera que este documento afecta el requisito de novedad de la solicitud en estudio.
- Por su parte el documento US 2010/0069380 A1 (Choi et al), se refiere a compuestos que modulan la actividad de la peptidil tRNA hidrolasa bacteriana, así como composiciones que los comprenden y métodos para prevenir o inhibir la proliferación bacteriana o alguno de sus síntomas. Esta Oficina encuentra que los compuestos divulgados en este documento comparten características esenciales con los ahora reclamados, por lo que se considera pertinente para evaluar los requisitos de patentabilidad de la presente solicitud.
- A su vez, el documento US 2010/0261706 A1 (Jagtap et al), proporciona compuestos tetraciclicos análogos o derivados de 1H-indeno[1,2-b]piridine-2(5H)-ona, útiles para el tratamiento de una variedad de enfermedades y trastornos. Estos compuestos difieren de los reclamados en el anillo A que se encuentra fusionado a la piridona, el cual no se encuentra en los compuestos reclamados; puesto que este documento menciona que dichos compuestos son útiles para el tratamiento de una serie de trastornos, mas no se refiere particularmente a la acción de los mismos como agentes antibacteriales, esta Oficina considera que no afecta los requisitos de patentabilidad de la solicitud en estudio.
- De la misma forma, en cuanto al documento US 4,474,786 A (Smith et al), que

se refiere a compuestos derivados de lactamas tricíclicas útiles para incrementar la contractilidad cardiaca, esta Oficina considera que, dado que la disposición espacial de los anillos fusionados en los compuestos allí divulgados es distinta a los reclamados por la solicitud y puesto que pertenecen a otro campo técnico, este documento no se considera relevante para el análisis de patentabilidad de la solicitud en cuestión.

- Por último, el documento US 2007/0249583 A1 (Stein et al) proporciona compuestos inhibidores de la HMG CoA reductasa, y por lo tanto útiles como inhibidores de la síntesis de colesterol, sin embargo los compuestos allí divulgados difieren de los reclamados por la ausencia de un grupo ceto en el anillo de piridina, es decir en que no se presenta el anillo de piridona de los compuestos reclamados, y dado que pertenecen a otro campo técnico, este documento no se considera relevante para el análisis de patentabilidad de la solicitud en cuestión.

En conclusión, a pesar de que la opositora no realiza un análisis a profundidad de los documentos citados, la materia divulgada en los documentos US 2008/0312292 y US 2010/0069380, afecta los requisitos de patentabilidad de la presente solicitud, por lo que la oposición se considera fundada.

6. Unidad de invención (Art 25 D 486)

La solicitud no cumple con el requisito de unidad de invención porque no se encuentra un concepto estructural común nuevo e inventivo, a todos los compuestos reclamados bajo las formulas I, II y III, puesto que el concepto común a todos ellos, compuestos policíclicos derivados de piridona, se encuentra divulgado en el documento D1.

De acuerdo a la reivindicación 1, es posible definir tres grupos inventivos:

1. Compuestos de formula I.
2. Compuestos de formula II.
3. Compuestos de formula III

Se sugiere presentar las solicitudes divisionales que considere necesarias, o limitar la solicitud inicial a un solo grupo inventivo.

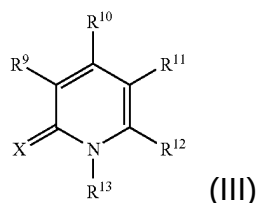
7. Determinación del Estado de la Técnica

El estado de la técnica se determinó con base en la fecha de presentación de la solicitud de prioridad: 29 de agosto de 2011 y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Íte m	Documento	Título	Fecha de Publicación
D1	US 20080312292	Antipruritics	18/Diciembre/2008
D2	Ivanov I. C., et al. Liebigs Annalen der Chemie. Volume 1992, Issue 3, pages 203–207	A Facile Synthesis of [1]Benzopyrano[4,3-b]pyridin-5-ones	12/Marzo/1992
D3	US 20100069380	Heterocyclic inhibitors of bacterial peptidyl tRNA hydrolase and uses thereof	18/Marzo/2010
D4	Ramesh, D et al. Indian Journal of Chemistry-	Synthesis of novel naphtho[2,1-b]furo[3,2-b]pyridine derivatives as	Mayo de 2008

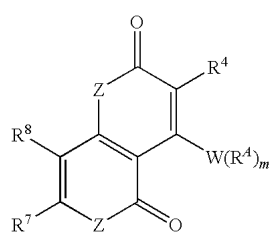
	Section B Vol.47B(05)	potential antimicrobial agents	
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El documento D1¹ divulga compuestos con acción antiprurítica, los cuales son agonistas de los receptores de cannabinoides (Pág. 1, Párr. [0001]), representados por la fórmula (III) (Pág. 2, Párr. [0019]).

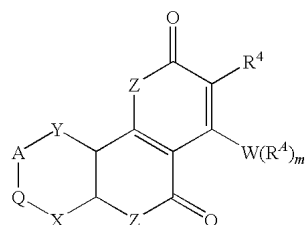


El documento D2² divulga la síntesis y caracterización de compuestos derivados de benzopirano[4,3-b]piridina (Resumen).

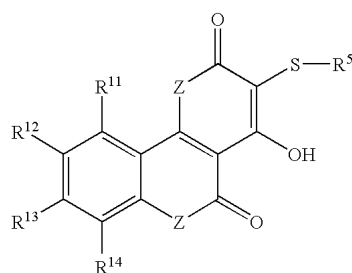
El documento D3³ divulga a compuestos que modulan la actividad de la peptidil tRNA hidrolasa bacteriana, así como composiciones que los comprenden y métodos para prevenir o inhibir la proliferación bacteriana o alguno de sus síntomas (Resumen). Particularmente el documento D3 divulga compuestos de fórmulas IA, IB e IC (Pág. 2, Párr. [0006]).



IA



IB



IC

El documento D4⁴ divulga la síntesis y caracterización de compuestos derivados de nafto[2,1-b]furo[3,2-b]piridina útiles como agentes antimicrobianos (Resumen).

8. Examen de Patentabilidad (Art 14 D486)

El examen de patentabilidad se realizará al primer grupo inventivo.

1[https://www.google.com.co/patents/US20080312292?](https://www.google.com.co/patents/US20080312292?dq=US2008312292&hl=en&sa=X&ved=0CBsQ6AEwAGoVChMIuYKi9dmAxwIVCSseCh3yIQu3)

[dq=US2008312292&hl=en&sa=X&ved=0CBsQ6AEwAGoVChMIuYKi9dmAxwIVCSseCh3yIQu3](https://www.google.com.co/patents/US20080312292?dq=US2008312292&hl=en&sa=X&ved=0CBsQ6AEwAGoVChMIuYKi9dmAxwIVCSseCh3yIQu3)

2<http://onlinelibrary.wiley.com/doi/10.1002/jlac.199219920138/abstract>

3[https://www.google.com.co/patents/US20100069380?](https://www.google.com.co/patents/US20100069380?dq=US+20100069380&hl=en&sa=X&ved=0CBsQ6AEwAGoVChMI6aDX_oeExwIVwiweCh1yTwdh)

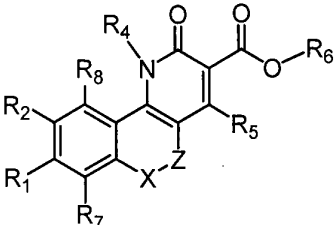
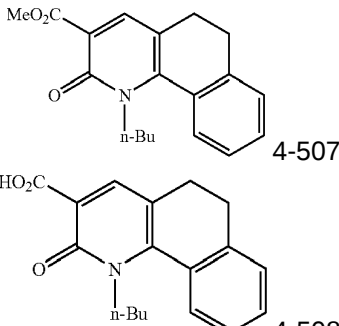
[dq=US+20100069380&hl=en&sa=X&ved=0CBsQ6AEwAGoVChMI6aDX_oeExwIVwiweCh1yTwdh](https://www.google.com.co/patents/US20100069380?dq=US+20100069380&hl=en&sa=X&ved=0CBsQ6AEwAGoVChMI6aDX_oeExwIVwiweCh1yTwdh)

4<http://nopr.niscair.res.in/handle/123456789/1730>

Novedad (Art 16 D486)

La reivindicación 1 consiste en: “Un compuesto de Fórmula (I) (...)” (Radicado N°. 14-065677-00006-00000).

Comparación de las características técnicas esenciales, con las del estado de la técnica:

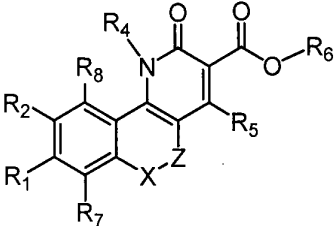
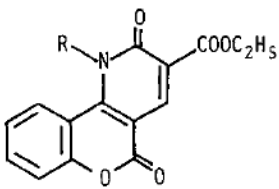
Características esenciales	D1
Compuestos de fórmula I  o una forma del mismo, en el cual	 4-507 4-508 (Pág. 113, tabla 102, compuestos 4-507, 4-508)
X es -CH(R ₉)	-CH ₂ -
Z -CH(R ₃)	-CH ₂ -
R ₁ , R ₂ , R ₃ , R ₅ , R ₇ , R ₈ y R ₉ , son hidrógeno	-H
R ₄ es alquilo C ₁ -C ₈	n-butilo -(CH ₂) ₃ CH ₃)
R ₆ es hidrógeno o alquilo C ₁ -C ₈	-H (Compuesto 4-508)
	-CH ₃ (Compuesto 4-507)

Compuestos con las características esenciales de la fórmula I de la reivindicación 1 habían sido divulgados previamente en el documento D1, el cual da a conocer compuestos agonistas de receptores cannabinoides entre los que se encuentran los compuestos 4-507 y 4-508 (Pág. 113, tabla 102).

En consecuencia, la reivindicación 1 no es nueva o carece de novedad, según lo divulgado en el documento D1.

Las reivindicaciones dependientes 3 y 6 no mencionan alguna característica que haga nuevos a los compuestos de la reivindicación 1, por lo cual se considera que la materia allí reclamada no es nueva.

Novedad con respecto a D2

Características esenciales	D2
Compuestos de fórmula I  o una forma del mismo, en el cual	 5a-c (Pág. 203, esquema 1, compuestos 5 a-c)
X es -O-	-O-
Z es -C(O)-	-C(O)-
R ₁ , R ₂ , R ₅ , R ₇ , y R ₈ son hidrógeno	-H

Características esenciales	D2
R ₄ es H o alquilo C ₁ -C ₈	H en 5a
	-CH ₃ en 5b
	-CH ₂ CH ₃ en 5c
R ₆ es hidrógeno o alquilo C ₁ -C ₈	-CH ₂ CH ₃

Compuestos con las características esenciales de la fórmula I de la reivindicación 1 habían sido divulgados previamente en el documento D2, el cual da a conocer métodos para la síntesis de compuestos derivados de benzopirano[4,3-b]piridina, entre los compuestos intermediarios identificados para la producción de dichos compuestos se encuentran los compuestos 5a-c, que presentan las características técnicas estructurales reclamadas en la reivindicación 1 (Pág. 203, esquema 1).

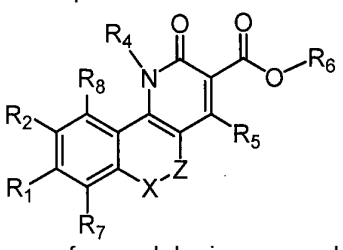
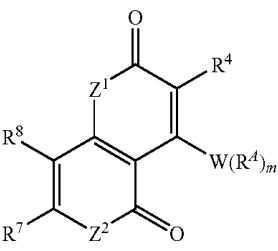
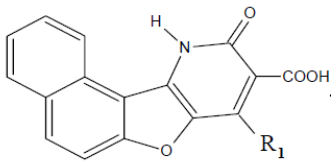
En consecuencia, la reivindicación 1 no es nueva o carece de novedad, según lo divulgado en el documento D2.

Las reivindicaciones dependientes 3 y 6 no mencionan alguna característica que haga nuevos a los compuestos de la reivindicación 1, por lo cual se considera que la materia allí reclamada no es nueva.

Nivel inventivo (Art 18 D486)

La reivindicación 2 consiste en: “El compuesto de la reivindicación 1, en el que R₁ es cicloalquiloC₃₋₁₄ (...)” (Radicado N°. 14-065677-00006-00000).

Comparación de las características técnicas esenciales, con las del estado de la técnica:

Características esenciales	D3	D4
Compuestos de fórmula I  o una forma del mismo, en el cual	 Z¹ es O o NR⁶ donde R7 y R8 junto a los carbonos a los que estan unidos forman un anillo de 5, 6 o 7 miembros y 1-3 dobles enlaces (Pág. 50, Reivindicación 1)	 8a-c (Pág. 755, esquema 1, compuestos 5a-c, 6a-c, y 8a-c)
X es un enlace, N(R₁₄), S, O, -CH(R₉)-, -CH(R₉)-CH(R₁₀)-, -CH(R₉)-CH(R₁₀)-CH(R₁₁)-, -C(R₉)=C(R₁₀)-, -C(R₉)=C(R₁₀)-CH(R₁₁)-, -CH(R₉)-C(R₁₀)=C(RU)-, -O-CH(R₁₀)-, -CH(R₉)-O-, -N(R₁₄)-CH(R₁₀)-, -CH(R₉)-N(R₁₄)-, -S-CH(R₁₀)-, -CH(R₉)-S-, -O-CH(R₁₀)-CH(Rn)-, -CH(R₉)-O-CH(R₁₁)-, -CH(R₉)-CH(R₁₀)-O-, -N(R₁₄)-CH(R₁₀)-CH(R₁₁)-, -CH(R₉)-N(R₁₄)-CH(R₁₁)-, -CH(R₉)-CH(R₁₀)-N(R₁₄)-, -S-CH(R₁₀)-CH(R₁₁)-, -CH(R₉)-S-CH(R₁₁)-, -CH(R₉)-CH(R₁₀)-S-, -O-C(O)-CH(R₁₁)-, -C(O)-O-CH(R₁₁)-, -CH(R₉)-O-	Z² es O o NR⁶	-O-

Características esenciales	D3	D4
C(O)-, -CH(R ₉)-C(O)-O-, -N(R ₁₄)-C(O)-CH(R ₁₁)-, -C(O)-N(R ₁₄)-CH(R ₁₁)-, -CH(R ₉)-N(R ₁₄)-C(O)-, -CH(R ₉)-C(O)-N(R ₁₄)-, -S-C(O)-CH(Ru)-, -C(O)-S-CH(R ₁₁)-, -CH(R ₉)-S-C(O)- o -CH(R ₉)-C(O)-S-;		
Z es N(R ₁₄), S, O, C(O) -CH(R ₃)-	C(O)	No se menciona
R ₁ es C ₃₋₁₄ cicloalquilo seleccionado de entre ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo o cicloheptilo; fenilo; heteroarilo seleccionado de pirrolilo, tiazolilo, triazolilo-1H 1,2,3-, 1H-tetrazolilo, 2H-tetrazolilo, imidazolilo o piridinilo; heterociclilo seleccionado en cada caso, cuando está presente, entre azetidino, pirrolidinilo, tetrahidrofuranilo, piperidinilo, piperazinilo, morfolinilo, 1, 4-diazepanilo, 1,3-dioxolanilo, 2,5-dihidro-1H-pirrolilo, dihidro-1H-imidazolilo, 1,4,5,6- tetrahidropirimidin, 1,2, 3,6-tetrahidropiridinilo; tetrahidro-2H-piranilo, indolinilo, 2,3-dihidrobencodioxazolilo, benzo-2H-3,4-dihidro[b][1,4] oxazinilo, 3,4-dihidroisoquinolin- (1 H)-il, 1,2,3,4-tetrahidroisoquinolinilo, 1,2,3,4-tetrahidroquinoxalinilo, hexahidropirrol[3,4-b][1,4] oxazin-(2H)-il, (4aR,7aS)-hexahidropirrol[3 , 4-b][1, 4] oxazin-(4aH)ilo, 3,4-dihidro-2H-pirido[3,2-b][1,4]oxazinilo, (cis)-octahidrociclopenta[c]pirrolilo, hexahidropirrol[3,4-b] pirrol (1H) il, (3aR, 6aR) hexahidropirrol [3,4-b] pirrol (1H) il, (3aR, 6aS) -hexahidropirrol[3,4 -c]pirrol (1H)-il, 5H-pirrol[3,4-b]piridin (1H)-il, 5,7-dihidro-6H-pirrol[3, 4-b]piridinilo, tetrahidro- 1H-pirrol[3, 4-b]piridin(2H,7H,7aH) -il, hexahidro-1H-pirrol[3,4-b]piridin(2H)-il, (4aR,7aR) hexahidro1H-pirrol[3, 4-b] piridin(2H)-il, octahidro-6H-pirrol[3, 4-b]piridinilo, 2,3, 4,9-tetrahidro-1H-carbazolilo, 1,2,3,4-tetrahidropirazino[1,2-a] indol-8-ilo, 2,3-dihidro-1H-pirrol [1,2-a]indolilo, (3aR,6aR)-hexahidrociclopenta[c]pirrol(1H)il, (3aR,4R,6aS)-hexahidrociclopenta[c]pirrol(1H)il, (3aR, 4S, 6aS)-hexahidrociclopenta[c]pirrol(1H) il, (3aR,5r,6aS)-hexahidrociclopenta[c]pirrol(1H)-il,1,3-dihidro-2H-isoindolilo, octahidro-2H-isoindolilo, (3aS)-1,	Uno a cuatro sustituyentes seleccionados de halo, hidroxilo, C ₁₋₈ alquilo, C ₁₋₈ alcoxi, piperonil, C ₁₋₈ alquilsulfoxido, trihalometil	-H

Características esenciales	D3	D4
3,3a, 4,5,6-hexahidro-2H-isoindolil, (3aR,4R,7aS) -1H-isoindol- (3H, 3aH, 4H, 5H, 6H, 7H, 7aH) -il, (3aR, 7aS) octahidro-2H-isoindolilo, (3aR, 4R, 7aS) octahidro-2H-isoindolilo, (3aR, 4S, 7aS) octahidro-2H-isoindolilo, 2,5-diazabicyclo [2.2. 1] heptanilo, 2-azabicyclo [2.2.1] hept-5-enil, 3-azabicyclo [3.1.0] hexanilo, (LR, 5S, 6S) -3- azabicyclo [3.1.0] hexanilo, (cis, cis) -3-azabicyclo [3.1.0] hexanilo, 3,6- diazabicyclo [3.1.0] hexanilo, (LS, 5R, 6R) -3-azabicyclo [3.2.0] heptanilo, (LS, 5R, 6S) - 3- azabicyclo [3.2.0] heptanilo, 5-azaespiro [2.4] heptanilo, 2,6-diazaespiro [3.3] heptanilo, 2,5- diazaespiro [3.4] octanilo, 2,6-diazaespiro [3.4] octanilo, 2, 7-diazaespiro [3.5] nonanilo, 2,7- diazaespiro [4.4] nonanilo, 2-azaespiro [4,5] decanilo o 2,8-diazaespiro [4.5] decanilo.		
R ₂ es hidrógeno, halógeno, hidroxilo, C ₁₋₆ alquilo, amino, C ₁₋₆ alquilo-amino o (C ₁₋₆ alquilo) ₂ -amino		Se fusionan con un cuarto anillo de benceno
R ₇ y R ₈ son hidrógeno, halógeno, hidroxilo, C ₁₋₈ alquilo, amino, C ₁₋₈ alquil-amino, (C ₁₋₈ alquilo) ₂ -amino		
R ₄ es hidrógeno, hidroxilo, C ₁₋₈ alquilo, arilo C ₁₋₈ alquilo, donde el arilo es opcionalmente sustituido con un sustituyente adicional seleccionado entre C ₁₋₈ alquilo, halo- C ₁₋₈ alquilo, C ₁₋₈ alcoxi o alcoxi- C ₁₋₈ alquilo;	R ⁶ es H, C ₁₋₈ alquilo, C ₂₋₈ alquenilo, cicloalquilo, arilo, heteroarilo, aril- C ₁₋₈ alquilo, heteroaril- C ₁₋₈ alquilo sustituidos o no sustituido,	-H
R ₅ es hidrógeno, halógeno, hidroxilo, C ₁₋₈ alquilo, carboxilo, amino, C ₁₋₈ alquil-amino, (C ₁₋₈ alquilo) ₂ -amino o C ₁₋₈ alquil-SO ₂ -amino.	W(R ^A) _m donde W es O, S, N, o un enlace directo y R ^A es H, C ₁₋₈ alquilo, arilo, C(O) C ₁₋₈ alquilo, C(O) amino, o C(O)-arilo.	-CH ₃ en a
		-C ₆ H ₅ en b
		-OH en c
R ₆ es hidrógeno o C ₁₋₈ alquilo	R ⁴ es H, halo, NO ₂ , CN, C ₁₋₈ alquilo, arilo, heteroarilo, heterocicloalquilo, arilo- C ₁₋₈ alquilo, OR ₅ , S-C(O)-R ₅ , o S(O) _n -R ₅	

El documento D3 se considera el estado de la técnica cercano a la solicitud definida en la reivindicación 2 porque da a conocer compuestos que modulan la actividad de la peptidil tRNA hidrolasa bacteriana, así como composiciones que los comprenden y métodos para prevenir o inhibir la proliferación bacteriana o alguno de sus síntomas (Resumen).

La diferencia entre la solicitud, definida en la reivindicación 2 y los compuestos divulgados en D3 se encuentra en el sustituyente del carbono adyacente al grupo C(O) del anillo de piridona, que en la solicitud corresponde al grupo -C(O)R⁶, es decir, es un grupo éster, mientras que en los compuestos divulgados en el documento D3 corresponde, entre otros a un grupo tiol o sufoxido.

No hay evidencia de que exista un efecto técnico asociado a la inclusión de un grupo éster en el carbono adyacente al grupo ceto de la piridona en los compuestos de la solicitud. Los compuestos reclamados presentan valores de MIC en un rango de ≤ 1.0 ug/mL y ≤ 150 ug/mL (Pág. 311, Ej. 1), por su parte los compuestos descritos en el documento D3 presentan valores para esta constante en un rango de ≤ 0.1 ug/mL y ≤ 50 ug/mL (Págs. 35, Párr. [0386]-[0391]).

Por lo tanto, el problema técnico objetivo que pretende resolver esta invención se puede considerar como la necesidad de proporcionar compuestos alternativos a los divulgados en D3 que posean actividad antibacteriana.

Sin embargo, compuestos derivados de piridona que comprenden un grupo éster en esta posición se encuentran divulgados en el documento D4 que se refiere a la producción y caracterización de compuestos derivados de nafto[2,1-b]furo[3,2-b]piridina útiles como agentes antimicrobianos (Resumen).

En consecuencia, la persona del oficio normalmente versada en la materia, incluiría grupos éster de acuerdo a lo divulgado en D4 en la estructura de los compuestos del documento D3 para llegar así al objeto de la reivindicación 2 de la solicitud. Por lo cual se considera obvia.

Puesto que las reivindicaciones dependientes 4, 5, y 7-11 no mencionan características inventivas adicionales tampoco se pueden considerar inventivas.

Conclusión:

Las reivindicaciones 2, 4, 5, y 7-11 cumplen el requisito de novedad (Art. 16), pero no cumplen con el requisito de nivel inventivo (Art. 18).

9. Conclusión

Los requisitos de Patentabilidad de la presente solicitud están afectados así:

Ítem	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	US 20080312292	1, 3, 6	Novedad
D2	Ivanov I. C., et al. Liebigs Annalen der Chemie. Volume 1992, Issue 3, pages 203–207	1, 3, 6	Novedad
D3	US 20100069380	2, 4, 5, y 7-11	Nivel Inventivo
D4	Ramesh, D et al. Indian Journal of Chemistry- Section B Vol.47B(05)	2, 4, 5, y 7-11	Nivel Inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta (60) días contados a partir del día siguiente de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Se invita al solicitante se sirva indicar, si así lo considera, su renuncia al término faltante de sesenta (60) días para dar respuesta a este requerimiento y presentarla por escrito.

Finalmente, se le recuerda al solicitante que si como respuesta a este requerimiento llegara a modificar el capítulo reivindicatorio y éste contenga más de diez (10) reivindicaciones, no pagará la tasa de modificación voluntaria pero sí la correspondiente al pago por reivindicación adicional.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No. 10 de 2001.



JOSÉ LUIS SALAZAR LÓPEZ
Director de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista, de fecha 2015-08-18

Elaboró: Ruth Andrea Rodriguez
Revisó: Jeny Paola Villate Becerra

INFORME DE BÚSQUEDA DE PATENTES PARA EL RADICADO 14-064677-00006-0000						
CRITERIOS PARA LA BÚSQUEDA						
Palabras clave utilizadas		antibacterial				
CLASIFICACIONES INTERNACIONALES UTILIZADAS PARA LA BÚSQUEDA		A61K31/473 C07D495/04				
BASES DE DATOS CONSULTADAS.						
Google patents		Espacenet		Science direct		Patbase
INFORMES DE EXÁMENES REALIZADOS EN OTRAS OFICINAS						
Oficina	Fecha del examen o de reporte de búsqueda de documentos	Anterioridades encontradas para el examen o reportados en el examen de búsqueda (relacionarlos todos)	Reiv. afectadas	RELEVANCIA (requisito que afecta)	FUERON TENIDOS EN CUENTA PARA EL EXAMEN EN LA OFICINA COLOMBIANA	
					SI	NO
EUROPE	07/03/13	US2008312292	1, 3, 6	Novedad	X	
		US2010069380				X
		US2010261706	2, 4, 5, y 7-11	Nivel Inventivo	X	
		US4474786				X
		US2007249583				X
DOCUMENTOS ADICIONALES ENCONTRADOS POR EL EXAMINADOR DE ACUERDO A LOS CRITERIOS DE BÚSQUEDA.						
US5527910						
BÚSQUEDA DE SECUENCIAS						
Número de depósito / patente y N° de secuencia % de identidad						
SEQ ID NO (de la solicitud)	NCBI	The Lens	EMBL-EBI	DDJB	Genome Quest	
N/A						

Ruth Rodriguez

Search history

- Search 1: TAC=(mGluR5 AND pyridine) (Results 119)
- Search 2: TAC=(mGluR5 AND pyridine) and CPC=(C07D213/74) (Results 5)
- Search 3: TAC=(mGluR5 AND pyridine) and CPC=(C07D237/22) (Results 0)
- Search 4: TAC=(mGluR5) and CPC=(C07D213/74) (Results 13)
- Search 5: TAC=(mGluR5) and CPC=(C07D237/22) (Results 1)
- Search 6: TAC=(mGluR5) and CPC=(C07D239/42) (Results 7)
- Search 7: [SP]: 1. a compound of formula i [ftimg=31947663] wherein y is n or ch with the proviso that y can only be ch, if at least one of u, v or w are n u is n or c-r4 v and w are independently n or ch with the proviso that only one of u, v or w can be simultaneously nitrogen r4 is hydrogen, methyl or halogen r1 is phenyl or heteroaryl, which are optionally substituted by halogen, lower alkyl or lower alkoxy r is hydrogen or lower alkyl r2 is hydrogen, lower alkyl, lower alkoxy, cf3 or s-lower alkyl r3/r3' are, independently from each other, hydrogen, lower alkyl or lower alkoxy or r3 and r3' form together a c3-5-cycloalkyl-, tetrahydrofuran- or an oxetane-ring or a pharmaceutically acceptable acid addition salt, a racemic mixture, or its corresponding enantiomer and/or optical isomer and/or stereoisomer thereof. 2. the compound of claim 1 having the formula [ftimg=31947664] wherein y is n u is -ch- or n v and w are independently n or ch with the proviso that only one of u, v or w can be simultaneously nitrogen r1 is phenyl, which is optionally substituted by halogen r is hydrogen or lower alkyl r2 is lower alkyl, lower alkoxy, cf3 or s-lower alkyl r3/r3' are independently from each other hydrogen or lower alkyl or a pharmaceutically acceptable acid addition salt, a racemic mixture, or its corresponding enantiomer and/or optical isomer and/or stereoisomer thereof. 3. a compound of claim 2, selected from the group consisting of 2,2-dimethyl-n-(5-phenylethynyl-pyridin-2-yl)-propionamide, n-(5-phenylethynyl-pyridin-2-yl)-butyramide, pentanoic acid (5-phenylethynyl-pyridin-2-yl)-amide, 3-methyl-n-(5-phenylethynyl-pyridin-2-yl)-butyramide, (rs)-2-methyl-pentanoic acid (5-phenylethynyl-pyridin-2-yl)-amide, 2-methylsulfanyl-n-(5-phenylethynyl-pyridin-2-yl)-acetamide, 2,2-dimethyl-n-(5-phenylethynyl-pyrimidin-2-yl)-propionamide, 2,2,n-trimethyl-n-(5-phenylethynyl-pyrimidin-2-yl)-propionamide, 2,2-dimethyl-n-(6-phenylethynyl-pyridazin-3-yl)-propionamide, 2-methoxy-n-(5-phenylethynyl-pyridin-2-yl)-acetamide, n-[5-(3-fluoro-phenylethynyl)-pyridin-2-yl]-2,2-dimethyl-propionamide, 2-methoxy-2-methyl-n-(5-phenylethynyl-pyridin-2-yl)-propionamide, n-[5-(3-fluoro-phenylethynyl)-pyridin-2-yl]-2-methoxy-2-methyl-propionamide, n-[5-(2,5-difluoro-phenylethynyl)-pyridin-2-yl]-2-methoxy-2-methyl-propionamide, n-[5-(3-chloro-phenylethynyl)-pyridin-2-yl]-3,3,3-trifluoro-2,2-dimethyl-propionamide and n-[6-(3-chloro-phenylethynyl)-pyridazin-3-yl]-2,2-dimethyl-propionamide. 4. the compound of claim 1 having the formula [ftimg=31947665] wherein r1 is phenyl or heteroaryl, which are optionally substituted by halogen, lower alkyl or lower alkoxy r is hydrogen or lower alkyl r2 is hydrogen, lower alkyl, lower alkoxy, cf3 or s-lower alkyl r3/r3' are, independently from each other, hydrogen, lower alkyl or lower alkoxy or r3 and r3' form together a c3-5-cycloalkyl-, tetrahydrofuran- or an oxetane-ring or a pharmaceutically acceptable acid addition salt, a racemic mixture, or its corresponding enantiomer and/or optical isomer and/or stereoisomer thereof. 5. a compound of claim 4 selected from the group consisting of 2,2-dimethyl-n-(5-phenylethynyl-pyridin-2-yl)-propionamide, n-(5-phenylethynyl-pyridin-2-yl)-butyramide, pentanoic acid (5-phenylethynyl-pyridin-2-yl)-amide, 3-methyl-n-(5-phenylethynyl-pyridin-2-yl)-butyramide, (rs)-2-methyl-pentanoic acid (5-phenylethynyl-pyridin-2-yl)-amide, 2-methylsulfanyl-n-(5-phenylethynyl-pyridin-2-yl)-acetamide, 2-methoxy-n-(5-phenylethynyl-pyridin-2-yl)-acetamide, n-[5-(3-fluoro-phenylethynyl)-pyridin-2-yl]-2,2-dimethyl-propionamide, 2-methoxy-2-methyl-n-(5-phenylethynyl-pyridin-2-yl)-propionamide, n-[5-(3-fluoro-phenylethynyl)-pyridin-2-yl]-2-methoxy-2-methyl-n-(5-phenylethynyl-pyridin-2-yl)-propionamide, n-[5-(3-fluoro-phenylethynyl)-pyridin-2-yl]-2-methoxy-2-methyl-propionamide, n-[5-(2,5-difluoro-phenylethynyl)-pyridin-2-yl]-2-methoxy-2-methyl-propionamide, n-[5-(3-chloro-phenylethynyl)-pyridin-2-yl]-3,3,3-trifluoro-2,2-dimethyl-propionamide and n-[5-(3-chloro-phenylethynyl)-pyridazin-3-yl]-2,2-dimethyl-propionamide. 6. the compound of claim 1 having the formula [ftimg=31947666] wherein r1 is phenyl or heteroaryl, which are optionally substituted by halogen, lower alkyl or lower alkoxy r is hydrogen or lower alkyl r2 is hydrogen, lower alkyl, lower alkoxy, cf3 or s-lower alkyl r3/r3' are, independently from each other, hydrogen, lower alkyl or lower alkoxy or r3 and r3' form together a c3-5-cycloalkyl-, tetrahydrofuran- or an oxetane-ring or a pharmaceutically acceptable acid addition salt, a racemic mixture, or its corresponding enantiomer and/or optical isomer and/or stereoisomer thereof. 7. a compound of claim 6 selected from 2,2-dimethyl-n-(5-phenylethynyl-pyrimidin-2-yl)-propionamide or 2,2,n-trimethyl-n-(5-phenylethynyl-pyrimidin-2-yl)-propionamide. 8. the compound of claim 1 having the formula [ftimg=31947667] wherein r1 is phenyl or heteroaryl, which are optionally substituted by halogen, lower alkyl or lower alkoxy r is hydrogen or lower alkyl r2 is hydrogen, lower alkyl, lower alkoxy, cf3 or s-lower alkyl r3/r3' are independently from each other hydrogen, lower alkyl or lower alkoxy or r3 and r3' form together a c3-5-cycloalkyl-, tetrahydrofuran- or an oxetane-ring or a pharmaceutically acceptable acid addition salt, a racemic mixture, or its corresponding enantiomer and/or optical isomer and/or stereoisomer thereof. 9. a compound of claim 8, selected from 2,2-dimethyl-n-(6-phenylethynyl-pyridazin-3-yl)-propionamide or n-[6-(3-chloro-phenylethynyl)-pyridazin-3-yl]-2,2-dimethyl-propionamide. 10. the compound of claim 1 having the formula [ftimg=31947668] wherein r1 is phenyl or heteroaryl, which are optionally substituted by halogen, lower alkyl or lower alkoxy r is hydrogen or lower alkyl r2 is hydrogen, lower alkyl, lower alkoxy, cf3 or s-lower alkyl r3/r3' are independently from each other hydrogen, lower alkyl or lower alkoxy or r3 and r3' form together a c3-5-cycloalkyl-, tetrahydrofuran- or an oxetane-ring or a pharmaceutically acceptable acid addition salt, a racemic mixture, or its corresponding enantiomer and/or optical isomer and/or stereoisomer thereof. 11. the compound of claim 1 having the formula [ftimg=31947669] wherein r1 is phenyl or heteroaryl, which are optionally substituted by halogen, lower alkyl or lower alkoxy r is hydrogen or lower alkyl r2 is hydrogen, lower alkyl, lower alkoxy, cf3 or s-lower alkyl r3/r3' are independently from each other hydrogen, lower alkyl or lower alkoxy or r3 and r3' form together a c3-5-cycloalkyl-, tetrahydrofuran- or an oxetane-ring or a pharmaceutically acceptable acid addition salt, a racemic mixture, or its corresponding enantiomer and/or optical isomer and/or stereoisomer thereof. 12. a process for preparation of a compound of claim 1 comprising a) reacting a compound of formula [ftimg=31947670] with a suitable compound of formula [ftimg=31947671] to a compound of formula [ftimg=31947672] wherein the substituents are defined in claim 1, or if desired, converting the compounds obtained into pharmaceutically acceptable acid addition salts, or b) reacting a compound of formula [ftimg=31947673] with a suitable compound of formula [ftimg=31947674] to a compound of formula [ftimg=31947675] wherein the substituents are defined in claim 1, or if desired, converting the compounds obtained into pharmaceutically acceptable acid addition salts, or c) reacting a compound of formula [ftimg=31947676] with a suitable compound of formula [ftimg=31947677] to a compound of formula [ftimg=31947678] wherein the substituents are defined in claim 1, or d) reacting a compound of formula [ftimg=31947679] with a suitable compound of formula r-hal to a compound of formula [ftimg=31947680] wherein r is alkyl and hal is halogen and wherein the other substituents are defined in claim 1, or if desired, converting the compounds obtained into pharmaceutically acceptable acid addition salts. 13. a pharmaceutical composition comprising a compound of claim 1 together with at least one therapeutically inert carrier. (Results 99)
- Search 8: (7) AND PD=(2005 OR 2007 OR 2003 OR 2006 OR 2004 OR 2008 OR 2011 OR 2002 OR 2009 OR 2000 OR 2001 OR 2010) (Results 83)
- Search 9: (8) AND IPC=(C07) (Results 83)
- Search 10: fn=(42647780 or 42647780 or 32886770 or 32849686 or 32886770 or 33397783 or 32090793 or 42647780 or 44320998) (Results 6)
- Search 11: TAC=(c-kit OR PDGFR) and CPC=(C07D498/04) (Results 8)
- Search 12: TAC=(c-kit OR PDGFR) and CPC=(C07D471/04 or C07D491/044 or C07D491/048 or C07D491/107 or C07D498/04) (Results 134)
- Search 13: (12) AND PD=(2007 OR 2006 OR 2005 OR 2008 OR 2009 OR 2011 OR 2010 OR 2012 OR 2003 OR 2004 OR 2002) (Results 112)
- Search 14: PN=(wo2013033167) (Results 1)
- Search 15: fn=(53180003 or 53179963 or 34298802 or 52846395 or 53180003 or 53179963 or 53179963 or 30222475 or 43941857 or 32711703 or 30737034 or 41802181 or 53182986 or 53183176) (Results 11)
- Search 16: PN=(WO2013033167) (Results 1)
- Search 17: fn=(53180003 or 53179963 or 34298802 or 52846395 or 53180003 or 53179963 or 53179963 or 30222475 or 43941857 or 32711703 or 30737034 or 41802181 or 53182986 or 53183176) (Results 11)
- Search 18: [SP]: 1. a method for treating a disease or disorder where modulation of a kinase is implicated, wherein the method comprises administering to a system or subject in need of such treatment an effective amount of a compound of formula (i) or formula (ii), or pharmaceutically acceptable salt thereof, [ftimg=68000466] wherein: m is 1 and r20 is selected from h, halo, c1-c6alkyl, c1-c6haloalkyl, c1-c6haloalkoxy, deuterium, deuterated c1-c6alkyl, -cn, -(cr92)nor4, -c(o)r4, -(cr92)nc -(o)r4, r10, -(cr92)nr10, -((cr92)no)tr4, -(cr92)no(cr92)nr7, -(cr92)nc(o)r4, -c(o)n(r4)2, -or4, and -(cr92)ncn or m is 4 and r20 is deuterium r1 is selected from c1-c6alkyl and halo each r11 is independently selected from h, halo and c1-c6alkyl i1 is a bond, -nh- or -c(o)nh- i2 is -(cr92)n-, -chr6-, -(cr92)no-, -nh-, -(cr92)nc -(o)-, -c(o)o(cr92)n-, -(cr92)noc(o)nr4-, -(cr92)nnr4c(o)(cr92)n-, -(cr92)nnr4c(o)-, or -(cr92)nnr4c(o)-o- r2 is r3 or i2r3 r3 is selected from an unsubstituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from n, o and s, a piperidinone, a oxazolidin-2-one, pyrrolidinone, a pyrrolidin-2-one and a substituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from n, o and s, wherein the substituted 4-6 membered heterocycloalkyl of r3 is substituted with 1-4 substituents independently selected from c1-c6alkyl halo, -cn, c1-c6haloalkyl, -or4, -c(o)or4, -c(o)r4, -c(o)r7, -c(o) or5, -(cr92)nor4, -o(cr92)nor4, -c(o)o(cr92)nor4, -n(r4)2, -c(o)nr42, -nr4c(o)or4, -nr4c(o)(cr92)nor4, -nr4(cr92)nor4, -nr4s(o)2r4, -n(c(o)or4)2, r8, -(cr92)nr8,

21: [SP] 1. a method for treating a disease or disorder where modulation of a kinase is implicated, wherein the method comprises administering to a system or subject in need of such treatment an effective amount of a compound of formula (i) or formula (ii), or pharmaceutically acceptable salt thereof, [ftimg=68000467] wherein: m is 1 and r20 is selected from h, halo, c1-c6alkyl, c1-c6haloalkoxy, deuterium, deuterated c1-c6alkyl, -cn, -(cr2)nr4, -(c-o)r4, -(cr2)nc -(o)r4, r10, -(cr2)nr10, -(cr2)no)r4, -(cr2)no(c)r2)nr7, -(cr2)nc-(o)r4, -(c-o)(r4)2, -or4, and -(cr2)ncn or m is 4 and r20 is deuterium r1 is selected from c1-c6alkyl and halo each r11 is independently selected from h, halo and c1-c6alkyl 11 is a bond, -nh- or -(c-o)nh- 12 is -(cr2)n-, -chr6-, -(cr2)no-, -nh-, -(cr2)nc -(o)-, -(c-o)(cr2)n-, -(cr2)nc-(o)r4-, -(cr2)nnr4c-(o)(cr2)n-, -(cr2)nnr4c-(o)-, -(cr2)nnr4c-(o)-r2 or r3 or 12r3 r3 is selected from an unsubstituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from n, o and s, a piperidinone, an oxazolidin-2-one, pyrrolidinone, a pyrrolidin-2-one and a substituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from n, o and s, wherein the substituted 4-6 membered heterocycloalkyl of r3 is substituted with 1-4 substituents independently selected from c1-c6alkyl halo, -cn, c1-c6haloalkyl, -or4, -(c-o)r4, -(c-o)r4, -(c-o)r7, -(c-o) or5, -(cr2)nr4, -(cr2)nr4, -(c-o)(cr2)nr4, -(n-r4)2, -(c-o)r4r2, -nr4c-(o)r4, -nr4c-(o)(cr2)nr4, -nr4(c)r2)nr4, -nr4s-(o)2r4, -n-(c-o)r4r2, r8, -(cr2)nr8, deuterated c1-c6alkoxy, -(s-o)2r4, -(s-o)2r7, -(s-o)2r8, -(s-o)2n(r4)2, -(s-o)2nhc-(o)r4, -(s-o)2(c)r2)nc-(o)r4, -(s-o)2(c)r2)nr4, a spiro attached dioxolane, a spiro attached dioxolane which is substituted with c1-c6alkyl, a spiro attached dioxane, a spiro attached tetrahydrofuran, a spiro attached oxetane, a spiro attached cyclobutanone, a spiro attached cyclobutanol, a c1 alkyl bridge, an unsubstituted 5-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from n, o and s and a 5-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from n, o and s substituted with 1-3 substituents independently selected from c1-c6alkyl, halo, c1-c6haloalkyl, c1-c6haloalkoxy, -or4 and r8 each r4 is independently selected from h and c1-c6alkyl r5 is an unsubstituted c3-c8cycloalkyl, an unsubstituted 5-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from n or o or a c3-c8cycloalkyl substituted with 1-3 substituents independently selected from c1-c6alkyl each r6 is independently selected from -nr4c(o)r4, -or4 and -(cr2)nr4 each r7 is independently selected from c1-c6haloalkyl r8 is selected from an unsubstituted phenyl, unsubstituted 5-6 membered heterocycloalkyl with 1-3 heteroatoms independently selected from n, o and s, an unsubstituted 5 membered heterocycloalkyl with 1-4 heteroatoms selected from n, an unsubstituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from n, o and s, a substituted phenyl, a substituted 5 membered heterocycloalkyl with 1-4 heteroatoms selected from n, o and s, a substituted phenyl, a substituted 5 membered heterocycloalkyl with 1-4 heteroatoms selected from n, o and s, a substituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from n, o and s, a substituted c3-c8cycloalkyl, a tetrahydro-1h-oxazolo [3,4-a]pyrazin-3(5h)-one, an oxazolidin-2-one, pyrrolidinone and a pyrrolidin-2-one, wherein the substituted phenyl, the substituted 5-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from n, o and s, the substituted 5 membered heterocycloalkyl with 1-4 heteroatoms selected from n, substituted c3-c8cycloalkyl and substituted 4-6 membered heterocycloalkyl of r8 are substituted with 1-3 substituents independently selected from c1-c6alkyl, -(cr2)nr4, -(cr2)nr5, -(c-r2)nc(o)r4, -(c-o)r4 and -(s-o)2r4 each r9 is independently selected from h and c1-c6alkyl r10 is selected from an unsubstituted phenyl, unsubstituted 5-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from n, o and s, an unsubstituted 5 membered heterocycloalkyl with 1-4 heteroatoms selected from n, an unsubstituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from n, o and s, an unsubstituted c3-c8cycloalkyl, a substituted 5-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from n, o and s, a substituted phenyl, a substituted 5 membered heterocycloalkyl with 1-4 heteroatoms selected from n, a substituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from n, o and s, a substituted c3-c8cycloalkyl, an oxazolidin-2-one, pyrrolidinone and a pyrrolidin-2-one, wherein the substituted phenyl, the substituted 5-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from n, o and s, the substituted 5 membered heterocycloalkyl with 1-4 heteroatoms selected from n, substituted c3-c8cycloalkyl and substituted 4-6 membered heterocycloalkyl of r8 are substituted with 1-3 substituents independently selected from c1-c6alkyl [me], -(cr2)nr4, -(cr2)nr5, -(c-r2)nc(o)r4 and -(s-o)2r4 t is 1, 2 or 3, and each n is independently selected from 1, 2, 3 and 4 wherein the kinase is selected from c-kit, pdgfra and pdgfr beta, and wherein the disease is selected from asthma, allergic rhinitis, allergic sinusitis and crohn's disease. 2. the method of claim 1, wherein the compound is a compound of formula (ia), formula (iia), formula (ib) or formula (iib): [ftimg=68000467] wherein: m is 1 and r20 is selected from h, halo, c1-c6alkyl, c1-c6haloalkoxy, c1-c6haloalkoxy, deuterium, deuterated c1-c6alkyl, -cn, -(cr2)nr4, -(c-o)r4, -(cr2)nc-(o)r4, r10, -(cr2)nr10, -(cr2)no)r4, -(cr2)no (cr2)nr7, -(cr2)nc-(o)r4, -(c-o)(r4)2, -or4, and -(cr2)ncn or m is 4 and r20 is deuterium r1 is selected from c1-c6alkyl and halo each r11 is independently selected from h, halo and c1-c6alkyl 12 is -(cr2)n-, -chr6-, -(cr2)no-, -nh-, -(cr2)nc-(o)-, -(c-o)(cr2)n-, -(cr2)no(c-o)r4-, -(cr2)nnr4c-(o)(cr2)n-, -(cr2)nnr4c-(o)-, or -(cr2)nnr4c-(o)-r2 r3 is r3 or 12r3 r3 is selected from an unsubstituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from n, o and s, a piperidinone, an oxazolidin-2-one, pyrrolidinone, a pyrrolidin-2-one and a substituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from n, o and s, wherein the substituted 4-6 membered heterocycloalkyl of r3 is substituted with 1-4 substituents independently selected from c1-c6alkyl halo, -cn, c1-c6haloalkoxy, -or4, -(c-o)r4, -(c-o)r4, -(c-o)r7, -(c-o) or5, -(cr2)nr4, -(cr2)nr4, -(c-o)(cr2)nr4, -(n-r4)2, -(c-o)r4r2, r8, -(cr2)nr8, deuterated c1-c6alkoxy, -(s-o)2r4, -(s-o)2r7, -(s-o)2r8, -(s-o)2n(r4)2, -(s-o)2nhc-(o)r4, -(s-o)2(c)r2)nc-(o)r4, -(s-o)2(c)r2)nr4, a spiro attached dioxolane, a spiro attached dioxane, a spiro attached tetrahydrofuran, a spiro attached oxetane, a spiro attached cyclobutanone, a spiro attached cyclobutanol, a c1 alkyl bridge, an unsubstituted 5-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from n, o and s and a 5-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from n, o and s substituted with 1-3 substituents independently selected from c1-c6alkyl, halo, c1-c6haloalkyl, c1-c6haloalkoxy, -or4 and r8 each r4 is independently selected from h and c1-c6alkyl r5 is an unsubstituted c3-c8cycloalkyl, an unsubstituted 5-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from n or o or a c3-c8cycloalkyl substituted with 1-3 substituents independently selected from c1-c6alkyl each r6 is independently selected from -nr4c(o)r4, -or4 and -(cr2)nr4 each r7 is independently selected from c1-c6haloalkyl r8 is selected from an unsubstituted phenyl, unsubstituted 5-6 membered heterocycloalkyl with 1-3 heteroatoms independently selected from n, o and s, an unsubstituted 5 membered heterocycloalkyl with 1-4 heteroatoms selected from n, an unsubstituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from n, o and s, a substituted phenyl, a substituted 5 membered heterocycloalkyl with 1-4 heteroatoms selected from n, o and s, a substituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from n, o and s, a substituted c3-c8cycloalkyl, a tetrahydro-1h-oxazolo [3,4-a]pyrazin-3(5h)-one, an oxazolidin-2-one, pyrrolidinone and a pyrrolidin-2-one, wherein the substituted phenyl, the substituted 5-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from n, o and s, the substituted 5 membered heterocycloalkyl with 1-4 heteroatoms selected from n, substituted c3-c8cycloalkyl and substituted 4-6 membered heterocycloalkyl of r8 are substituted with 1-3 substituents independently selected from c1-c6alkyl, -(cr2)nr4, -(cr2)nr5, -(c-r2)nc(o)r4 and -(s-o)2r4 each r9 is independently selected from h and c1-c6alkyl r10 is selected from an unsubstituted phenyl, unsubstituted 5-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from n, o and s, an unsubstituted 5 membered heterocycloalkyl with 1-4 heteroatoms selected from n, an unsubstituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from n, o and s, a substituted phenyl, a substituted 5 membered heterocycloalkyl with 1-4 heteroatoms selected from n, o and s, a substituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from n, o and s, a substituted c3-c8cycloalkyl, a tetrahydro-1h-oxazolo [3,4-a]pyrazin-3(5h)-one, an oxazolidin-2-one, pyrrolidinone and a pyrrolidin-2-one, wherein the substituted phenyl, the substituted 5-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from n, o and s, the substituted 5 membered heterocycloalkyl with 1-4 heteroatoms selected from n, substituted c3-c8cycloalkyl and substituted 4-6 membered heterocycloalkyl of r8 are substituted with 1-3 substituents independently selected from c1-c6alkyl, -(cr2)nr4, -(cr2)nr5, -(c-r2)nc(o)r4 and -(s-o)2r4 each r9 is independently selected from h and c1-c6alkyl r10 is selected from an unsubstituted phenyl, unsubstituted 5-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from n, o and s, an unsubstituted 5 membered heterocycloalkyl with 1-4 heteroatoms selected from n, an unsubstituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from n, o and s, a substituted phenyl, a substituted 5 membered heterocycloalkyl with 1-4 heteroatoms selected from n, o and s, a substituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from n, o and s, a substituted c3-c8cycloalkyl, a tetrahydro-1h-oxazolo [3,4-a]pyrazin-3(5h)-one, an oxazolidin-2-one, pyrrolidinone and a pyrrolidin-2-one, wherein the substituted phenyl, the substituted 5-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from n, o and s, the substituted 5 membered heterocycloalkyl with 1-4 heteroatoms selected from n, substituted c3-c8cycloalkyl and substituted 4-6 membered heterocycloalkyl of r8 are substituted with 1-3 substituents independently selected from c1-c6alkyl, -(cr2)nr4, -(cr2)nr5, -(c-r2)nc(o)r4 and -(s-o)2r4 each r9 is independently selected from h and c1-c6alkyl r10 is selected from an unsubstituted phenyl, unsubstituted 5-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from n, o and s, an unsubstituted 5 membered heterocycloalkyl with 1-4 heteroatoms selected from n, an unsubstituted 4-6 membered

Search [SP]: cross-reference to related applications this application is a continuation of prior application ser. no. 14/031,792, filed sep. 19, 2013, which is a continuation

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associated myelopathy.the term "carrier," as used herein, refers to chemical compounds or agents that facilitate the incorporation of a compound described herein into cells or tissues.the terms "co-administration" or "combined administration" or the like as used herein are meant to encompass administration of the selected therapeutic agents to a single patient, and are intended to include treatment regimens in which the agents are not necessarily administered by the same route of administration or at the same time.the term "dermatological disease" or "dermatological disorder," as used herein refers to a skin disorder. such dermatological disorders include, but are not limited to, proliferative or inflammatory disorders of the skin such as, atopic dermatitis, bullous disorders, collagenoses, contact dermatitis eczema, kawasaki disease, rosacea, sjogren-larssou syndrome, actinic keratosis, basal cell carcinoma and urticaria.the term "diluent," as used herein, refers to chemical compounds that are used to dilute a compound described herein prior to delivery. diluents can also be used to stabilize compounds described herein.the terms "effective amount" or "therapeutically effective amount," as used herein, refer to a sufficient amount of a compound described herein being administered which will relieve to some extent one or more of the symptoms of the disease or condition being treated. the result can be reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. for example, an "effective amount" for therapeutic uses is the amount of the composition comprising a compound as disclosed herein required to provide a clinically significant decrease in disease symptoms. an appropriate "effective" amount in any individual case may be determined using techniques, such as a dose escalation study.the terms "enhance" or "enhancing," as used herein, means to increase or prolong either in potency or duration a desired effect. thus, in regard to enhancing the effect of therapeutic agents, the term "enhancing" refers to the ability to increase or prolong, either in potency or duration, the effect of other therapeutic agents on a system. an "enhancing-effective amount," as used herein, refers to an amount adequate to enhance the effect of another therapeutic agent in a desired system.the terms "fibrosis" or "fibrosis disease," as used herein, refers to conditions that follow acute or chronic inflammation and are associated with the abnormal accumulation of cells and/or collagen and include but are not limited to fibrosis of individual organs or tissues such as the heart, kidney, joints, lung, or skin, and includes such disorders as idiopathic pulmonary fibrosis and cryptogenic fibrosing alveolitis.the term "inflammatory disease or disorders," as used herein, refers to those diseases or conditions that are characterized by one or more of the signs of pain (dolor, from the generation of noxious substances and the stimulation of nerves), heat (calor, from vasodilatation), redness (rubor, from vasodilatation and increased blood flow), swelling (tumor, from excessive inflow or restricted outflow of fluid), and loss of function (functio laesa, which may be partial or complete, temporary or permanent). inflammation takes many forms and includes, but is not limited to, inflammation that is one or more of the following: acute, adhesive, atrophic, catarrhal, chronic, cirrhotic, diffuse, disseminated, exudative, fibrinous, fibrosing, focal, granulomatous, hyperplastic, hypertrophic, interstitial, metastatic, necrotic, obliterative, parenchymatous, plastic, productive, proliferous, pseudomembranous, purulent, sclerosing, seroplastic, serous, simple, specific, subacute, suppurative, toxic, traumatic, and/or ulcerative. inflammatory disorders further include, without being limited to those affecting the blood vessels (polyarteritis, temporal arthritis) joints (arthritis: crystalline, osteo-, psoriatic, reactive, rheumatoid, reiter's) gastrointestinal tract (disease) skin (dermatitis) or multiple organs and tissues (systemic lupus erythematosus).as used herein, the term "inhibit", "inhibition" or "inhibiting" refers to the reduction or suppression of a given condition, symptom, or disorder, or disease, or a significant decrease in the baseline activity of a biological activity or process.the term "pharmaceutically acceptable," as used herein, refers to a material, such as a carrier or diluent, which does not abrogate the biological activity or properties of the compounds described herein. such materials are administered to an individual without causing undesirable biological effects or interacting in a deleterious manner with any of the components of the composition in which it is contained. the term "pharmaceutically acceptable" carrier, as used herein, includes any and all solvents, dispersion media, coatings, surfactants, antioxidants, preservatives (e.g., antibacterial agents, antifungal agents), isotonic agents, absorption delaying agents, salts, preservatives, drug stabilizers, binders, excipients, disintegration agents, lubricants, sweetening agents, flavoring agents, dyes, and the like and combinations thereof, as would be known to those skilled in the art (see, for example, remington's pharmaceutical sciences, 18th ed. mack printing company, 1990, pp. 1289-1329). except insofar as any conventional carrier is incompatible with the active ingredient, its use in the therapeutic or pharmaceutical compositions is contemplated.the term "pharmaceutically acceptable salt," as used herein, refers to a formulation of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compounds described herein.the terms "combination" or "pharmaceutical combination," as used herein mean a product that results from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. the term "fixed combination" means that the active ingredients, by way of example, a compound of formula (i) or formula (ii) and an additional therapeutic agent, are both administered to a patient simultaneously in the form of a single entity or dosage. the term "non-fixed combination" means that the active ingredients, by way of example, a compound of formula (i) or formula (ii) and an additional therapeutic agent, are both administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific time limits, wherein such administration provides therapeutically effective levels of the 2 compounds in the body of the patient. the latter also applies to cocktail therapy, e.g. the administration of 3 or more active ingredients.the terms "composition" or "pharmaceutical composition," as used herein, refers to a mixture of at least one compound, such as the compounds of formula (i) or formula (ii) provided herein, with at least one and optionally more than one other pharmaceutically acceptable chemical components, such as carriers, stabilizers, diluents, dispersing agents, suspending agents, thickening agents, and/or excipients.the term "respiratory disease," as used herein, refers to diseases affecting the organs that are involved in breathing, such as the nose, throat, larynx, trachea, bronchi, and lungs. respiratory diseases include, but are not limited to, asthma, adult respiratory distress syndrome and allergic (extrinsic) asthma, non-allergic (intrinsic) asthma, acute severe asthma, chronic asthma, clinical asthma, nocturnal asthma, allergen-induced asthma, aspirin-sensitive asthma, exercise-induced asthma, isocapnic hyperventilation, child-onset asthma, adult-onset asthma, cough-variant asthma, occupational asthma, steroid-resistant asthma, seasonal asthma, seasonal allergic rhinitis, perennial allergic rhinitis, chronic obstructive pulmonary disease, including chronic bronchitis or emphysema, pulmonary hypertension, interstitial lung fibrosis and/or airway inflammation and cystic fibrosis, and hypoxia.the term "subject" or "patient," as used herein, encompasses mammals and non-mammals. examples of mammals include, but are not limited to, humans, chimpanzees, apes, monkeys, cattle, horses, sheep, goats, swine rabbits, dogs, cats, rats, mice, guinea pigs, and the like. examples of non-mammals include, but are not limited to, birds, fish and the like. frequently the subject is a human, and may be a human who has been diagnosed as in need of treatment for a disease or disorder disclosed herein.as used herein, a subject is "in need of" a treatment if such subject would benefit biologically, medically or in quality of life from such treatment.the term "c-kit inhibitor," as used herein, refers to a compound which inhibits c-kit kinase.the term "disease or disorder associated with c-kit activity," as used herein, refers to any disease state associated with a c-kit kinase. such diseases or disorders include, but are not limited to, a mast-cell associated disease, inflammatory diseases, respiratory diseases, fibrosis diseases, a dermatological disease, metabolic diseases and autoimmune diseases, such as, by way of example only, asthma, dermatitis, allergic rhinitis, pulmonary fibrosis, hepatic fibrosis, cardiac fibrosis, scleroderma, irritable bowel syndrome (ibs), inflammatory bowel disease (ibd), urticaria, rheumatoid arthritis, multiple sclerosis, uticaria, pulmonary arterial hypertension (pah), primary pulmonary hypertension (pph), dermatosis, diabetes, type i diabetes and type ii diabetes.the term "pdgfr inhibitor," as used herein, refers to a compound which inhibits pdgfr kinase.the term "disease or disorder associated with pdgfr activity," as used herein, refers to any disease state associated with a pdgfr kinase. such diseases or disorders include, but are not limited to, inflammatory diseases, respiratory diseases, fibrosis diseases, metabolic diseases and autoimmune diseases, such as, by way of example only, asthma, dermatitis, allergic rhinitis, scleroderma, irritable bowel syndrome (ibs), inflammatory bowel disease (ibd), urticaria, rheumatoid arthritis, multiple sclerosis, pulmonary arterial hypertension and diabetes.the term "an optical isomer" or "a stereoisomer," as used herein, refers to any of the various stereo isomeric configurations which may exist for a given compound of the present invention and includes geometric isomers. it is understood that a substituent may be attached at a chiral center of a carbon atom. the term "chiral" refers to molecules which have the property of non-superimposability on their mirror image partner, while the term "achiral" refers to molecules which are superimposable on their mirror image partner. therefore, the invention includes enantiomers, diastereomers or racemates of the compound. "enantiomers" are a pair of stereoisomers that are non-superimposable mirror images of each other. a 1:1 mixture of a pair of enantiomers is a "racemic" mixture. the term is used to designate a racemic mixture where appropriate."diastereoisomers" are stereoisomers that have at least two asymmetric atoms, but which are not mirror-images of each other. the absolute stereochemistry is specified according to the cahn-ingold-prelog r-s system. when a compound is a pure enantiomer the stereochemistry at each chiral carbon may be specified by either r or s. resolved compounds whose absolute configuration is unknown can be designated (+) or (-) depending on the direction (dextro- or levorotatory) which they rotate plane polarized light at the wavelength of the sodium d line. certain compounds described herein contain one or more asymmetric centers or axes and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (r)- or (s)-.the term "a therapeutically effective amount" of a compound of the present invention, as used herein, refers to an amount of the compound of the present invention that will elicit the biological or medical response of a subject, for example, reduction or inhibition of an enzyme or a protein activity, or ameliorate symptoms, alleviate conditions, slow or delay disease progression, or prevent a disease, etc. in one non-limiting embodiment, the term "a therapeutically effective amount" refers to the amount of the compound of the present invention that, when administered to a subject, is effective to (1) at least partially alleviating, inhibiting, preventing and/or ameliorating a condition, or a disorder or a disease (i) mediated by c-kit kinase or c-kit and pdgfr kinases, or (ii) associated with c-kit kinase or c-kit and pdgfr kinase activity, or (iii) characterized by activity (normal or abnormal) of c-kit kinase or c-kit and pdgfr kinases or (2) reducing or inhibiting the activity of c-kit kinase or c-kit and pdgfr kinases or (3) reducing or inhibiting the expression of c-kit kinase or c-kit and pdgfr kinases. in another non-limiting embodiment, the term "a therapeutically effective amount" refers to the amount of the compound of the present invention that, when administered to a cell, or a tissue, or a non-cellular biological material, or a medium, is effective to at least partially reducing or inhibiting the activity of c-kit kinase or c-kit and pdgfr kinases or at least partially reducing or inhibiting the expression of c-kit kinase or c-kit and pdgfr kinases.the terms "treat", "treating" or "treatment," as used herein, refers to methods of alleviating, abating or ameliorating a disease or condition symptoms, preventing additional symptoms, ameliorating or preventing the underlying metabolic causes of symptoms, inhibiting the disease or condition, arresting the development of the disease or condition, relieving the disease or condition, causing regression of the disease or condition, relieving a condition caused by the disease or condition, or stopping the symptoms of the disease or condition either prophylactically and/or therapeutically.in addition, as used herein, the term "treat", "treating" or "treatment" of any disease or disorder refers in one embodiment, to ameliorating the disease or disorder (i.e., slowing or arresting or reducing the development of the disease or at least one of the clinical symptoms thereof). in another embodiment "treat", "treating" or "treatment" refers to alleviating or ameliorating at least one physical parameter including those which may not be discernible by the patient. in yet another embodiment, "treat", "treating" or "treatment" refers to modulating the disease or disorder, either physically, (e.g., stabilization of a discernible symptom), physiologically, (e.g., stabilization of a physical parameter), or both. in yet another embodiment, "treat", "treating" or "treatment" refers to preventing or delaying the onset or development or progression of the disease or disorder.the compound names provided herein were obtained using chemdraw ultra 10.0 (cambridgesoft(r)) or jchem version 5.3.1 (chemaxon).unless specified otherwise, the term "compounds of the present invention" or "compounds provided herein" refers to compounds of formula (i) and formula (ii), and subformulae thereof (such as formula (ia), formula (iia), formula (ib), formula (iib), formula (ic), formula (iic), formula (id), formula (iid), formula (ie), formula (iie), formula (if) and formula (iif)), and pharmaceutically acceptable salts, hydrates or solvates, stereoisomers (including diastereoisomers and enantiomers), tautomers and isotopically labeled compounds (including deuterium substitutions) thereof. compounds of the present invention further comprise polymorphs of compounds of formula (i) and formula (ii) (or subformulae thereof) and salts thereof.as used herein, the term "a," "an," "the" and similar terms used in the context of the present invention (especially in the context of the claims) are to be construed to cover both the singular and plural unless otherwise indicated herein or clearly contradicted by the context.all methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. the use of any and all examples, or exemplary language (e.g. "such as") provided herein is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention otherwise claimed.various enumerated embodiments of the invention are described herein. it will be recognized that features specified in each embodiment may be combined with other specified features to provide further embodiments of the present invention.description of the preferred embodimentsprovided herein are compounds, pharmaceutically acceptable salts, solvates, n-oxides and isomers thereof, that are inhibitors of c-kit kinase or c-kit and pdgfr kinases. certain embodiments of compounds provided herein have an ic50 for pdgfr inhibition to ic50 for c-kit inhibition ratio (ic50 pdgfr/ic50 c-kit) in the range of 750 to 1000. certain embodiments of compounds provided herein have an ic50 for pdgfr inhibition to ic50 for c-kit inhibition ratio (ic50 pdgfr/ic50 c-kit) in the range of 500 to 750. certain embodiments of compounds provided herein have an ic50 for pdgfr inhibition to ic50 for c-kit inhibition ratio (ic50 pdgfr/ic50 c-kit) in the range of 250 to 500. certain embodiments of compounds provided herein have an ic50 for pdgfr inhibition to ic50 for c-kit inhibition ratio (ic50 pdgfr/ic50 c-kit) in the range of 100 to 250. certain embodiments of compounds provided herein have an ic50 for pdgfr inhibition to ic50 for c-kit inhibition ratio (ic50 pdgfr/ic50 c-kit) in the range of 75 to 100. certain embodiments of compounds provided herein have an ic50 for pdgfr inhibition to ic50 for c-kit inhibition ratio (ic50 pdgfr/ic50 c-kit) in the range of 50 to 75. certain embodiments of compounds provided herein have an ic50 for pdgfr inhibition to ic50 for c-kit inhibition ratio (ic50 pdgfr/ic50 c-kit) in the range of 25 to 50. certain embodiments of compounds provided herein have an ic50 for pdgfr inhibition to ic50 for c-kit inhibition ratio (ic50 pdgfr/ic50 c-kit) in the range of 10 to 25. certain embodiments of compounds provided herein have an ic50 for pdgfr inhibition to ic50 for c-kit inhibition ratio (ic50 pdgfr/ic50 c-kit) in the range of 7.5 to 10. certain embodiments of compounds provided herein have an ic50 for pdgfr inhibition to ic50 for c-kit inhibition ratio (ic50 pdgfr/ic50 c-kit) in the range of 5 to 7.5. certain embodiments of compounds provided herein have an ic50 for pdgfr inhibition to ic50 for c-kit inhibition ratio (ic50 pdgfr/ic50 c-kit) in the range of 2.5 to 5. certain embodiments of compounds provided herein have an ic50 for pdgfr inhibition to ic50 for c-kit inhibition ratio (ic50 pdgfr/ic50 c-kit) in the range of 1 to 2.5. certain embodiments of compounds provided herein have an ic50 for ic50 for pdgfr inhibition to c-kit inhibition ratio (ic50 pdgfr/ic50 c-kit) in the range of 0.95 to 2.5.also provided herein are pharmaceutical compositions that include such compounds. further provided herein are methods for the treatment of diseases and/or disorders associated with c-kit kinase or c-kit and pdgfr kinases using such compounds and pharmaceutical compositions.the c-kit kinase, or c-kit

and pdgfr kinase, inhibitors of the present invention are compounds having the structure of formula (i) or formula (ii), and pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the n-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof: [ftimg=680000442] wherein: m is 1 and r20 is selected from h, halo, c1-c6alkyl, c1-c6haloalkyl, c1-c6haloalkoxy, deuterium, deuterated c1-c6alkyl, -cn, -(cr92)nor4, -(c(o)r4), -(cr92)nc(o)or4, r10, -(cr92)nr10, -((cr92)no)tr4, -(cr92)no(cr92)nr7, -(cr92)nc(o)r4, -(c(o)n(r4)2, -or4, and -(cr92)ncnor m is 4 and r20 is deuteriumr1 is selected from c1-c6alkyl and haloeach r11 is independently selected from h, halo and c1-c6alkylr11 is a bond, -nh- or -c(o)nh-12 is -(cr92)n-, -chr6-, -(cr92)no-, -nh-, -(cr92)nc(o)-, -(c(o)o(cr92)n-, -(cr92)noc(o)nr4-, -(cr92)nnr4c(o)(cr92)n-(cr92)nnr4c(o)-, or -(cr92)nnr4c(o)o-r2 is r3 or l2r3r3 is selected from an unsubstituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from n, o and s, a piperidinone, an oxazolidin-2-one, pyrrolidinone, a pyrrolidin-2-one and a substituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from n, o and s, wherein the substituted 4-6 membered heterocycloalkyl of r3 is substituted with 1-4 substituents independently selected from c1-c6alkyl halo, -cn, c1-c6haloalkyl, -or4, -(c(o)or4, -(c(o)r4), -(c(o)r7, -(c(o)or5, -(cr92)nor4, -(o(cr92)nor4, -(c(o)o(cr92)nor4, -n(r4)2, -(c(o)nr42, -nr4c(o)or4, -nr4c(o)(cr92)nor4, -nr4(cr92)nor4, -nr4s(o)2r4, -n(c(o)or4)2, r8, -(cr92)nr8, deuterated c1-c6alkoxy, -(o)2r4, -(s(o)2r7, -(s(o)2r8, -(s(o)2n(r4)2, -(s(o)2nhc(o)or4, -(s(o)2(cr92)nc(o)or4, s(o)2(cr92)nor4, a spiro attached dioxolane, a spiro attached dioxolane which is substituted with c1-c6alkyl, a spiro attached dioxane, a spiro attached tetrahydrofuran, a spiro attached oxetane, a spiro attached cyclobutanone, a spiro attached cyclobutanol, a c1 alkyl bridge, an unsubstituted 5-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from n, o and s and a 5-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from n, o and s, wherein the substituted 4-6 membered heterocycloalkyl of r3 is substituted with 1-3 substituents independently selected from c1-c6alkyl, halo, c1-c6haloalkyl, c1-c6haloalkoxy, -or4 and r8each r4 is independently selected from h and c1-c6alkylr5 is an unsubstituted c3-c8cycloalkyl, an unsubstituted 5-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from n or o or a c3-c8cycloalkyl substituted with 1-3 substituents independently selected from c1-c6alkyleach r6 is independently selected from -nr4c(o)or4, -or4 and -(cr92)nor4each r7 is independently selected from c1-c6haloalkylr8 is selected from an unsubstituted phenyl, unsubstituted 5-6 membered heteroaryl with 1-3 heteroatoms independently selected from n, o and s, an unsubstituted 5 membered heteroaryl with 1-4 heteroatoms selected from n, an unsubstituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from n, o and s, a substituted phenyl, a substituted 5 membered heteroaryl with 1-4 heteroatoms selected from n, a substituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from n, o and s, a substituted c3-c8cycloalkyl, a substituted 5-6 membered heteroaryl with 1-3 heteroatoms independently selected from n, o and s, a substituted phenyl, a substituted 5 membered heteroaryl with 1-4 heteroatoms selected from n, substituted c3-c8cycloalkyl and substituted 4-6 membered heterocycloalkyl of r8 are substituted with 1-3 substituents independently selected from c1-c6alkyl, -(cr92)nor4, -(c(r92)nr5, -(cr92)nc(o)or4, -(c(o)or4 and -(s(o)2r4each r9 is independently selected from h and c1-c6alkylr10 is selected from an unsubstituted phenyl, unsubstituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from n, o and s, an unsubstituted 5 membered heteroaryl with 1-4 heteroatoms selected from n, an unsubstituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from n, o and s, an unsubstituted c3-c8cycloalkyl, a substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from n, o and s, a substituted phenyl, a substituted 5 membered heteroaryl with 1-4 heteroatoms selected from n, a substituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from n, o and s, a substituted c3-c8cycloalkyl, an oxazolidin-2-one, pyrrolidinone and a pyrrolidin-2-one, wherein the substituted phenyl, the substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from n, o and s, the substituted 5 membered heteroaryl with 1-4 heteroatoms selected from n, substituted c3-c8cycloalkyl and substituted 4-6 membered heterocycloalkyl of r8 are substituted with 1-3 substituents independently selected from c1-c6alkyl [me], -(cr92)nor4, -(c(r92)nr5, -(c(r92)nc(o)or4 and -(s(o)2r4t is 1, 2 or 3, andeach n is independently selected from 1, 2, 3 and 4.in certain embodiments of compounds of formula (i) or formula (ii), and the pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the n-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, the compound of formula (i) or formula (ii) is a compound having a structure of formula (ia), formula (iia), formula (ib) or formula (iib):[ftimg=68000043] wherein: m is 1 and r20 is selected from h, halo, c1-c6alkyl, c1-c6haloalkyl, c1-c6haloalkoxy, deuterium, deuterated c1-c6alkyl, -cn, -(cr92)nor4, -(c(o)r4, -(cr92)nc(o)or4, r10, -((cr92)no)tr4, -(cr92)no(cr92)nr7, -(cr92)nc(o)r4, -(c(o)n(r4)2, -or4, and -(cr92)ncnor m is 4 and r20 is deuteriumr1 is selected from c1-c6alkyl and haloeach r11 is independently selected from h, halo and c1-c6alkylr12 is -(cr92)n-, -chr6-, -(cr92)no-, -nh-, -(cr92)nc(o)-, -(c(o)o(cr92)n-, -(cr92)noc(o)nr4-, -(cr92)nnr4c(o)(cr92)n-, -(cr92)nnr4c(o)-, or -(cr92)nnr4c(o)o-r2 is r3 or l2r3r3 is selected from an unsubstituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from n, o and s, a piperidinone, an oxazolidin-2-one, pyrrolidinone, a pyrrolidin-2-one and a substituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from n, o and s, wherein the substituted 4-6 membered heterocycloalkyl of r3 is substituted with 1-4 substituents independently selected from c1-c6alkyl halo, -cn, c1-c6haloalkyl, -or4, -(c(o)or4, -(c(o)r4, -(c(o)r7, -(c(o)or5, -(cr92)nor4, -(o(cr92)nor4, -(c(o)o(cr92)nor4, -n(r4)2, -(c(o)nr42, -nr4c(o)or4, -nr4c(o)(cr92)nor4, -nr4(cr92)nor4, -nr4s(o)2r4, -n(c(o)or4)2, r8, -(cr92)nr8, deuterated c1-c6alkoxy, -(o)2r4, -(s(o)2r7, -(s(o)2r8, -(s(o)2n(r4)2, -(s(o)2nhc(o)or4, -(s(o)2(cr92)nc(o)or4, s(o)2(cr92)nor4, a spiro attached dioxolane, a spiro attached dioxolane which is substituted with c1-c6alkyl, a spiro attached dioxane, a spiro attached tetrahydrofuran, a spiro attached oxetane, a spiro attached cyclobutanone, a spiro attached cyclobutanol, a c1 alkyl bridge, an unsubstituted 5-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from n, o and s and a 5-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from n, o and s, wherein the substituted 4-6 membered heterocycloalkyl of r3 is substituted with 1-3 substituents independently selected from c1-c6alkyl, halo, c1-c6haloalkyl, c1-c6haloalkoxy, -or4 and r8each r4 is independently selected from h and c1-c6alkylr5 is an unsubstituted c3-c8cycloalkyl, an unsubstituted 5-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from n or o or a c3-c8cycloalkyl substituted with 1-3 substituents independently selected from c1-c6alkyleach r6 is independently selected from -nr4c(o)or4, -or4 and -(cr92)nor4each r7 is independently selected from c1-c6haloalkylr8 is selected from an unsubstituted phenyl, unsubstituted 5-6 membered heteroaryl with 1-3 heteroatoms independently selected from n, o and s, an unsubstituted 5 membered heteroaryl with 1-4 heteroatoms selected from n, an unsubstituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from n, o and s, a substituted phenyl, a substituted 5 membered heteroaryl with 1-4 heteroatoms selected from n, substituted c3-c8cycloalkyl and substituted 4-6 membered heterocycloalkyl of r8 are substituted with 1-3 substituents independently selected from c1-c6alkyl [me], -(cr92)nor4, -(c(r8)2)nr5, -(c(r92)nc(o)or4 and -(s(o)2r4t is 1, 2 or 3, andeach n is independently selected from 1, 2, 3 and 4.in certain embodiments of compounds of formula (i) or formula (ii), and the pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the n-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, the compound of formula (i) or formula (ii), is a compound having a structure of formula (ia), formula (iia), formula (ib), formula (iib), formula (ic), formula (iic), formula (id), formula (iid), formula (ie), formula (iie), formula (if) or formula (iif): [ftimg=68000044][ftimg=68000045][ftimg=68000046] wherein: m is 1 and r20 is selected from h, halo, c1-c6alkyl, c1-c6haloalkyl, c1-c6haloalkoxy, deuterium, deuterated c1-c6alkyl, -cn, -(cr92)nor4, -(c(o)r4, -(cr92)nc(o)or4, r10, -(cr92)no)tr4, -(cr92)no(cr92)nr7, -(cr92)nc(o)r4, -(c(o)n(r4)2, -or4, and -(cr92)ncnor m is 4 and r20 is deuteriumr1 is selected from c1-c6alkyl and haloeach r11 is independently selected from h, halo and c1-c6alkylr12 is -(cr92)n-, -chr6-, -(cr92)no-, -nh-, -(cr92)nc(o)-, -(c(o)o(cr92)n-, -(cr92)noc(o)nr4-, -(cr92)nnr4c(o)(cr92)n-, -(cr92)nnr4c(o)-, or -(cr92)nnr4c(o)o-r2 is r3 or l2r3r3 is selected from an unsubstituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from n, o and s, a piperidinone, an oxazolidin-2-one, pyrrolidinone, a pyrrolidin-2-one and a substituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from n, o and s, wherein the substituted 4-6 membered heterocycloalkyl of r3 is substituted with 1-4 substituents independently selected from c1-c6alkyl halo, -cn, c1-c6haloalkyl, -or4, -(c(o)or4, -(c(o)r4, -(c(o)r7, -(c(o)or5, -(cr92)nor4, -(o(cr92)nor4, -(c(o)o(cr92)nor4, -n(r4)2, -(c(o)nr42, -nr4c(o)or4, -nr4c(o)(cr92)nor4, -nr4(cr92)nor4, -nr4s(o)2r4, r8, -(cr92)nr8, deuterated c1-c6alkoxy, -(o)2r4, -(s(o)2r7, -(s(o)2r8, -(s(o)2n(r4)2, -(s(o)2nhc(o)or4, -(s(o)2(cr92)nc(o)or4, s(o)2(cr92)nor4, a spiro attached dioxolane, a spiro attached dioxolane which is substituted with c1-c6alkyl, a spiro attached dioxane, a spiro attached tetrahydrofuran, a spiro attached oxetane, a spiro attached cyclobutanone, a spiro attached cyclobutanol, a c1 alkyl bridge, an unsubstituted 5-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from n, o and s and a 5-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from n, o and s substituted with 1-3 substituents independently selected from c1-c6alkyl, halo, c1-c6haloalkyl, c1-c6haloalkoxy, -or4 and r8each r4 is independently selected from h and c1-c6alkylr5 is an unsubstituted c3-c8cycloalkyl, an unsubstituted 5-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from n or o or a c3-c8cycloalkyl substituted with 1-3 substituents independently selected from c1-c6alkyleach r6 is independently selected from -nr4c(o)or4, -or4 and -(cr92)nor4each r7 is independently selected from c1-c6haloalkylr8 is selected from an unsubstituted phenyl, unsubstituted 5-6 membered heteroaryl with 1-3 heteroatoms independently selected from n, o and s, an unsubstituted 5 membered heteroaryl with 1-4 heteroatoms selected from n, an unsubstituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from n, o and s, a substituted phenyl, a substituted 5 membered heteroaryl with 1-4 heteroatoms selected from n, a substituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from n, o and s, a substituted c3-c8cycloalkyl, a substituted 5-6 membered heteroaryl with 1-4 heteroatoms selected from n, substituted c3-c8cycloalkyl and substituted 4-6 membered heterocycloalkyl of r8 are substituted with 1-3 substituents independently selected from c1-c6alkyl [me], -(c(r92)nr5, -(c(r92)nc(o)or4 and -(s(o)2r4t is 1, 2 or 3, andeach n is independently selected from 1, 2, 3 and 4.the compounds of formula (i) or formula (ii), pharmaceutically acceptable salts, solvates, n-oxides and isomers thereof, and pharmaceutical compositions provided herein also includes all suitable isotopic variations of such compounds, and pharmaceutically acceptable salts, solvates, n-oxides and isomers thereof, and pharmaceutical compositions. therefore, any formula given herein is also intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. isotopically labeled compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, and chlorine, such as 2h, 3h, 11c, 13c, 14c, 15n, 18f 31p, 32p, 35s, 36cl, 125i respectively. the invention includes various isotopically labeled compounds as defined herein, for example those into which radioactive isotopes, such as 3h and 14c, or those into which non-radioactive isotopes, such as 2h and 13c are present. such isotopically labelled compounds are useful in metabolic studies (with 14c), reaction kinetic studies (with, for example 2h or 3h), detection or imaging techniques, such as positron emission tomography (pet) or single-photon emission computed tomography (spect) including drug or substrate tissue distribution assays, or in radioactive treatment of patients. in particular, an 18f or labeled compound may be particularly desirable for pet or spect studies. isotopically-labeled compounds of formula (i) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying examples and preparations using an appropriate isotopically-labeled reagents in place of the non-labeled reagent previously employed.further, substitution with heavier isotopes, particularly deuterium (i.e., 2h or d) may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements or an improvement in therapeutic index. it is understood that deuterium in this context is regarded as a substituent of a compound of the formula (i). the concentration of such a heavier isotope, specifically deuterium, may be defined by the isotopic enrichment factor. the term "isotopic enrichment factor" as used herein means the ratio between the isotopic abundance and the natural abundance of a specified isotope. if a substituent in a compound of this invention is denoted deuterium, such compound has an isotopic enrichment factor for each designated deuterium atom of at least 3500 (52.5 percent deuterium incorporation at each designated deuterium atom), at least 4000 (60 percent deuterium incorporation), at least

4500 (67.5 percent deuterium incorporation), at least 5000 (75 percent deuterium incorporation), at least 5500 (82.5 percent deuterium incorporation), at least 6000 (90 percent deuterium incorporation), at least 6333.3 (95 percent deuterium incorporation), at least 6466.7 (97 percent deuterium incorporation), at least 6600 (99 percent deuterium incorporation), or at least 6633.3 (99.5 percent deuterium incorporation).pharmaceutically acceptable solvates in accordance with the invention include those wherein the solvent of crystallization may be isotopically substituted, e.g. d₂o, d₆-acetone, d₆-dms_o.compounds of the invention, i.e. compounds of formula (i) and formula (ii) that contain groups capable of acting as donors and/or acceptors for hydrogen bonds may be capable of forming co-crystals with suitable co-crystal formers. these co-crystals may be prepared from compounds of formula (i) by known co-crystal forming procedures. such procedures include grinding, heating, co-subliming, co-melting, or contacting in solution compounds of formula (i) with the co-crystal former under crystallization conditions and isolating co-crystals thereby formed. suitable co-crystal formers include those described in wo 2004/078163. hence the invention further provides co-crystals comprising a compound of formula (i) and formula (ii).processes for making compounds of formula (i) or formula (ii)general procedures for preparing compounds of formula (i) or formula (ii) are described in the examples, infra. in the reactions described, reactive functional groups, for example hydroxy, amino, imino, thio or carboxy groups, where these are desired in the final product, may be protected to avoid their unwanted participation in the reactions. conventional protecting groups may be used in accordance with standard practice (see e.g., t. w. greene and p. g. m. wuts in "protective groups in organic chemistry," john wiley and sons, 1991).in certain embodiments, the compounds of formula (i) or formula (ii) provided herein are prepared as a pharmaceutically acceptable acid addition salt by reacting the free base form of the compound of formula (i) or formula (ii) with a stoichiometric amount of an appropriate pharmaceutically acceptable organic acid or inorganic acid or a suitable anion exchange reagent. in other embodiments, a pharmaceutically acceptable base addition salt of compounds of formula (i) or formula (ii) is prepared by reacting the free acid form of the compound of formula (i) or formula (ii) with a stoichiometric amount of an appropriate pharmaceutically acceptable organic base or inorganic base or a suitable ion exchange reagent. such reactions are typically carried out in water or in an organic solvent, or in a mixture of the two. generally, use of non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile is desirable, where practicable.alternatively, the salt forms of the compounds of formula (i) or formula (ii) are prepared using salts of the starting materials or intermediates. in certain embodiments, the compounds of formula (i) or formula (ii) are in the form of other salts including, but not limited to, oxalates and trifluoroacetates. in certain embodiments, hemisalts of acids and bases are formed, for example, hemisulphate and hemicalcium salts.such pharmaceutically acceptable acid addition salts of compounds of formula (i) or formula (ii) include, but are not limited to, a hydrobromide, hydrochloride, sulfate, nitrate, succinate, maleate, formate, acetate, adipate, besylate, bicarbonate/carbonate, propionate, fumarate, citrate, tartrate, lactate, benzoate, salicylate, glutamate, aspartate, p-toluenesulfonate, benzenesulfonate, methanesulfonate, ethanesulfonate, ethanedisulfonate, camphorsulfonate, chlorotheophyllonate, naphthalenesulfonate (e.g. 2-naphthalenesulfonate), hexanoate salt, bisulphate/sulphate, borate, camsylate, cyclamate, edisylate, esylate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hippurate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactobionate, laurylsulphate, malate, malonate, mandelate, mesylate, methylsulphate, naphthoate, napsylate, naphthylate, 2-napsylate, nicotinate, octadecanoate, oleate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, polygalacturonate, pyroglutamate, saccharate, stearate, sulfosalicylate, tannate, tosylate, trifluoroacetate and xinofoate salts.the organic acid or inorganic acids used to form certain pharmaceutically acceptable acid addition salts of compounds of formula (i) or formula (ii) include, but are not limited to, hydrobromic acid, hydrochloric acid, sulfuric acid, nitric acid, phosphoric acid, succinic acid, maleic acid, malonic acid, mandelic acid, formic acid, acetic acid, propionic acid, glycolic acid, oxalic acid, fumaric acid, citric acid, tartaric acid, lactic acid, benzoic acid, salicylic acid, glutamic acid, aspartic acid, toluenesulfonic acid, sulfosalicylic acid, benzenesulfonic acid, methanesulfonic acid, ethanesulfonic acid, naphthalenesulfonic acid, such as 2-naphthalenesulfonic acid, or hexanoic acid.such pharmaceutically acceptable base addition salt of compounds of formula (i) or formula (ii) include, but are not limited to, ammonium, aluminium, arginine, benzathine, calcium, choline, copper, diethylamine, diolamine, glycine, isopropylamine, choline, diethanolamine, piperazine, iron, lysine, magnesium, meglumine, olamine, potassium, silver, sodium, tromethamine and zinc salts.the organic or inorganic bases used to form certain pharmaceutically acceptable base addition salt of compounds of formula (i) or formula (ii) include, but are not limited to, salts derived from ammonium salts and metals from columns i to xii of the periodic table, or salts derived from primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like.in certain embodiments, the free acid or free base forms of the compounds of formula (i) or formula (ii) provided herein are prepared from the corresponding base addition salt or acid addition salt from, respectively. for example a compound formula (i) in an acid addition salt form is converted to the corresponding free base by treating with a suitable base (by way of example only, an ammonium hydroxide solution, a sodium hydroxide, and the like). for example, a compound of formula (i) in a base addition salt form is converted to the corresponding free acid by treating with a suitable acid (by way of example only, hydrochloric acid).lists of additional suitable salts can be found, e.g., in "remington's pharmaceutical sciences", 20th ed., mack publishing company, easton, pa., (1985) and in "handbook of pharmaceutical salts: properties, selection, and use" by stahl and wermuth (wiley-vch, weinheim, germany, 2002).in certain embodiments, compounds of formula (i) or formula (ii) in unoxidized form are prepared from n-oxides of compounds formula (i) or formula (ii) by treating with a reducing agent (by way of example only, sulfur, sulfur dioxide, triphenyl phosphine, lithium borohydride, sodium borohydride, phosphorus trichloride, tribromide, or the like) in a suitable inert organic solvent (by way of example only, acetonitrile, ethanol, aqueous dioxane, or the like) at 0 to 80 degrees centigrade in certain embodiments, compounds of formula (i) or formula (ii) are prepared as protected derivatives using methods known to those of ordinary skill in the art. a detailed description of the techniques applicable to the creation of protecting groups and their removal can be found in t. w. greene, "protecting groups in organic chemistry," 3rd edition, john wiley and sons, inc., 1999. in certain embodiments, compounds of formula (i) or formula (ii) are prepared or formed, as solvates (e.g., hydrates). in certain embodiments, hydrates of compounds of formula (i) or formula (ii) are prepared by recrystallization from an aqueous/organic solvent mixture, using organic solvents such as dioxin, tetrahydrofuran or methanol.furthermore, the compounds of the present invention, including their salts, can also be obtained in the form of their hydrates, or include other solvents used for their crystallization. the compounds of the present invention may inherently or by design form solvates with pharmaceutically acceptable solvents (including water) therefore, it is intended that the invention embrace both solvated and unsolvated forms. the term "solvate" refers to a molecular complex of a compound of the present invention (including pharmaceutically acceptable salts thereof) with one or more solvent molecules. such solvent molecules are those commonly used in the pharmaceutical art, which are known to be innocuous to the recipient, e.g., water, ethanol, and the like. the term "hydrate" refers to the complex where the solvent molecule is water. the compounds of the present invention, including salts, hydrates and solvates thereof, may inherently or by design form polymorphs.any asymmetric atom (e.g., carbon or the like) of the compound(s) of the present invention can be present in racemic or enantiomerically enriched, for example the (r)-, (s)- or (r,s)-configuration. in certain embodiments, each asymmetric atom has at least 50 percent enantiomeric excess, at least 60 percent enantiomeric excess, at least 70 percent enantiomeric excess, at least 80 percent enantiomeric excess, at least 90 percent enantiomeric excess, at least 95 percent enantiomeric excess, or at least 99 percent enantiomeric excess in the (r)- or (s)-configuration. substituents at atoms with unsaturated double bonds may, if possible, be present in cis-(z)- or trans-(e)-form.accordingly, as used herein a compound of the present invention can be in the form of one of the possible isomers, rotamers, atropisomers, tautomers or mixtures thereof, for example, as substantially pure geometric (cis or trans) isomers, diastereomers, optical isomers (antipodes), racemates or mixtures thereof.any resulting mixtures of isomers can be separated on the basis of the physicochemical differences of the constituents, into the pure or substantially pure geometric or optical isomers, diastereomers, racemates, for example, by chromatography and/or fractional crystallization.any resulting racemates of final products or intermediates can be resolved into the optical antipodes by known methods, e.g., by separation of the diastereomeric salts thereof, obtained with an optically active acid or base, and liberating the optically active acidic or basic compound. in particular, a basic moiety may thus be employed to resolve the compounds of the present invention into their optical antipodes, e.g., by fractional crystallization of a salt formed with an optically active acid, e.g., tartaric acid, dibenzoyl tartaric acid, diacetyl tartaric acid, di-o,o'-p-toluoyl tartaric acid, mandelic acid, malic acid or camphor-10-sulfonic acid. racemic products can also be resolved by chiral chromatography, e.g., high pressure liquid chromatography (hplc) using a chiral adsorbent.in certain embodiments, compounds of formula (i) or formula (ii) are prepared as their individual stereoisomers. in other embodiments, the compounds of formula (i) or formula (ii) provided herein are prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds, separating the diastereomers and recovering the optically pure enantiomers. in certain embodiments, resolution of enantiomers is carried out using covalent diastereomeric derivatives of the compounds of formula (i) or formula (ii), or by using dissociable complexes (e.g., crystalline diastereomeric salts). diastereomers have distinct physical properties (e.g., melting points, boiling points, solubility, reactivity, etc.) and are readily separated by taking advantage of these dissimilarities. in certain embodiments, the diastereomers are separated by chromatography, or by separation/resolution techniques based upon differences in solubility. the optically pure enantiomer is then recovered, along with the resolving agent, by any practical means that would not result in racemization. a more detailed description of the techniques applicable to the resolution of stereoisomers of compounds from their racemic mixture can be found in jean jacques, andre collet, samuel h. wilen, "enantiomers, racemates and resolutions," john wiley and sons, inc., 1981.mixtures of isomers obtainable according to the invention can be separated in a manner known to those skilled in the art into the individual isomers diastereoisomers can be separated, for example, by partitioning between polyphasic solvent mixtures, recrystallisation and/or chromatographic separation, for example over silica gel or by e.g. medium pressure liquid chromatography over a reversed phase column, and racemates can be separated, for example, by the formation of salts with optically pure salt-forming reagents and separation of the mixture of diastereoisomers so obtainable, for example by means of fractional crystallisation, or by chromatography over optically active column materials.depending on the choice of the starting materials and procedures, certain embodiments of the compounds of the present invention are present in the form of one of the possible isomers or as mixtures thereof, for example as pure optical isomers, or as isomer mixtures, such as racemates and diastereoisomer mixtures, depending on the number of asymmetric carbon atoms. the present invention is meant to include all such possible isomers, including racemic mixtures, diastereomeric mixtures and optically pure forms. optically active (r-) and (s)-isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. if the compound contains a double bond, the substituent may be e or z configuration. if the compound contains a disubstituted cycloalkyl, the cycloalkyl substituent may have a cis- or trans-configuration. all tautomeric forms are also intended to be included.compounds of formula (i) or formula (ii) are made by processes described herein and as illustrated in the examples. intermediates and final products can be worked up and/or purified according to standard methods, e.g. using chromatographic methods, distribution methods, (re-) crystallization, and the like. the invention relates also to those forms of the process in which a compound obtainable as an intermediate at any stage of the process is used as starting material and the remaining process steps are carried out, or in which a starting material is formed under the reaction conditions or is used in the form of a derivative, for example in a protected form or in the form of a salt, or a compound obtainable by the process according to the invention is produced under the process conditions and processed further in situ. all starting materials, building blocks, reagents, acids, bases, dehydrating agents, solvents and catalysts utilized to synthesize the compounds of the present invention are either commercially available or can be produced by organic synthesis methods known to one of ordinary skill in the art.non-limiting examples of synthetic schemes used to make compounds of the invention are illustrated in reaction schemes (i)-(iv). the r₁, r₂₀, r₁₁ and r₂ groups as defined herein.scheme (i) illustrates the synthesis of compounds of formula (i) by coupling the amine with the carboxylic acid in the presence of a base and a coupling reagent. by way of example only, the coupling reagent is hatu and the base is diisopropylethylamine.[ftimg=68000047]scheme (ii) illustrates the synthesis of compounds of formula (ii) by coupling the amine with the carboxylic acid in the presence of a base and a coupling reagent. by way of example only, the coupling reagent is hatu and the base is diisopropylethylamine.[ftimg=68000048]scheme (iii) illustrates the synthesis of compounds of formula (i) by formation of the oxadiazole from the corresponding n'-hydroxyformimidamide and carboxylic acid.[ftimg=68000049]scheme (iv) illustrates the synthesis of compounds of formula (ii) by formation of the oxadiazole from the corresponding n'-hydroxyformimidamide and carboxylic acid.[ftimg=68000050]the examples provided herein are offered to illustrate, but not to limit, the compounds of formula (i) or formula (ii) provided herein, and the preparation of such compounds.pharmacology and utilityprotein tyrosine kinases (ptk) play a central role in the regulation of a wide variety of cellular processes and maintaining control over cellular function. protein kinases catalyze and regulate the process of phosphorylation, whereby the kinases covalently attach phosphate groups to proteins or lipid targets in response to a variety of extracellular signals. examples of such stimuli include hormones, neurotransmitters, growth and differentiation factors, cell cycle events, environmental stresses and nutritional stresses. an extracellular stimulus may affect one or more cellular responses related to cell growth, migration, differentiation, secretion of hormones, activation of transcription factors, muscle contraction, glucose metabolism, control of protein synthesis, and regulation of the cell cycle.many diseases are associated with abnormal cellular responses triggered by protein kinase-mediated events. these diseases include, but are not limited to, autoimmune diseases, inflammatory diseases, bone diseases, metabolic diseases, neurological and neurodegenerative diseases, cancer, cardiovascular diseases, respiratory diseases, allergies and asthma, alzheimer's disease, and hormone-related diseases.examples of protein-tyrosine kinases include, but are not limited to, (a) tyrosine kinases such as irk, igfr-1, zap-70, bmx, btk, chk (csk homologous kinase), csk (c-terminal src kinase), itk-1, src (c-src, lyn, fyn, ick, syk, hck, yes, blk, fgr and frk), tec, txk/rlk, abl, egfr (egfr-1/erb-1, erb-2/neu/her-2, erb-3 and erb-4), fak, fgfr1r (also fgfr1 or fgr-1), fgfr2r (also fgr-2), met (also met-i or c-met), pdgfr (a and beta), tie-1, tie-2 (also tek-1 or tek), vegfr1 (also flt-1), vegfr2 (also kdr), flt-3, flt-4, c-kit, jak1, jak2, jak3, tyk2, lok, ret, trka, pyk2, alk (anaplastic lymphoma kinase), epha (1-8), ephb (1-6), ron, fes, fer or ephb4 (also ephb4-1), and (b) and serine/threonine kinases such as aurora, c-raf, sgk, map kinases (e.g., mkk4, mkk6, etc.), sapk2a, sapk2 beta, ark, atm (1-3), camk (1-iv), camkk, chk1 and 2 (checkpoint kinases), ck1, ck2, erk, ikk-i (also ikk-a or chuk), ikk-2 (also ikk- beta), ilk, jnk (1-3), limk (1 and 2), mlk3raf (a, b, and c), cdk (1-10), pkc (including all pkc subtypes), plk (1-3), nik, pak (1-3), pdk1, pkr, rhok, rip, rip-2, gsk3 (a and beta), pka, p38, erk (1-3), pkb (including all pkb subtypes) (also akt-1, akt-2, akt-3 or akt3-1), irak, frk, sgk, tak1 and tp1-2 (also cot).phosphorylation modulates or regulates a variety of cellular processes such as proliferation, growth, differentiation, metabolism, apoptosis, motility, transcription, translation and other signaling processes. aberrant or excessive ptk activity has been observed in

many disease states including, but not limited to, benign and malignant proliferative disorders, diseases resulting from inappropriate activation of the immune system and diseases resulting from inappropriate activation of the nervous systems. specific diseases and disease conditions include, but are not limited to, autoimmune disorders, allograft rejection, graft vs. host disease, diabetic retinopathy, choroidal neovascularization due to age-related macular degeneration, psoriasis, arthritis, osteoarthritis, rheumatoid arthritis, synovial pannus invasion in arthritis, multiple sclerosis, myasthenia gravis, diabetes mellitus, diabetic angiopathy, retinopathy of prematurity, infantile hemangiomas, non-small cell lung, bladder and head and neck cancers, prostate cancer, breast cancer, ovarian cancer, gastric and pancreatic cancer, psoriasis, fibrosis, rheumatoid arthritis, atherosclerosis, stenosis, auto-immune disease, allergy, respiratory diseases, asthma, transplantation rejection, inflammation, thrombosis, retinal vessel proliferation, inflammatory bowel disease, crohn's disease, ulcerative colitis, bone diseases, transplant or bone marrow transplant rejection, lupus, chronic pancreatitis, cachexia, septic shock, fibroproliferative and differentiative skin diseases or disorders, central nervous system diseases, neurodegenerative diseases, disorders or conditions related to nerve damage and axon degeneration subsequent to brain or spinal cord injury, acute or chronic cancer, ocular diseases, viral infections, heart disease, lung or pulmonary diseases or kidney or renal diseases and bronchitis. tyrosine kinases can be broadly classified as receptor-type (having extracellular, transmembrane and intracellular domains) or the non-receptor type (being wholly intracellular) protein tyrosine kinases. tyrosine kinases transfer the terminal phosphate of atp to tyrosine residues of proteins thereby activating or inactivating signal transduction pathways. inappropriate or uncontrolled activation of many of these kinase (aberrant protein tyrosine kinase activity), for example by over-expression or mutation, results in uncontrolled cell growth. many of the protein tyrosine kinases, whether a receptor or non-receptor tyrosine kinase have been found to be involved in cellular signaling pathways involved in numerous pathogenic conditions, including, but not limited to, immunomodulation, inflammation, or proliferative disorders such as cancer. ckitmast cells are tissue elements derived from a particular subset of hematopoietic stem cells that express cd34, c-kit and cd13 antigens. mast cells are characterized by their heterogeneity, not only regarding tissue location and structure but also at the functional and histochemical levels. immature mast cell progenitors circulate in the bloodstream and differentiate into various tissues. these differentiation and proliferation processes are under the influence of cytokines, one of importance being stem cell factor (scf), also termed c-kit ligand, steel factor or mast cell growth factor. the stem cell factor receptor is encoded by the protooncogene, c-kit, which is expressed in hematopoietic progenitor cells, mast cells, germ cells, interstitial cells of cajal (icc), and some human tumors, and is also expressed by non hematopoietic cells. stem cell factor (scf), also known as c-kit ligand, is the primary regulating factor for human mast cell growth and function. the scf receptor, c-kit receptor, is a type ii transmembrane receptor protein tyrosine kinase which initiates cell growth and proliferation signal transduction cascades in response to scf binding. ligation of c-kit receptor by scf induces its dimerization followed by its transphosphorylation, leading to the recruitment and activation of various intracytoplasmic substrates. these activated substrates induce multiple intracellular signaling pathways responsible for cell proliferation and activation. these proteins are known to be involved in many cellular mechanisms, which in case of disruption, lead to disorders such as abnormal cell proliferation and migration, as well as inflammation. the relationship between mast cells, scf and c-kit receptor is discussed in the following references: huang, e. et al., "the hematopoietic growth factor kl is encoded by the sl locus and is the ligand of the c-kit receptor, the gene product of the w locus", cell, 63, 225-233, 1990 zsebo, k. m. et al., "stem cell factor is encoded at the sl locus of the mouse and is the ligand for the c-kit tyrosine kinase receptor", cell, 63, 213-224, 1990 zhang, s. et al., "cytokine production by cell cultures from bronchial subepithelial myofibroblasts", j. pathol., 180, 95-10, 1996 zhang, s. et al., "human mast cells express stem cell factor", j. pathol., 186, 59-66, 1998 kassel, o. et al., "up and down-regulation by glucocorticoids of the constitutive expression of the mast cell growth factor stem cell factor by human lung fibroblasts in culture", 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1992, and kinashi, t. et al., "steel factor and c-kit regulate cell-matrix adhesion", blood, 83, 1033-1038, 1994. the following references discuss the c-kit signaling pathway and its relationship with various downstream pathways and the relationship with diseases associated with mast cells: thommes, k. et al., "identification of tyr-703 and tyr-936 as the primary association sites for grb2 and grb7 in the c-kit/stem cell factor receptor", biochem. j. 341, 211-216, 1999 ishizuka, t. et al., "stem cell factor augments fc epsilon r1-mediated tnfr-alpha production and stimulates map kinases via a different pathway in mc/9 mast cells", j. immunol., 161, 3624-3630, 1998 timokhina, i. et al., "kit signaling through pi 3-kinase and src kinase pathways: an essential role for rac1 and jnk activation in mast cell proliferation", embo j., 17, 6250-6262, 1998 tang, b. et al., "tec kinase associates with c-kit and is tyrosine phosphorylated and activated following stem cell factor binding", mol. cell. biol., 14, 8432-8437, 1994, and ueda. s. et al., "critical roles of c-kit tyrosine residues 567 and 719 in stem cell factor-induced chemotaxis: contribution of src family kinase and pi3-kinase on calcium mobilization and cell migration", blood, 99, 3342-3349, 2002. mast cells are the primary effector cells in allergic inflammation. mast cells are also involved in other pathogenic processes such as acute inflammation and fibrosis. mast cells present in tissues of patients are implicated in or contribute to the genesis of diseases such as autoimmune diseases (multiple sclerosis, rheumatoid arthritis, inflammatory bowel diseases (ibd)), allergic diseases (allergic rhinitis, allergic sinusitis, anaphylactic syndrome, urticaria, angioedema, atopic dermatitis, allergic contact dermatitis, erythema nodosum, erythema multiforme, cutaneous necrotizing venulitis and insect bite skin inflammation and bronchial asthma), tumor angiogenesis, germ cell tumors, mast cell tumors, gastrointestinal stromal tumors, small-cell lung cancer, melanoma, breast cancer, acute myelogenous leukemia, glioblastoma, neuroblastoma and mastocytosis, inflammatory diseases, diabetes, type i diabetes, type ii diabetes, irritable bowel syndrome (ibs), cns disorders and interstitial cystitis. in these diseases, mast cells participate in the destruction of tissues by releasing a cocktail of different proteases and mediators categorized into three groups: preformed granule-associated mediators (histamine, proteoglycans, and neutral proteases), lipid-derived mediators (prostaglandins, thromboxanes and leukotrienes), and various cytokines ((il-1, il-2, il-3, il-4, il-5, il-6, il-8, tnfr-a, gm-csf, mip-la, mip-i beta, mip-2 and ifn-gamma). the liberation by activated mast cells of mediators (tnfr-a, histamine, leukotrienes, prostaglandins etc.) as well as proteases may i) induce inflammation and vasodilatation and ii) participate in the tissue destruction process. in addition, mast cell activation induces diverse effector responses, such as secretion of allergic mediators, proteases, chemokines such as mcp-1 and rantes, leukotrienes, prostaglandins and neurotrophins and induction of cytokine gene transcription (il-4, il-5, il-6, il-13, tnfr-a and gm-csf). these mediators contribute to creating the asthmatic phenotype by their effects on endothelial cells, smooth muscle cells and fibroblasts and on extracellular matrix, and by recruiting other inflammatory cells. asthma is characterized by airflow obstruction, bronchial hyper responsiveness and airway inflammation. airway inflammation is the major factor in the development and perpetuation of asthma. in allergic asthma, allergens are thought to initiate the inflammatory process by inducing a t-lymphocyte mediated response (th2) that results in the production of allergen-specific ige. ige binds to its high-affinity receptor fc epsilon r1 on pulmonary mast cells, triggering a type i (ige-mediated) immediate allergic response. thus, mast cells play a role in asthma. the activation of mast cells by different stimuli such as stress, trauma, infection and neurotransmitters, also participate in the exacerbation of the chemical imbalance causing cns disorders. more specifically, mast cell degranulation is stimulated by common neurotransmitters such as neurotensin, somatostatin, substance p and acetylcholine, by growth or survival factors, notably such as ngf. mast cells involved in the response to such stimulus can be brain mast cells but also other mast cells releasing the content of their granules in the blood stream that ultimately reach sensory, motor or brain neurons. following mast cells activation, released granules liberate various factors capable of modulating and altering neurotransmission and neurons survival. among such factors, serotonin is important since an increase of the level of free serotonin has been observed in depressed patients. alternatively, the sudden burst of serotonin may be followed by a period of serotonin shortage, leading to pain and migraine. as a consequence, it is believed that mast cells exacerbate in autocrine or paracrine manner the deregulation of neurotransmission. for example, anxiety or stress-induced release of neurotransmitters such as serotonin activates mast cells, which in turn release the content of their granules, further contributing to the chemical imbalance in the brain leading to cns disorders. other mediators released by mast cells can be categorized into vasoactive, nociceptive, proinflammatory and other neurotransmitters. taken together, these factors are able to induce disturbance in the activity of neurons, whether they are sensory, motor, or cns neurons. in addition, patients afflicted with mastocytosis are more inclined to develop cns disorders than the normal population. this can be explained by the presence of activating mutations in the c-kit receptor, which induce degranulation of mast cells and a burst of factors contributing to chemical imbalance and neurotransmission alteration. the activation of mast cells by different drugs, including, but not limited to, salicylic derivatives, morphine derivatives, opioids, heroin, amphetamines, alcohol, nicotine, analgesics, anesthetics, and anxiolytics results in the degranulation of mast cells, which participate in the exacerbation of the chemical imbalance responsible for drug habituation and withdrawal syndrome. following mast cells activation, released granules liberate various factors capable of modulating and altering neurotransmission. among such factors is morphine which is bound or stored in mast cells granules. tobacco smoke also induces the release of mediators from canine mast cells and modulates prostaglandin production leading to asthma. in addition, patients afflicted with mastocytosis are more inclined to develop substance use disorders than the normal population. this can be explained by the presence of activating mutations in the c-kit receptor, which induce degranulation of mast cells and a burst of factors contributing to chemical imbalance and neurotransmission alteration. mast cells have also been identified to be involved in or to contribute to drug dependence and withdrawal symptoms. the relationship between mast cells, scf and c-kit kinase in various diseases is discussed in the following references: oliveira et al., "stem cell factor: a hemopoietic cytokine with important targets in asthma", current drug targets, 2: 313-318, 2003 puxeddu et al., "mast cells in allergy and beyond", the international journal of biochemistry and cell biology, 35: 1601-1607, 2003 rottem et al., "mast cells and autoimmunity", autoimmune reviews, 4: 21-27, 2005 woolley, d. e. et al., "the mast cell in inflammatory arthritis", n. engl. j. med., 348:1709-1711, 2003 benoit, c. et al., "mast cells in autoimmune disease", nature, 420:875-878, 2002 nigrovic, p. a. et al., "mast cells in inflammatory arthritis", arthritis res. ther., 7:1-11, 2005 wang, 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and the normal functional activity of this c-kit gene product is important for the maintenance of normal hematopoiesis, melanogenesis, genotogenesis, and growth and differentiation of mast cells. inhibition of c-kit kinase activity reduces the growth and differentiation of mast cells and thereby mediates the diseases and/or conditions associated with mast cells, such as autoimmune diseases, multiple sclerosis, rheumatoid arthritis, inflammatory bowel diseases (ibd), respiratory diseases, allergic diseases, allergic rhinitis, allergic sinusitis, anaphylactic syndrome, urticaria, angioedema, atopic dermatitis, allergic contact dermatitis, erythema nodosum, erythema multiforme, cutaneous necrotizing venulitis and insect bite skin inflammation, bronchial asthma, tumor angiogenesis, germ cell tumors, mast cell tumors, gastrointestinal stromal tumors, small-cell lung cancer, melanoma, breast cancer, acute myelogenous leukemia, glioblastoma, neuroblastoma and mastocytosis, inflammatory diseases, diabetes, type i diabetes, type ii diabetes, irritable bowel syndrome (ibs), cns disorders and interstitial cystitis in addition to its importance in normal cellular physiologic activities, c-kit kinase plays a role in the biological aspects of certain human cancers, and unregulated c-kit kinase activity is implicated in the pathogenesis of human cancers, and in certain tumors types. proliferation of tumor cell growth mediated by c-kit can occur by a specific mutation of the c-kit polypeptide that results in ligand independent activation or by autocrine stimulation of the receptor. in the former case, mutations that cause constitutive activation of c-kit kinase activity in the absence of scf binding are implicated in malignant human cancers, including germ cell tumors, mast cell tumors, gastrointestinal stromal tumors, small-cell lung cancer, melanoma, breast cancer, acute myelogenous leukemia, glioblastoma, neuroblastoma and mastocytosis. a proliferation assay for the evaluation of the efficacy of c-kit inhibitors and pdgfr inhibitors is given in kuriu et al., "proliferation of human myeloid leukemia cell line associated with the tyrosine-phosphorylation and activation of the proto-oncogene c-kit product", blood, 78(11): 2834-2840, 1991 heinrich et al., "inhibition of c-kit receptor tyrosine kinase activity by sti571, a selective tyrosine kinase inhibitor", blood, 96(3): 925-932, 2000 buchdunger et al., "abl protein-tyrosine kinase inhibitor sti571 inhibits in vitro signal transduction mediated by c-kit and platelet-derived growth factor receptors", the journal of pharmacology and experimental therapeutics, 295(1): 139-145,

2000 and simlich et al., "the antiangiogenic protein kinase inhibitors su5416 and su6668 inhibit the sce receptor (c-kit) in a human myeloid leukemia cell line and in acute myeloid leukemia blasts", blood, 97(5): 1413-1421, 2001. this assay use mo7e cells, which are a human promegakaryocytic leukemia cell line that depend on scf for proliferation. these references in combination with berlin et al., ekland et al., and miyachi et al., (cited above) show that that a c-kit kinase inhibitor screened via this proliferation assay was later found to treat rheumatoid arthritis and asthma.in addition, a compound that was initially evaluated for its efficacy as a c-kit inhibit) using a proliferation assay based on ba/f3 cells and ba/f3-derived cells (see wo 2004/01903) was later found to be effective in the treatment of mast cell tumours and asthma (see bellamy f, et al., "pharmacokinetics of mastinib in cats", vet. res. commun., june 16 (epub) 2009 hahn k. a. et al., "mastinib is safe and effective for treatment of canine mast cell tumours, j. vet. intern. med., 22, 1301-1309, 2008 and humbert m. et al., "mastinib, a c-kit/pdgfr receptor tyrosine kinase inhibitor, improves disease control in severe corticosteroid-dependent asthmatics", 64, 1194-1201, 2009. c-kit receptor has a substantial homology to the pdgfr receptor and to the csf-1 receptor (c-fms).platelet-derived growth factor (pdgf) receptor familypdgf (platelet-derived growth factor) is commonly occurring growth factor which plays an important role both in normal growth and in pathological cell proliferation. by way of example, such as that observed in carcinogenesis and in diseases of the smooth-muscle cells of blood vessels, for example in atherosclerosis and thrombosis. the pdgf growth factor family consists of pdgf-a, pdgf-b, pdgf-c and pdgf-d, which form either homo- or heterodimers (aa, ab, bb, cc, dd) that bind to the protein tyrosine kinase receptors pdgfr-a and pdgfr- beta. dimerization of the growth factors is a prerequisite for activation of the kinase, as the monomeric forms are inactive. the two receptor isoforms dimerize upon binding resulting in three possible receptor combinations, pdgfr-aa, pdgfr- beta beta and pdgfra beta. growth factor aa binds only to -aa, growth factor bb can bind with -aa, - beta beta and -a beta, growth factors cc and ab specifically interact with -aa and -a beta, and growth factor dd binds to - beta beta pp. the pdgf-receptor plays an important role in the maintenance, growth and development of hematopoietic and non-hematopoietic cells.key downstream mediators of pdgfr signaling are ras/mitogen-activated protein kinase (mapk), pi-3 kinase and phospholipase-gamma (plcgamma) pathways. mapk family members regulate various biological functions by phosphorylation of target molecules (transcription factors and other kinases) and thus contribute to regulation of cellular processes such as proliferation, differentiation, apoptosis and immunoresponses. pi-3 kinase activation generated pip3 which functions as a second messenger to activate downstream tyrosine kinases btk and itk, the ser/thr kinases pdk1 and akt (pkb). akt activation is involved in survival, proliferation and cell growth. after activation plc hydrolyses its substrate, ptdlns(4,5)p2, and forms two secondary messengers, diacylglycerol and ins(1,4,5)p3 which stimulates intracellular processes such as proliferation, angiogenesis and cell motility.pdgfr is expressed on early stem cells, mast cells, myeloid cells, mesenchymal cells and smooth muscle cells. only pdgfr- beta is implicated in myeloid leukemias-usually as a translocation partner with tel, huntingtin interacting protein (hip1) or rabaptin5. activation mutations in pdgfr-a kinase domain are associated with gastrointestinal stromal tumors (gist).certain embodiments of compounds of formula (i) and formula (ii) provided herein inhibit pdgf receptor (pdgfra and pdgfrp) activity and c-kit kinase activity, and are useful for the treatment of diseases, which respond to an inhibition of the pdgf receptor kinase. therefore, certain compounds of formula (i) and formula (ii) provided herein are useful for the treatment of tumor diseases, such as gliomas, sarcomas, prostate tumors, small cell lung cancer and tumors of the colon, breast, and ovary. in addition certain embodiments of compounds of formula (i) and formula (ii) provided herein are useful to treat disorders, such as thrombosis, psoriasis, scleroderma, fibrosis, asthma, metabolic diseases and hyper eosinophilia. compounds of formula (i) and formula (ii) provided herein are also effective against diseases associated with vascular smooth-muscle cell migration and proliferation, such as restenosis and atherosclerosis.patients with obliterative bronchiolitis (ob), a chronic rejection of allogenic lung transplants, often show an elevated pdgf concentration in bronchoalveolar lavage fluids. in certain embodiments, compounds of formula (i) and formula (ii) provided herein exhibit useful effects in the treatment of disorders arising as a result of transplantation, for example, allogenic transplantation, especially tissue rejection, such as obliterative bronchiolitis (ob).in certain embodiments, compounds of formula (i) and formula (ii) provided herein are useful for the protection of stem cells, for example to combat the hemotoxic effect of chemotherapeutic agents, such as 5-fluorouracil.the compounds of formula (i) and formula (ii) provided herein, and the pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the n-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, are inhibitors of c-kit kinase activity or are inhibitors of c-kit kinase activity and pdgfr (a and beta) kinase activity. in certain embodiments, the compounds of formula (i) and formula (ii) provided herein, and the pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the n-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, are inhibitors of c-kit kinase activity and pdgfr (a and beta) kinase activity. in other embodiments, the compounds of formula (i) and formula (ii) provided herein, and the pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the n-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, are inhibitors of either c-kit kinase activity. such compounds of formula (i) and formula (ii) provided herein, and the pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the n-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, are useful for treating diseases or disorders in which c-kit kinase, or c-kit and pdgfr (a and/or beta) kinase, contributes to the pathology and/or symptomology of a disease or disorder. such diseases or disorders include, but are not limited to, a mast cell associated disease, inflammatory diseases, respiratory diseases, an allergy disorder, fibrosis diseases, metabolic diseases, autoimmune diseases, a cns related disorder, a neurodegenerative disorder, neurological diseases, dermatological diseases, a graft-versus-host disease, a pain condition, a neoplastic disorder, a cardiovascular disease and cancer.non-limiting examples of such diseases include asthma, allergic rhinitis, allergic sinusitis, bronchial asthma, irritable bowel syndrome (ibs), inflammatory bowel disease (ibd), pulmonary arterial hypertension (pah), idiopathic arterial hypertension (ipah), primary pulmonary hypertension (pph), pulmonary fibrosis, liver fibrosis, cardiac fibrosis, scleroderma, urticaria, dermatoses, atopic dermatitis, allergic contact dermatitis, diabetes, type i diabetes, type ii diabetes, rheumatoid arthritis, multiple sclerosis, cytopenias (by way of example only, anemia, leucopenia, neutropenia, thrombocytopenia, granulocytopenia, pancytopenia and idiopathic thrombocytopenic purpura), systemic lupus erythematosus, chronic obstructive pulmonary disease (copd), adult respiratory distress syndrome (ards), ulcerative colitis, crohns disease, psoriasis, lymphomas (by way of example only, b and t cell lymphomas), myelodysplastic syndrome, breast cancer, pancreatic cancer, papillary thyroid carcinoma, ovarian carcinoma, human adenoid cystic carcinoma, non small cell lung cancer, secretory breast carcinoma, congenital fibrosarcoma, congenital mesoblastic nephroma, acute myelogenous leukemia, chronic myeloid leukemia metastasis, cancer-related pain, neuroblastoma, osteosarcoma, melanoma, bone metastases, a tumor of breast, renal, lung, prostate, pancreas, colon, ovary, thyroid, colorectal tumors, neuronal tumors, uterine tumors, gastrointestinal stromal tumors (gist), gliomas, sarcomas, tumor angiogenesis, germ cell tumors, mast cell tumors, glioblastoma, neuroblastoma, mastocytosis, osteoporosis, hyper eosinophilia, restenosis, atherosclerosis, anaphylactic syndrome, angioedema, erythema nodosum, erythema multiforme, cutaneous necrotizing venulitis, insect bite skin inflammation, cns disorders and interstitial cystitis.in certain embodiments, the compounds of formula (i) and formula (ii) provided herein, and the pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the n-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, are useful for treating diseases or disorders in which c-kit kinase contributes to the pathology and/or symptomology of a disease or disorder. non-limiting examples of such diseases include asthma, allergic rhinitis, allergic sinusitis, bronchial asthma, irritable bowel syndrome (ibs), inflammatory bowel disease (ibd), pulmonary arterial hypertension (pah), pulmonary fibrosis, liver fibrosis, cardiac fibrosis, scleroderma, urticaria, dermatoses, atopic dermatitis, allergic contact dermatitis, diabetes, type i diabetes, type ii diabetes, rheumatoid arthritis, multiple sclerosis, cytopenias (by way of example only, anemia, leucopenia, neutropenia, thrombocytopenia, granulocytopenia, pancytopenia and idiopathic thrombocytopenic purpura), systemic lupus erythematosus, chronic obstructive pulmonary disease (copd), adult respiratory distress syndrome (ards), ulcerative colitis, crohns disease, psoriasis, lymphomas (by way of example only, b and t cell lymphomas), myelodysplastic syndrome, breast cancer, pancreatic cancer, papillary thyroid carcinoma, ovarian carcinoma, human adenoid cystic carcinoma, non small cell lung cancer, secretory breast carcinoma, congenital fibrosarcoma, congenital mesoblastic nephroma, acute myelogenous leukemia, chronic myeloid leukemia metastasis, cancer-related pain, neuroblastoma, osteosarcoma, melanoma, bone metastases, a tumor of breast, renal, lung, prostate, pancreas, colon, ovary, thyroid, colorectal tumors, neuronal tumors, uterine tumors, gastrointestinal stromal tumors (gist), gliomas, sarcomas, tumor angiogenesis, germ cell tumors, mast cell tumors, glioblastoma, neuroblastoma, mastocytosis, osteoporosis, hyper eosinophilia, restenosis, atherosclerosis, anaphylactic syndrome, angioedema, erythema nodosum, erythema multiforme, cutaneous necrotizing venulitis, insect bite skin inflammation, cns disorders and interstitial cystitis.in certain embodiments, the compounds of formula (i) and formula (ii) provided herein, and the pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the n-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, are useful for treating diseases or disorders in which c-kit kinase and pdgfr (a and/or p) kinase contribute to the pathology and/or symptomology of a disease or disorder. non-limiting examples of such diseases include asthma, allergic rhinitis, allergic sinusitis, bronchial asthma, irritable bowel syndrome (ibs), inflammatory bowel disease (ibd), pulmonary arterial hypertension (pah), pulmonary fibrosis, liver fibrosis, cardiac fibrosis, scleroderma, urticaria, dermatoses, atopic dermatitis, allergic contact dermatitis, diabetes, type i diabetes, type ii diabetes, rheumatoid arthritis, multiple sclerosis, cytopenias (by way of example only, anemia, leucopenia, neutropenia, thrombocytopenia, granulocytopenia, pancytopenia and idiopathic thrombocytopenic purpura), systemic lupus erythematosus, chronic obstructive pulmonary disease (copd), adult respiratory distress syndrome (ards), ulcerative colitis, crohns disease, psoriasis, lymphomas (by way of example only, b and t cell lymphomas), myelodysplastic syndrome, breast cancer, pancreatic cancer, papillary thyroid carcinoma, ovarian carcinoma, human adenoid cystic carcinoma, non small cell lung cancer, secretory breast carcinoma, congenital fibrosarcoma, congenital mesoblastic nephroma, acute myelogenous leukemia, chronic myeloid leukemia metastasis, cancer-related pain, neuroblastoma, osteosarcoma, melanoma, bone metastases, a tumor of breast, renal, lung, prostate, pancreas, colon, ovary, thyroid, colorectal tumors, neuronal tumors, uterine tumors, gastrointestinal stromal tumors (gist), gliomas, sarcomas, tumor angiogenesis, germ cell tumors, mast cell tumors, glioblastoma, neuroblastoma, mastocytosis, osteoporosis, hyper eosinophilia, restenosis, atherosclerosis, anaphylactic syndrome, angioedema, erythema nodosum, erythema multiforme, cutaneous necrotizing venulitis, insect bite skin inflammation, cns disorders and interstitial cystitis.another aspect provided herein includes methods for treating a cell-proliferative disease, comprising administering to a system or subject in need of such treatment an effective amount of a compound of formula (i) and formula (ii), or pharmaceutically acceptable salts or pharmaceutical compositions thereof wherein the cell-proliferative disease is lymphoma, osteosarcoma, melanoma, or a tumor of breast, renal, prostate, colorectal, thyroid, ovarian, pancreatic, neuronal, lung, uterine or gastrointestinal tumor.in certain embodiments, the compounds of formula (i) and formula (ii), pharmaceutically acceptable salts, solvates, n-oxides and isomers thereof, pharmaceutical compositions, and/or combinations provided herein are used in the treatment of diseases and/or disorders including, but not limited to, asthma, bronchial asthma, allergic asthma, intrinsic asthma, extrinsic asthma, exercise-induced asthma, drug-induced asthma (including aspirin and nsaid-induced) and dust-induced asthma, chronic obstructive pulmonary disease (copd) bronchitis, including infectious and eosinophilic bronchitis emphysema bronchiectasis cystic fibrosis sarcoidosis farmers lung and related diseases hypersensitivity pneumonitis lung fibrosis, including cryptogenic fibrosing alveolitis, idiopathic interstitial pneumonias, fibrosis complicating anti-neoplastic therapy and chronic infection, including tuberculosis and aspergillosis and other fungal infections complications of lung transplantation vasculitic and thrombotic disorders of the lung vasculature, and pulmonary hypertension antitussive activity including treatment of chronic cough associated with inflammatory and secretory conditions of the airways, and iatrogenic cough acute and chronic rhinitis including rhinitis medicamentosa, and vasomotor rhinitis perennial and seasonal allergic rhinitis including rhinitis nervosa (hay fever) nasal polyposis acute viral infection including the common cold, and infection due to respiratory syncytial virus, influenza, coronavirus (including sars) and adenovirus.in certain embodiments, the compounds of formula (i) and formula (ii), pharmaceutically acceptable salts, solvates, n-oxides and isomers thereof, pharmaceutical compositions, and/or combinations provided herein are used in the treatment of dermatological disorders including, but not limited to, psoriasis, atopic dermatitis, contact dermatitis or other eczematous dermatoses, and delayed-type hypersensitivity reactions phyto- and photodermititis seborrheic dermatitis, dermatitis herpetiformis, lichen planus, lichen sclerosis et atrophica, pyoderma gangrenosum, skin sarcoid, basal cell carcinoma, actinic keratosis, discoid lupus erythematosus, pemphigus, pemphigoid, epidermolysis bullosa, urticaria, angioedema, vasculitides, toxic erythemas, cutaneous eosinophilias, alopecia areata, male-pattern baldness, sweet's syndrome, weber-christian syndrome, erythema multiforme cellulitis, both infective and non-infective panniculitis cutaneous lymphomas, non-melanoma skin cancer and other dysplastic lesions drug-induced disorders including fixed drug eruptions.in certain embodiments, the compounds of formula (i) and formula (ii), pharmaceutically acceptable salts, solvates, n-oxides and isomers thereof, pharmaceutical compositions, and/or combinations provided herein are used in the treatment of rheumatoid arthritis, irritable bowel syndrome, systemic lupus erythematosus, multiple sclerosis, hashimoto's thyroiditis, crohns disease, inflammatory bowel disease (ibd), graves' disease, addison's disease, diabetes mellitus, idiopathic thrombocytopenic purpura, eosinophilic fasciitis, hyper-ige syndrome, antiphospholipid syndrome and sazary syndrome.in certain embodiments, the compounds of formula (i) and formula (ii), pharmaceutically acceptable salts, solvates, n-oxides and isomers thereof, and pharmaceutical compositions provided herein are used in the treatment of cancer including, but not limited to, prostate, breast, lung, ovarian, pancreatic, bowel and colon, stomach, skin and brain tumors and malignancies affecting the bone marrow (including the leukaemias) and lymphoproliferative systems, such as hodgkin's and non-hodgkin's lymphoma including the prevention and treatment of metastatic disease and tumor recurrences, and paraneoplastic syndromes.provided herein are compounds of formula (i) and formula (ii), pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the n-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, and pharmaceutical compositions containing at least one compound of formula (i) or formula (ii), or pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the n-oxide derivatives, protected derivatives, individual isomers or mixture of isomers thereof, for use in activating c-kit kinase activity, or c-kit kinase and pdgfr (a and/or p) kinase activity, and thereby are used to in the prevention or treatment of diseases and/or disorders associated with c-kit kinase activity, or c-kit kinase and pdgfr (a and/or p) kinase activity.also provided herein are methods for the treatment of a subject suffering from a disease and/or disorder associated with c-kit kinase activity, wherein the method includes administering to the subject in need thereof, an effective amount of a compound of formula (i) or formula (ii), or pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the n-oxide derivatives, protected derivatives, individual isomers or mixture of isomers thereof, either alone or as part of a pharmaceutical composition as described herein.also provided herein are

methods for the treatment of a subject suffering from a disease and/or disorder associated with c-kit kinase activity and pdgfr (a and/or p) kinase activity, wherein the method includes administering to the subject in need thereof, an effective amount of a compound of formula (i) or formula (ii), or pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the n-oxide derivatives, protected derivatives, individual isomers or mixture of isomers thereof, either alone or as part of a pharmaceutical composition as described herein, provided herein is the use of a compound of formula (i) or formula (ii), or pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the n-oxide derivatives, protected derivatives, individual isomers or mixture of isomers thereof, in the manufacture of a medicament for the treatment of a disease or disorder associated with c-kit kinase activity. also provided herein is the use of a compound of formula (i) or formula (ii), or pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the n-oxide derivatives, protected derivatives, individual isomers or mixture of isomers thereof, in the manufacture of a medicament for the treatment of a disease or disorder associated with c-kit kinase activity and pdgfr (a and/or beta) kinase activity. furthermore, provided herein is the use of a compound having formula (i) or formula (ii), or pharmaceutically acceptable salts or pharmaceutical compositions thereof, and optionally in combination with a therapeutically effective amount of a second agent, in the manufacture of a medicament for treating a disease or condition modulated by kinase activity, particularly c-kit, or c-kit and pdgfr (a and beta). in accordance with the foregoing, the present invention further provides a method for preventing or treating any of the diseases or disorders described above in a subject in need of such treatment, which method comprises administering to said subject a therapeutically effective amount of a compound of formula (i) or formula (ii), or a pharmaceutically acceptable salt thereof, for any of the above uses, the required dosage will vary depending on the mode of administration, the particular condition to be treated and the effect desired. (see, "administration and pharmaceutical compositions," infra). administration and pharmaceutical compositions for the therapeutic uses of compounds of formula (i) and formula (ii), or pharmaceutically acceptable salts, solvates, n-oxides or isomers thereof, described herein, such compounds are administered in therapeutically effective amounts either alone or as part of a pharmaceutical composition. accordingly, provided herein are pharmaceutical compositions, which comprise at least one compound of formula (i) or formula (ii), or pharmaceutically acceptable salts solvates, n-oxides or isomers thereof, and one or more pharmaceutically acceptable carriers, diluents, or excipients. in addition, such compounds and compositions are administered singly or in combination with one or more additional therapeutic agents. the method of administration of such compounds and compositions include, but are not limited to, oral administration, rectal administration, transdermal administration, parenteral, intravenous administration, intravitreal administration, intramuscular administration, pulmonary administration, inhalation administration, intranasal administration, topical administration, ophthalmic administration or otic administration. in certain embodiments the method of administration of such compounds and compositions is oral administration. in other embodiments the method of administration of such compounds and compositions is pulmonary administration, inhalation administration or intranasal administration. the therapeutically effective amount will vary depending on, among others, the disease indicated, the severity of the disease, the age and relative health of the subject, the potency of the compound administered, the mode of administration and the treatment desired. in certain embodiments, the daily dosage of a compound of formula (i) and formula (ii), satisfactory results are indicated to be obtained systemically at daily dosages of from about 0.03 to 2.5 mg/kg per body weight. in certain embodiments, the daily dosage of a compound of formula (i) and formula (ii), administered by inhalation, is in the range from 0.05 micrograms per kilogram body weight (micro g/kg) to 100 micrograms per kilogram body weight (micro g/kg). in other embodiments, the daily dosage of a compound of formula (i) and formula (ii), administered orally, is in the range from 0.01 micrograms per kilogram body weight (micro g/kg) to 100 milligrams per kilogram body weight (mg/kg). an indicated daily dosage in the larger mammal, e.g. humans, is in the range from about 0.5 mg to about 100 mg of a compound of formula (i) and formula (ii), conveniently administered, e.g. in divided doses up to four times a day or in controlled release form. in certain embodiment, unit dosage forms for oral administration comprise from about 1 to 50 mg of a compound of formula (i) and formula (ii). other aspects provided herein are processes for the preparation of pharmaceutical composition which comprise at least one compound of formula (i) or formula (ii), or pharmaceutically acceptable salts, solvates, n-oxides or isomers thereof. in certain embodiments, such processes include admixing a compound of the formula (i) or formula (ii), or pharmaceutically acceptable salts, solvates, n-oxides or isomers thereof, with one or more pharmaceutically acceptable carriers, diluents or excipients. in certain embodiments, the pharmaceutical compositions comprising a compound of formula (i) or formula (ii) in free form, or in a pharmaceutically acceptable salt, solvate, n-oxide or isomeric form, in association with at least one pharmaceutically acceptable carrier, diluent or excipient are manufactured by mixing, granulating and/or coating methods. in other embodiments, such compositions optionally contain excipients, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. in other embodiments, such compositions are sterilized. in certain embodiments, the pharmaceutical compositions comprising at least one compound of formula (i) or formula (ii) are adapted for oral administration for the treatment of diseases and/or disorders associated with c-kit kinase activity. in other embodiments, the pharmaceutical compositions comprising at least one compound of formula (i) or formula (ii) are adapted for oral administration for the treatment of diseases and/or disorders associated with c-kit kinase and pdgfr (a and/or p) kinase activity. in certain embodiments, the pharmaceutical compositions comprising at least one compound of formula (i) or formula (ii) are adapted for inhalation administration, including pulmonary administration, inhalation administration or intranasal administration, for the treatment of diseases and/or disorders associated with c-kit kinase activity. in other embodiments, the pharmaceutical compositions comprising at least one compound of formula (i) or formula (ii) are adapted for inhalation administration, including pulmonary administration, inhalation administration or intranasal administration, for the treatment of diseases and/or disorders associated with c-kit kinase and pdgfr (a and/or beta) kinase activity. in certain embodiments, the pharmaceutical compositions comprising at least one compound of formula (i) or formula (ii) are adapted for inhalation administration, including pulmonary administration, inhalation administration or intranasal administration, for the treatment of respiratory diseases with c-kit kinase activity. in certain embodiments, the respiratory disease is allergic rhinitis or asthma. in other embodiments, the pharmaceutical compositions comprising at least one compound of formula (i) or formula (ii) are adapted for inhalation administration, including pulmonary administration, inhalation administration or intranasal administration, for the treatment of respiratory diseases associated with c-kit kinase and pdgfr (a and/or beta) kinase activity. in certain embodiments, the respiratory disease is allergic rhinitis or asthma. in certain embodiments, the pharmaceutical compositions comprising at least one compound of formula (i) or formula (ii) are adapted for parenteral or intravenous administration, for the treatment of diseases and/or disorders associated with c-kit kinase activity. in other embodiments, the pharmaceutical compositions comprising at least one compound of formula (i) or formula (ii) are adapted for parenteral or intravenous administration, for the treatment of diseases and/or disorders associated with c-kit kinase and pdgfr (a and/or p) kinase activity. oral dosage forms in certain embodiments, the pharmaceutical compositions containing at least one compound of formula (i) or formula (ii) are administered orally as discrete dosage forms, wherein such dosage forms include, but are not limited to, capsules, gelatin capsules, caplets, tablets, chewable tablets, powders, granules, syrups, flavored syrups, solutions or suspensions in aqueous or non-aqueous liquids, edible foams or whips, and oil-in-water liquid emulsions or water-in-oil liquid emulsions. the capsules, gelatin capsules, caplets, tablets, chewable tablets, powders or granules, used for the oral administration of at least one compound of formula (i) and formula (ii) are prepared by admixing at least one compound of formula (i) and formula (ii) (active ingredient) together with at least one excipient using conventional pharmaceutical compounding techniques. non-limiting examples of excipients used in oral dosage forms described herein include, but are not limited to, binders, fillers, disintegrants, lubricants, absorbents, colorants, flavors, preservatives and sweeteners. non-limiting examples of such binders include, but are not limited to, corn starch, potato starch, starch paste, pre-gelatinized starch, or other starches, sugars, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, tragacanth, guar gum, cellulose and its derivatives (by way of example only, ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethylcellulose, methyl cellulose, hydroxypropyl methylcellulose and microcrystalline cellulose), magnesium aluminum silicate, polyvinyl pyrrolidone and combinations thereof. non-limiting examples of such fillers include, but are not limited to, talc, calcium carbonate (e.g., granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof. in certain embodiments, the binder or filler in pharmaceutical compositions provided herein are present in from about 50 to about 99 weight percent of the pharmaceutical composition or dosage form. non-limiting examples of such disintegrants include, but are not limited to, agar-agar, alginic acid, sodium alginate, calcium carbonate, sodium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrillin potassium, sodium starch glycolate, potato or tapioca starch, pre-gelatinized starch, other starches, clays, other alginates, other celluloses, gums, and combinations thereof. in certain embodiments, the amount of disintegrant used in the pharmaceutical compositions provided herein is from about 0.5 to about 15 weight percent of disintegrant, while in other embodiments the amount is from about 1 to about 5 weight percent of disintegrant. non-limiting examples of such lubricants include, but are not limited to, sodium stearate, calcium stearate, magnesium stearate, stearic acid, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, sodium lauryl sulfate, talc, hydrogenated vegetable oil (by way of example only, peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil), zinc stearate, sodium oleate, ethyl oleate, ethyl laureate, agar, silica, a syloid silica gel (aerosil 200, manufactured by w.r. grace co. of baltimore, md.), a coagulated aerosol of synthetic silica (marketed by degussa co. of plano, tex.), cab-o-sil (a pyrogenic silicon dioxide product sold by cabot co. of boston, mass.) and combinations thereof. in certain embodiments, the amount of lubricants used in the pharmaceutical compositions provided herein is in an amount of less than about 1 weight percent of the pharmaceutical compositions or dosage forms. non-limiting examples of such diluents include, but are not limited to, lactose, dextrose, sucrose, mannitol, sorbitol, cellulose, glycine or combinations thereof. in certain embodiments, tablets and capsules are prepared by uniformly admixing at least one compound of formula (i) or formula (ii) (active ingredients) with liquid carriers, finely divided solid carriers, or both, and then shaping the product into the desired presentation if necessary. in certain embodiments, tablets are prepared by compression. in other embodiments, tablets are prepared by molding. in certain embodiments, at least one compound of formula (i) or formula (ii) is orally administered as a controlled release dosage form. such dosage forms are used to provide slow or controlled-release of one or more compounds of formula (i) or formula (ii). controlled release is obtained using, for example, hydroxypropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, microspheres, or a combination thereof. in certain embodiments, controlled-release dosage forms are used to extend activity of the compound of formula (i) or formula (ii), reduce dosage frequency, and increase patient compliance. administration of compounds of formula (i) or formula (ii) as oral fluids such as solution, syrups and elixirs are prepared in unit dosage forms such that a given quantity of solution, syrups or elixirs contains a predetermined amount of a compound of formula (i) or formula (ii). syrups are 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 are formulated by dispersing the compound in a non-toxic vehicle. non-limiting examples of excipients used in oral fluids for oral administration include, but are not limited to, solubilizers, emulsifiers, flavoring agents, preservatives, and coloring agents. non-limiting examples of solubilizers and emulsifiers include, but are not limited to, water, glycols, oils, alcohols, ethoxylated isostearyl alcohols and polyoxy ethylene sorbitol ethers. non-limiting examples of preservatives include, but are not limited to, sodium benzoate. non-limiting examples of flavoring agents include, but are not limited to, peppermint oil or natural sweeteners or saccharin or other artificial sweeteners. parenteral dosage forms in certain embodiments pharmaceutical compositions containing at least one compound of formula (i) or formula (ii) are administered parenterally by various routes including, but not limited to, subcutaneous, intravenous (including bolus injection), intramuscular, and intraarterial. such parenteral dosage forms are administered in the form of sterile or sterilizable injectable solutions, suspensions, dry and/or lyophilized products ready to be dissolved or suspended in a pharmaceutically acceptable vehicle for injection (reconstitutable powders) and emulsions. vehicles used in such dosage forms include, but are not limited to, water for injection up aqueous vehicles such as, but not limited to, sodium chloride injection, ringer's injection, dextrose injection, dextrose and sodium chloride injection, and lactated ringer's injection water-miscible vehicles such as, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol and non-aqueous vehicles such as, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate. transdermal dosage forms in certain embodiments pharmaceutical compositions containing at least one compound of formula (i) or formula (ii) are administered transdermally. such transdermal dosage forms include "reservoir type" or "matrix type" patches, which are applied to the skin and worn for a specific period of time to permit the penetration of a desired amount of a compound of formula (i) or formula (ii). by way of example only, such transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compound to the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin. in other embodiments, matrix transdermal formulations are used. formulations for transdermal delivery of a compound of formula (i) or formula (ii) include an effective amount of a compound of formula (i) or formula (ii), a carrier and an optional diluent. a carrier includes, but is not limited to, absorbable pharmacologically acceptable solvents to assist passage through the skin of the host, such as water, acetone, ethanol, ethylene glycol, propylene glycol, butane-1,3-diol, isopropyl myristate, isopropyl palmitate, mineral oil, and combinations thereof. in certain embodiments, such transdermal delivery systems include penetration enhancers to assist in delivering one or more compounds of formula (i) or formula (ii) to the tissue. such penetration enhancers include, but are not limited to, acetone various alcohols such as ethanol, oleyl, and tetrahydrofuryl alkyl sulfoxides such as dimethyl sulfoxide dimethyl acetamide dimethyl formamide polyethylene glycol pyrrolidones such as polyvinylpyrrolidone kollidon grades (povidone, polyvidone) urea and various water-soluble or insoluble sugar esters such as tween 80 (polysorbate 80) and span 60 (sorbitan monostearate). in other embodiments, the ph of such a transdermal pharmaceutical composition or dosage form, or of the tissue to which the pharmaceutical composition or dosage form is applied, is adjusted to improve delivery of one or more compounds of formula (i) or formula (ii). in other embodiments, the polarity of a solvent carrier, its ionic strength, or tonicity are adjusted to improve delivery. in other embodiments, compounds such as stearates are added to advantageously alter the hydrophilicity or lipophilicity of one or more compounds of formula (i) or formula (ii) so as to improve delivery. in certain embodiments, such stearates serve as a lipid vehicle for the formulation, as an emulsifying agent or surfactant, and as a delivery-enhancing or penetration-enhancing agent. in other embodiments, different salts, hydrates or solvates of the compounds of formula (i) or formula (ii) are used to further adjust the properties of the resulting composition. in certain embodiments compounds of formula (i) or formula (ii) are transdermally delivered from a patch by iontophoresis. topical dosage forms in certain embodiments at least one

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compound of formula (i) or formula (ii) of the present invention, or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the n-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, include, but are not limited to antiemetic agents, anti-inflammatory agents, immunomodulatory agents, cytokines, antidepressants, hormones, alkylating agents, antimetabolites, antitumour antibiotics, antimitotic agents, topoisomerase inhibitors, cytostatic agents, anti-invasion agents, antiangiogenic agents, inhibitors of growth factor function, anticancer agents and toll-like receptor modulators.in some embodiments, the compounds of formula (i) or formula (ii), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the n-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, are used in combination with a second therapeutic agent for treating asthma. in certain combinations, the second therapeutic agent is a bronchodilator, an anti-inflammatory agent, a leukotriene antagonist, or an ige blocker.the antiemetic agents used in combination with compounds of formula (i) or formula (ii), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the n-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, include, but are not limited to, metoclopramide, domperidone, prochlorperazine, promethazine, chlorpromazine, trimethobenzamide, ondansetron, granisetron, hydroxyzine, acetylcholine monoethanolamine, alzapiride, azasetron, benzquinamide, betanautine, bromopride, buclizine, clebopride, cyclizine, dimenhydrinate, diphenidol, dolasetron, meclizine, methallatal, metopimazine, nabilone, oxypemndyl, pipamazine, scopolamine, sulpiride, tetrahydrocannabinols, thiethylperazine, thiopropazine, tropisetron, and combinations thereof.the anti-inflammatory agents used in combination with compounds of formula (i) or formula (ii), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the n-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, include, but are not limited to, non-steroidal anti-inflammatory drugs such as salicylic acid, acetylsalicylic acid, methyl salicylate, diflunisal, salsalate, olsalazine, sulfasalazine, acetaminophen, indomethacin, sulindac, etodolac, mefenamic acid, meclofenamate sodium, tolmetin, ketorolac, dichlofenac, ibuprofen, naproxen, naproxen sodium, fenopofen, ketoprofen, flurbiprofen, oxaprozin, piroxicam, meloxicam, ampiroxicam, droxicam, pivoxicam, tenoxicam, nabumetome, phenylbutazone, oxyphenbutazone, antipyrine, aminopyrine, apazone and nimesulide, leukotriene antagonists including, but not limited to, zileuton, aurothiogluucose, gold sodium thiomalate and auranofin, steroids including, but not limited to, alclometasone dipropionate, amcinonide, beclomethasone dipropionate, betametasone, betamethasone benzoate, betamethasone dipropionate, betamethasone sodium phosphate, betamethasone valerate, clobetasol propionate, clocortolone pivalate, hydrocortisone, hydrocortisone derivatives, desonide, desoximetasone, dexamethasone, flunisolide, flucxinolide, flurandrenolide, halcinonide, medrysone, methylprednisolone, methprednisolone acetate, methylprednisolone sodium succinate, mometasone furoate, paramethasone acetate, prednisolone, prednisolone acetate, prednisolone sodium phosphate, prednisolone tebutate, prednisone, triamcinolone, triamcinolone acetonide, triamcinolone diacetate, and triamcinolone hexacetonide and other anti-inflammatory agents including, but not limited to, methotrexate, colchicine, allopurinol, probenecid, thalidomide or a derivative thereof, 5-aminosalicylic acid, retinoid, dithranol or calcipotriol, sulfapyrazone and benzbromarone.the immunomodulatory agents used in combination with compounds of formula (i) or formula (ii), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the n-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, include, but are not limited to, azathioprine, tacrolimus, cyclosporin methothrexate, leflunomide, corticosteroids, cyclophosphamide, cyclosporine a, cyclosporin g, mycophenolate mofetil, ascomycin, rapamycin (sirolimus), fk-506, mizoribine, deoxyspergualin, brequinar, mycophenolic acid, malononitriloamines (such as, by way of example only, leflunamide), t cell receptor modulators, and cytokine receptor modulators, peptide mimetics, and antibodies (such as, by way of example only, human, humanized, chimeric, monoclonal, polyclonal, fvs, scfvs, fab or f(ab)2 fragments or epitope binding fragments), nucleic acid molecules (such as, by way of example only, antisense nucleic acid molecules and triple helices), small molecules, organic compounds, and inorganic compounds. examples of t cell receptor modulators include, but are not limited to, anti-t cell receptor antibodies (such as, by way of example only, anti-cd4 antibodies (such as, by way of example only, cm-t412 (boehringer), idec-ce9.1 (idec and skb), mab 4162w94, orthoclone and oktcd4ra (janssen-cilag)), anti-cd3 antibodies (such as, by way of example only, nuvion (product design labs), okt3 (johnson and johnson), or rituxan (idec)), anti-cd5 antibodies (such as, by way of example only, an anti-cd5 ricin-linked immunconjugate), anti-cd7 antibodies (such as, by way of example only, chh-380 (novartis)), anti-cd8 antibodies, anti-cd40 ligand monoclonal antibodies (such as, by way of example only, idec-131 (idec)), anti-cd52 antibodies (such as, by way of example only, campath 1h (llex)), anti-cd2 antibodies, anti-cd11a antibodies (such as, by way of example only, xanelim (genentech)), anti-b7 antibodies (such as, by way of example only, idec-114 (idec)), ctla4-immunoglobulin, and toll receptor-like (tlr) modulators. examples of cytokine receptor modulators include, but are not limited to, soluble cytokine receptors (such as, by way of example only, the extracellular domain of a tnfr-a receptor or a fragment thereof, the extracellular domain of an il-1 beta receptor or a fragment thereof, and the extracellular domain of an il-6 receptor or a fragment thereof), cytokines or fragments thereof (such as, by way of example only, interleukin (il)-2, il-3, il-4, il-5, il-6, il-7, il-8, il-9, il-10, il-11, il-12, il-15, tnfr-a, interferon (ifn)-a, ifn- beta, ifn-gamma, and gm-csf), anti-cytokine receptor antibodies (such as, by way of example only, anti-ifn receptor antibodies, anti-il-2 receptor antibodies (such as, by way of example only, zenapax (protein design labs)), anti-il-4 receptor antibodies, anti-il-6 receptor antibodies, anti-il-10 receptor antibodies, and anti-il-12 receptor antibodies), anti-cytokine antibodies (such as, by way of example only, anti-ifn antibodies, anti-tnfr-a antibodies, anti-il-1 beta antibodies, anti-il-6 antibodies, anti-il-8 antibodies (such as, by way of example only, abx-il-8 (abgenix)), and anti-il-12 antibodies).the alkylating agents used in combination with compounds of formula (i) or formula (ii), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the n-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, include, but are not limited to, nitrogen mustards, ethylenimines, methylmelamines, alkyl sulfonates, nitrosoureas, carmustine, lomustine, triazenes, melphalan, mechlorethamine, cis-platin, oxaliplatin, carboplatin, cyclophosphamide, ifosfamide, melphalan, chlorambucil, hexamethylmelaine, thiopeta, busulfan, carmustine, streptozocin, dacarbazine and temozolomide.the antimetabolites used in combination with compounds of formula (i) or formula (ii), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the n-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, include, but are not limited to, cytarabine, gemcitabine and antifolates such as, by way of example only, fluoropyrimidines (by way of example only, 5-fluorouracil and tegafur), raltitrexate, methotrexate, cytosine arabinoside, and hydroxyurea.the antitumour antibiotics used in combination with compounds of formula (i) or formula (ii), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the n-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, include, but are not limited to, anthracyclines, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-c, dactinomycin and mithramycin.the antimitotic agents used in combination with compounds of formula (i) or formula (ii), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the n-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, include, but are not limited to, vinca alkaloids (by way of example only, vincristine, vinblastine, vindesine and vinorelbine), taxoids (by way of example only, taxol, paclitaxel and taxotere) and polikinase inhibitors.the topoisomerase inhibitors used in combination with compounds of formula (i) or formula (ii), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the n-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, include, but are not limited to, epipodophyllotoxins by way of example only, etoposide and teniposide, amascrine, topotecan, irinotecan and camptothecin.in other embodiments, the combinations described herein include combination of a compound of formula (i) or formula (ii), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the n-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, with a leukotriene biosynthesis inhibitor, 5-lipoxygenase (5-lo) inhibitor or 5-lipoxygenase activating protein (flap) antagonist such as zileuton abt-761 fenleuton tepoxalin abbott-79175 abbott-85761 a n-(5-substituted)-thiophene-2-alkylsulfonamide 2,6-di-tert-butylphenolhydrazones a methoxytetrahydropyrans such as zeneca zd-2138 the compound sb-210661 a pyridinyl-substituted 2-cyanonaphthalene compound such as l-739,010 a 2-cyanquinoline compound such as l-746,530 or an indole or quinoline compound such as mk-591, mk-886, and bayx1005.in other embodiments, the combinations described herein include combination of a compound of formula (i) or formula (ii), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the n-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, with a receptor antagonist for leukotrienes (ltb4, lt4, ltd4, and lte4) selected from the group consisting of the phenothiazin-3-is such as l-651,392 amidino compounds such as cgs-25019c benzoxalamines such as ontazolast benzenecarboximidamides such as bilil 284/260 and compounds such as zafirlukast, ablukast, montelukast, singulair, pranlukast, verlukast (mk-679), rg-12525, ro-245913, iralukast (cgp 45715a), and bayx1795.in other embodiments, the combinations described herein include combination of a compound of formula (i) or formula (ii), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the n-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, with a phosphodiesterase (pde) inhibitor such as a methylxanthanine including theophylline and aminophylline a selective pde isoenzyme inhibitor including a pde4 inhibitor, including, but not limited to, cilomilast or roflumilast, an inhibitor of the isoform pde4d, or an inhibitor of pde5.in other embodiments, the combinations described herein include combination of a compound of formula (i) or formula (ii), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the n-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, with a histamine type 1 receptor antagonist such as cetirizine, loratadine, desloratadine, fexofenadine, acrivastine, terfenadine, astemizole, azelastine, levocabastine, chlorpheniramine, promethazine, cyclizine, or mizolastine.in other embodiments, the combinations described herein include combination of a compound of formula (i) or formula (ii), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the n-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, with a gastroprotective histamine type 2 receptor antagonist. in other embodiments, the combinations described herein include combination of a compound of formula (i) and formula (ii), or a pharmaceutically acceptable salt or solvate thereof, described herein, with an antagonist of the histamine type 4 receptor.in other embodiments, the combinations described herein include combination of a compound of formula (i) or formula (ii), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the n-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, with an alpha-i/alpha-2 adrenoceptor agonist vasoconstrictor sympathomimetic agent, such as propylhexedrine, phenylephrine, phenylpropanolamine, ephedrine, pseudoephedrine, naphazoline hydrochloride, oxymetazoline hydrochloride, tetrahydrozoline hydrochloride, xylometazoline hydrochloride, tramazoline hydrochloride or ethylnorepinephrine hydrochloride.in other embodiments, the combinations described herein include combination of a compound of formula (i) or formula (ii), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the n-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, with a glucocorticoid, such as flunisolide, triamcinolone acetonide, beclomethasone dipropionate, budesonide, fluticasone propionate, ciclesonide or mometasone furoate.in other embodiments, the combinations described herein include combination of a compound of formula (i) or formula (ii), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the n-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, with an immunoglobulin (ig), gamma globulin, ig preparation or an antagonist or antibody modulating ig function such as anti-ige (omalizumab).in other embodiments, the combinations described herein include combination of a compound of formula (i) or formula (ii), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the n-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, with a chemotherapeutic agent to treat a cell proliferative disorder, including but not limited to, lymphoma, osteosarcoma, melanoma, or a tumor of breast, renal, prostate, colorectal, thyroid, ovarian, pancreatic, neuronal, lung, uterine or gastrointestinal tumor. non-limiting examples of chemotherapeutic agents used in such combinations are anthracyclines, alkylating agents (e.g., mitomycin c), alkyl sulfonates, aziridines, ethylenimines, methylmelamines, nitrogen mustards, nitrosoureas, antibiotics, antimetabolites, folic acid analogs (e.g., dihydrofolate reductase inhibitors such as methotrexate), purine analogs, pyrimidine analogs, enzymes, podophyllotoxins, platinum-containing agents, interferons, and interleukins. other non-limiting examples of chemotherapeutic agents used in such combinations are busulfan, improfusulfan, pipsosulfan, benzodepa, carboquone, meturedopa, uredepa, altretamine, triethylenemelamine, triethylenephosphoramidate, triethylenethiophosphoramidate, trimethylolmelamine, chlorambucil, chlornaphazine, cyclophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard, carmustine, chlorozotacin, fotemustine, lomustine, nimustine, ranimustine, dacarbazine, mannometustine, mitobronitol, mitolactol, pipobroman, acalacinomycins, actinomycin f(1), anthramycin, azaserine, bleomycin, cactinomycin, carubicin, carzinophillin, chromomycin, dactinomycin, daunorubicin, daunomycin, 6-diazo-5-oxo-1-norleucine, doxorubicin, epirubicin, mitomycin c, mycophenolic acid, nogalamycin, olivomycin, peplomycin, plicamycin, porfiriomycin, puromycin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin, denopoterin, methotrexate, pteropterin, trimetrexate, fludarabine, 6-mercaptopurine, thiampirine, thioguanine, ancitabine, azacitidine, 6-azauridine, camofur, cytarabine, dideoxyuridine, doxifluridine, encitabine, floxuridine, fluorouracil, tegafur, l-asparaginase, pulmozyme, aceglatone, aldophosphamide glycoside, aminolevulinic acid, amxuridine, bestrabucil, bisantrene, carboplatin, cisplatin, defofamide, demecolone, diaziqunone, elformithine, elliptinium acetate, etoglugicid, etoposide, flutamide, gallium nitrate, hydroxyurea, interferon-alpha, interferon-beta, interferon-gamma, interleukin-2, lentinan, lonidamine, mitoguazone, mitoxantrone, mopidamol, nitracrine, pentostatin, phenamet, pirarubicin, podophyllinic acid, 2-ethylhydrazide, procarbazine, razoxane, sizofuran, spiropogermanium, paclitaxel, tamoxifen, teniposide, tenuazonic acid, triaziquone, 2,2',27-trichlorotriethylamine, urethane, vinblastine, vincristine, and vindesine.in certain embodiments, the combination treatments provided herein include administration of a compound of formula (i) or formula (ii), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the n-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, or a pharmaceutical composition containing a compound of formula (i) and formula (ii) in combination with one or more additional therapeutic agents, for the treatment of pulmonary arterial hypertension (pah). such additional therapeutic agents include phosphodiesterase-5 inhibitors, prostanoids, endothelin receptor antagonists, calcium channel blockers, oxygen therapy, iloprost, sildenafil, tadalafil, digoxin, furosemide, spirinolactone, warfarin, epoprostenol, treprostiniil, bosentan and ambrisentan.examples the following examples were offered to illustrate, but not to limit, the compounds of formula (i) or formula (ii) of the present invention, and the preparation of such compounds. synthesis of intermediates synthesis of 3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylbenzoic acid (4) [ftimg=68000051]to a suspension of imidazo[1,2-a]pyridine-3-carboxylic acid (1) (4.09 g, 25.3 mmol) in dichloromethane (100 ml) and dmf (0.25 ml) at 0 degrees centigrade was added oxaly chloride (4.15 ml, 48.0 mmol) dropwise over 10 minutes. the reaction was slowly warmed to room temperature and stirred

until complete conversion was detected by lcms. the reaction was subsequently reduced to dryness and suspended in dichloromethane (100 ml) and was added a solution of methyl 3-amino-4-methylbenzoate (2) (4.6 g, 27.9 mmol) in dichloromethane (100 ml) and triethylamine (7.1 ml). contents were stirred at room temperature for 4 hours and diluted with dichloromethane (100 ml). the reaction was washed with water, saturated nahco3, brine, dried over magnesium sulfate, filtered and reduced to dryness. the crude solid was triturated with diethyl ether to remove excess aniline and dried to afford methyl 3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylbenzoate (3) as a white solid. ms m/z 310.1 (m+1)+ to a suspension of 3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylbenzoate (3) (5.43 g, 17.6 mmol) in thf (225 ml) and meoh (150 ml) was added lioh 3 m (17.5 ml) and water (50 ml). the reaction was stirred at room temperature for 12 hours then reduced in volume on roto-vap to remove thf and meoh. the mixture was diluted with water (75 ml) and neutralized with hcl (17.5 ml of a 3m solution). the resulting precipitate was filtered, washed with water and dried under vacuum to afford 3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylbenzoic acid (4) as a white solid. 1h nmr (400 mhz, d6-dmsol) delta 10.0 (s, 1h), 9.45 (dt, j=6.8, 1.2 hz, 1h), 8.58 (s, 1h), 7.98 (d, j=2.0 hz, 1h), 7.79 (dt, j=9.2, 1.2 hz, 1h), 7.76 (dd, j=8.0, 1.6 hz, 1h), 7.52 (ddd, j=9.2, 9.2, 1.2 hz, 1h), 7.43 (d, j=8.0 hz, 1h), 7.17 (td, j=6.8, 1.2 hz, 1h), 2.35 (s, 3h). ms m/z 296.1 (m+1)+. synthesis of 2-hydroxy-1-bhenylguanidine (5) [ftimg=68000052] to a solution of brcn (0.11 g, 1.1 mmol) in meoh (10 ml) at 0 degrees centigrade was added solid koac (0.32 g, 3.3 mmol) and a solution of aniline (0.1 ml, 1.1 mmol) in meoh (1 ml). the reaction was stirred for 3 hours then partitioned with water (15 ml) and dichloromethane (25 ml), the organic layer was separated, washed with brine, dried over magnesium sulfate, filtered and reduced to dryness to afford n-phenylcyanamide, which was immediately used without purification. n-phenylcyanamide was dissolved in etoh (7 ml) and treated with h2noh (1.5 eq of a 50 percent aq solution). the mixture was stirred at room temperature for 12 hours then reduced to dryness to afford 2-hydroxy-1-phenylguanidine (5) as a clear yellow oil, which was used without purification. synthesis of n'-hydroxy-6-methylpicolinimidamide (6) [ftimg=68000053] 6-methylpicolinonitrile (12 mg, 0.1 mmol) was dissolved in etoh (0.5 ml) and treated with nh2oh (1.5 eq of a 50 percent aq solution). the mixture was stirred at room temperature for 12 hours then reduced to dryness to afford n'-hydroxy-6-methylpicolinimidamide (6) as a clear yellow oil, which was used without purification. synthesis of n-(5-(n'-hydroxycarbamidimido)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (9) [ftimg=68000054] to a suspension of imidazo[1,2-a]pyridine-3-carboxylic acid (1) (16.6 g, 102 mmol) in dichloromethane (300 ml) and dmf (0.5 ml) at 0 degrees centigrade was added oxalyl chloride (45 ml, 510 mmol) dropwise over 10 minutes. the reaction was slowly warmed to room temperature and stirred until complete conversion was detected by lcms in meoh. the reaction was subsequently reduced to dryness and suspended in dichloroethane (100 ml) and was added to a solution of 3-amino-4-methylbenzonitrile (7) (15 g, 113 mmol) in dichloroethane (200 ml) and pr2net (55 ml) at 0 degrees centigrade after the addition, the cold bath was removed and contents were stirred at room temperature for 1 hour and then heated to 50 degrees centigrade for another 2 hours. after the completion of the reaction, the mixture was cooled and a white precipitate formed. the mixture was filtered and the solid was washed with cold dichloromethane. about 10 g of the desired n-(5-cyano-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (8) was obtained. the filtrate was washed with saturated nh4cl, saturated nahco3, brine, dried over magnesium sulfate, filtered and reduced to dryness. the crude solid was triturated with diethyl ether to remove excess aniline and filtered to afford another crop of n-(5-cyano-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (8) as a white solid. ms m/z 277.1 (m+1) to a stirred and cooled (0 degrees centigrade) suspension of n-(5-cyano-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (8) (10 g, 36.2 mmol) in etoh (225 ml) was added nh2oh (6 ml, 50 percent in water solution). after the addition, the reaction was stirred at room temperature for 2 hours then heated at 50 degrees centigrade for another 2 hours. after cooling to room temperature, the mixture was stored in the fridge overnight. the resulting precipitate was filtered, washed with cold etoh and dried under vacuum to afford n-(5-(n'-hydroxycarbamidimido)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (9) as a white solid. 1h nmr (400 mhz, d6-dmsol) delta 9.40 (dt, j=6.8, 1.2 hz, 1h), 8.15 (s, 1h), 7.88 (d, j=2.0 hz, 1h), 7.79 (dt, j=9.2, 1.2 hz, 1h), 7.76 (dd, j=8.0, 1.6 hz, 1h), 7.52 (ddd, j=9.2, 9.2, 1.2 hz, 1h), 7.43 (d, j=8.0 hz, 1h), 7.17 (td, j=6.8, 1.2 hz, 1h), 2.49 (s, 3h). ms m/z 310.1 (m+1)+. synthesis of 5,5-difluorotetrahydro-2h-pyran-2-carboxylic acid (17) [ftimg=68000055] 2-(benzyloxy)acetaldehyde (5 g, 33.3 mmol) in dry thf (10 ml) was added dropwise to a stirred and cooled solution of allylmagnesium chloride (25 ml, 2 m in thf, 50 mmol) in thf (100 ml) at -78 degrees centigrade after the addition, the solution was allowed to warm to 0 degrees centigrade and quenched with saturated nh4cl solution. after standard aqueous work up, the residue was purified over silica using etoac and hexane to give 1-(benzyloxy)pent-4-en-2-ol (11). nah (4.8 g, 120 mmol) was added portion wise to a stirred solution of 1-(benzyloxy)pent-4-en-2-ol (11) (15.3 g, 79.6 mmol) in thf (100 ml) at 0 degrees centigrade after addition, the mixture was warmed to room temperature and stirred for another hour before it was cooled to 0 degrees centigrade allyl bromide (9 ml, 103.5 mmol) was added to the reaction and the resulting mixture was warmed to room temperature and then heated to 50 degrees centigrade overnight. after cooling to room temperature, the mixture was quenched with saturated nh4cl and worked up under standard conditions. the residue was purified over silica using et2o and hexane to give ((2-(allyloxy)pent-4-enyloxy)methyl)benzene (12). benzylidene-bis(tricyclohexylphosphine)dichlororuthenium, bis(tricyclohexylphosphine)benzylidene ruthenium(iv) chloride-grubbs 1 generation catalyst (0.5 g, 0.54 mmol) was added in one portion to a stirred solution of ((2-(allyloxy)pent-4-enyloxy)methyl)benzene (12) (4 g, 17.2 mmol) in toluene (200 ml). the resulting mixture was heated at 50 degrees centigrade under n2 for 2 hours before isopropanol (18 ml) and naoh (0.17 g) were added. the mixture was then heated at 120 degrees centigrade overnight, the solvent was evaporated and the residue was purified over silica gel using et2o and hexane to give 2-(benzyloxyethyl)-3,4-dihydro-2h-pyran (13). bh3.sme2 (17 ml, 1 m in thf) was added slowly to a stirred solution of 2-(benzyloxyethyl)-3,4-dihydro-2h-pyran (2.87 g, 14.06 mmol) (13) in thf (100 ml) at -78 degrees centigrade the resulting mixture was allowed to warm to room temperature overnight. the mixture was quenched by the slow addition of 1m naoh (50 ml) at 0 degrees centigrade followed by h2o2 (13 ml, 30 percent in water). the resulting mixture was stirred for 2 hours at room temperature. after aqueous work up the residue was purified on silica gel using etoac and hexane to give 6-(benzyloxyethyl)tetrahydro-2h-pyran-3-ol (14). dmsol (1.15 ml, 16.2 mmol) was added to a stirred solution of oxalyl chloride (1 ml, 10.8 mmol) in dichloromethane (60 ml) at -78 degrees centigrade after 10 minutes, a dichloromethane solution of 6-(benzyloxyethyl)tetrahydro-2h-pyran-3-ol (14) (1.20 g, 5.40 mmol) was added. stirring was continued for one hour then triethylamine (3.8 ml, 27 mmol) was added and slowly warmed to 0 degrees centigrade the reaction was poured into saturated nh4cl solution and the organic phase was washed with brine and dried (na2so4). the residue was purified over silica gel using etoac and hexanes to give 6-(benzyloxyethyl)dihydro-2h-pyran-3 (4h)-one (15). deoxo-fluor (4.6 ml, 25 mmol) was added dropwise to a -78 degrees centigrade solution of 6-(benzyloxyethyl)dihydro-2h-pyran-3(4h)-one (15) (1.1 g, 5.06 mmol) in toluene (20 ml) in a plastic container. the mixture was warmed to room temperature overnight and poured into saturated nahco3 solution and extracted with et2o. after washing with brine and drying over mgso4, the residue was purified over silica gel using etoac and hexane to give 2-(benzyloxyethyl)-5,5-difluorotetrahydro-2h-pyran (16). h2 (balloon) was introduced to a stirred mixture of pd(oh)2/c (0.2 g) and 2-(benzyloxyethyl)-5,5-difluorotetrahydro-2h-pyran (16) (1.05 g, 4.3 mmol) in meoh (20 ml). after 2 hours, the mixture was filtered through a pad of celite and the solvent was evaporated to give the crude alcohol product. the oil was azeotroped with toluene to remove residual water and the product was used directly in the following step. dmsol (0.3 ml, 4.11 mmol) was added to a stirred solution of oxalyl chloride (0.28 ml, 3.15 mmol) in dichloromethane (20 ml) at -78 degrees centigrade after 10 minutes, a dichloromethane solution of the alcohol from previous step (0.33 g, 1.37 mmol) was added. the stirring continued for one hour before triethylamine (1.0 ml, 6.85 mmol) was added and after 10 minutes the reaction was warmed to 0 degrees centigrade the reaction was poured into saturated nh4cl solution and the organic phase was washed with brine and dried (na2so4). the crude aldehyde was filtration through a pad of silica gel and used directly in the following step. naclol2 (0.74 g, 8.22 mmol) was added in one portion to a stirred mixture of the aldehyde from previous step (1.37 mmol), 3-methyl-2-butene (2 ml) and nah2po4 (2.81 g, 20.5 mmol) in water (10 ml) and t-butoh (10 ml) at 0 degrees centigrade after stirring at room temperature for 2 hours, the mixture was partitioned with etoac and brine. the organic phase was dried (mgso4) and filtered. the residue was purified over silica gel using etoac and hexane to give 5,5-difluorotetrahydro-2h-pyran-2-carboxylic acid (17) as a clear oil. ms m/z 167.1 (m+1)+. synthesis of n-(5-(5-(azetidin-3-yl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (21) [ftimg=68000056] to a vial was added tert-butyl 3-(3-(3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (f39) (145 mg, 0.3 mmol) and 4n hcl in 1,4-dioxane (2 ml) and ch3cn (1 ml). the reaction was stirred for 45 minutes. the solvent was concentrated and placed under high vacuum. the solid was taken in water/acetone and the ph was adjusted to neutral with an aqueous solution of ammonium carbonate and lyophilized to afford n-(5-(5-(azetidin-3-yl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (21) which was used directly in the next step. 1h nmr (400 mhz, d6-dmsol) delta 10.85 (s, 1 h), 9.66-9.64 (m, 1 h), 9.42 (bs, 1 h), 9.28 (s, 1 h), 8.10-8.08 (m, 2 h), 8.02-7.98 (m, 1 h), 7.89-7.87 (m, 1 h), 7.59-7.53 (m, 2 h), 4.53-4.47 (m, 1 h), 4.36-4.29 (m, 4 h), 2.40 (s, 3 h). ms m/z 375.1 (m+1)+. synthesis of 7-(trifluoromethyl)imidazo[1,2-a]pyridine-3-carboxylic acid (24) [ftimg=68000057] ethyl 2-chloroacetate (20 ml, 187 mmol) and ethyl formate (15.1 ml, 187 mmol) were added simultaneously to a stirred and cooled suspension of potassium tert-butoxide (21.4 g, 188 mmol) in dry diisopropylether (300 ml). after the addition, the reaction was warmed to room temperature and stirred overnight. the yellow suspension was filtered and the solid potassium 2-chloro-3-ethoxy-3-oxoprop-1-en-1-olate (22) was vacuum dried and used directly in the following step. to a stirring suspension of 4-(trifluoromethyl)pyridin-2-amine (128 mg, 0.791 mmol) and potassium 2-chloro-3-ethoxy-3-oxoprop-1-en-1-olate (22) (500 mg, 2.64 mmol) in etoh (5 ml) at room temperature was added sulfuric acid (70 micro l, 1.32 mmol) dropwise. the reaction mixture was stirred at room temperature overnight then heated at 78 degrees centigrade for 3 hours. the reaction was cooled to room temperature and the solvent was concentrated. the residue was taken in water and the ph was adjusted between 6-8 with saturated sodium bicarbonate. the crude product was extracted with ethyl acetate. the organic was washed with brine and dried over anhydrous sodium sulfate. the crude product 7-(trifluoromethyl)imidazo[1,2-a]pyridine-3-carboxylate (23) was purified by silica chromatography. ms m/z 259.3 (m+1)+ to a stirring solution of ethyl 7-(trifluoromethyl)imidazo[1,2-a]pyridine-3-carboxylate (23) (100 mg, 0.387 mmol) in thf:meoh (4:1, 1.5 ml) was added 2n lioh (0.25 ml). the reaction was heated at 60 degrees centigrade for 1 hour. then, cooled to room temperature and the ph was adjusted between 4-5 with 1n hcl. the solvent was partially concentrated and the resulting aqueous layer was lyophilized to give 7-(trifluoromethyl)imidazo[1,2-a]pyridine-3-carboxylic acid (24). 1h nmr (400 mhz, d6-dmsol) delta 9.44 (d, j=7.2 hz, 1 h), 8.40 (s, 1 h), 8.31-8.30 (m, 1 h), 7.48 (dd, j=2.0, 7.6 hz, 1 h). ms m/z 231.2 (m+1)+. the following compounds were prepared according to the protocol described for 7-(trifluoromethyl)imidazo[1,2-a]pyridine-3-carboxylic acid (24). synthesis of 5,6,7,8-deutero-imidazo[1,2-a]pyridine-3-carboxylic acid (24n) [ftimg=68000058] 2-aminopyridine (d6) (10 g, 99.91 mmol) and potassium 2-chloro-3-ethoxy-3-oxoprop-1-en-1-olate (22) (46.93 g, 250 mmol) were suspended in dry etoh (300 ml) and h2so4 (6.65 ml, 128.8 mmol) was added dropwise at ambient temperature. after the addition, the resulting mixture was heated at reflux for 3 hours before pyridine (20 ml) was added and reflux continued overnight. the reaction was then cooled and solvent evaporated. the residue was partitioned between saturated nahco3 solution and etoac. the aqueous phase was further extracted with etoac and the combined organic phase was washed with brine and dried (mgso4). after filtration and concentration, the residue was purified over silica using etoac/hexane to give ethyl 5,6,7,8-deutero-imidazo[1,2-a]pyridine-3-carboxylate. 1h nmr (400 mhz, cdcl3) delta 8.30 (s, 1 h), 4.42 (q, j=8.4 hz, 2 h), 1.34 (t, j=8.4 hz, 3 h). ms m/z 195.1 (m+1)+. lioh (15.8 g, 377.1 mmol) was added to a stirred solution of ethyl 5,6,7,8-deutero-imidazo[1,2-a]pyridine-3-carboxylate (18.7 g, 95.3 mmol) in thf (100 ml), meoh (100 ml) and h2o (100 ml). after 3 hours, the solvent was evaporated and the solid was resuspended in water. nahso4 (50 g) was added to neutralize the solution and the precipitate was filtered. the solid 5,6,7,8-deutero-imidazo[1,2-a]pyridine-3-carboxylic acid (24 n) was dried in vacuum oven and used without further purification. 1h nmr (400 mhz, d6-dmsol) delta 8.22 (s, 1 h). ms m/z 167.0 (m+1)+. intermediate number structure physical data 24a [ftimg=68000059] 1h nmr (400 mhz, d6-dmsol) delta 9.64-9.62 (m, 1 h), 8.39 (s, 1 h), 8.01 (d, j = 9.2 hz, 1 h), 7.81 (dd, j = 2.0, 9.2 hz, 1 h). ms m/z 231.2 (m + 1)+. 24b [ftimg=68000060] ms m/z 181.2 (m + 1)+. 24c [ftimg=68000061] ms m/z 181.2 (m + 1)+. 24d [ftimg=68000062] ms m/z 188.1 (m + 1)+. 24e [ftimg=68000063] ms m/z 188.1 (m + 1)+. 24f [ftimg=68000064] ms m/z 241.0 (m + 1)+. 24g [ftimg=68000065] ms m/z 270.0 (m + 1)+. 24h [ftimg=68000066] 1h nmr (400 mhz, d6-dmsol) delta 8.94 (d, j = 2.0 hz, 1 h), 8.13 (s, 1 h), 7.70 (d, j = 9.6 hz, 1 h), 7.31 (dd, j = 0.8, 9.8 hz, 1 h), 3.85 (s, 3h). ms m/z 193.1 (m + 1)+. 24i [ftimg=68000067] ms m/z 177.6 (m + 1)+. 24j [ftimg=68000068] ms m/z 177.6 (m + 1)+. 24k [ftimg=68000069] ms m/z 209.06 (m + 1)+. 24l [ftimg=68000070] 1h nmr (400 mhz, d6-dmsol) delta 9.21 (s, 1 h), 8.22 (s, 1 h), 7.76 (d, j = 9.2 hz, 1 h), 7.50 (dd, j = 1.6, 9.2 hz, 1 h), 3.72-3.69 (m, 4 h), 3.40-3.28 (m, 2 h), 2.99-2.92 (m, 4 h), 2.88-2.82 (m, 2 h). ms m/z 276.13 (m + 1)+. 24m [ftimg=68000071] 1h nmr (400 mhz, d6-dmsol) delta 9.29 (d, j = 1.6 hz, 1 h), 9.15 (dd, j = 1.6, 4.4 hz, 1 h), 8.4 (s, 1 h), 8.20 (d, j = 4.4 hz, 1 h). ms m/z 164.1 (m + 1)+. 24n [ftimg=68000072] ms m/z 167.0 (m + 1)+. 24o [ftimg=68000073] 1h nmr (400 mhz, d6-dmsol) delta 8.79 (s, 1 h), 8.49 (s, 1 h), 7.84 (m, 2 h), 3.80 (m, 4 h), 3.16 (m, 4 h). ms m/z 248.1 (m + 1)+. 24p [ftimg=68000074] 1h nmr (400 mhz, d6-dmsol) delta 9.69 (dd, j = 0.8, 2.0 hz, 1 h), 9.54 (s, 1 h), 8.42 (s, 1 h), 8.23 (s, 1 h), 8.09 (dd, j = 0.8, 9.6 hz, 1 h), 7.95 (dd, j = 2.0, 9.6 hz, 1 h), 7.87 (s, 1 h). ms m/z 248.1 (m + 1)+. 24q [ftimg=68000075] ms m/z 216.0 (m + 1)+. 24r [ftimg=68000076] /ms m/z 205.0 (m + 1)+. 24s [ftimg=68000077] ms m/z 270.0 (m + 1)+. 24t [ftimg=68000078] ms m/z 207.1 (m + 1)+. 24u [ftimg=68000079] ms m/z 243.1 (m + 1)+. synthesis of 6-(3-cyanopropyl)imidazo[1,2-a]pyridine-3-carboxylic acid (25) [ftimg=68000080] to a stirring suspension of 5-bromopyridin-2-amine (1.2 g, 7.05 mmol) and ethyl 2-chloro-3-hydroxyacrylate potassium salt (6.6 g, 28.19 mmol) (prepared in a similar manner as 22) in etoh (100 ml) at room temperature was added sulfuric acid (751 micro l, 14.10 mmol) dropwise. the reaction mixture was heated at 78 degrees centigrade overnight. the reaction was cooled to room temperature and the solvent was concentrated. the residue was taken in water and the ph was adjusted between 6-8 with saturated sodium bicarbonate. the crude product was extracted with ethyl acetate. the organic was washed with brine and dried over anhydrous sodium sulfate. the crude product was purified by silica chromatography to yield ethyl 6-bromoimidazo[1,2-a]pyridine-3-carboxylate (24s). ms m/z 270.2 (m+1)+. a stirring mixture of ethyl 6-bromoimidazo[1,2-a]pyridine-3-carboxylate (24s) (500 mg, 1.86 mmol), allyl cyanide (224 ul, 2.79 mmol), tris(dibenzylideneacetone)dipalladium(0) (26 mg, 0.028 mmol), [(t-butyl)3ph]bf4 (16 mg, 0.056 mmol), and n-dicyclohexylmethylamine (433 micro l, 2.04 mmol) in anhydrous 1,4-dioxane (6 ml) was heated at 95 degrees centigrade overnight. the reaction was cooled to room temperature and filtered. the solvent was concentrated. the crude product was purified by silica chromatography to give ethyl 6-(3-cyanoprop-1-enyl)imidazo[1,2-a]pyridine-3-carboxylate (24v). ms m/z 256.4 (m+1)+. to a stirring solution of ethyl 6-(3-cyanoprop-1-enyl)imidazo[1,2-a]pyridine-3-carboxylate (24v) (400 mg, 1.57 mmol) in etoh:etoac (1:1, 10 ml) was added catalytic pd/c (10 wt percent, wet basis). the reaction was hydrogenated by balloon overnight then filtered through celite. the crude product ethyl 6-(3-cyanopropyl)imidazo[1,2-a]pyridine-3-carboxylate (24w) was used in the next step without further purification. ms m/z 258.4 (m+1)+. to a stirring

solution of ethyl 6-(3-cyanopropyl)imidazo[1,2-a]pyridine-3-carboxylate (24w) (375 mg, 1.46 mmol) in thf:meoh (4:1, 5 ml) was added 2n lioh (500 micro l). the reaction was heated at 50 degrees centigrade for 45 minutes then cooled to room temperature and the ph was adjusted between 3-4 with 1n hcl. the solvent was partially concentrated and the remaining aqueous was lyophilized to yield 6-(3-cyanopropyl)imidazo[1,2-a]pyridine-3-carboxylic acid (25). 1h nmr (400 mhz, d6-dms) delta 9.21-9.19 (m, 1 h), 8.45 (s, 1 h), 7.85 (dd, j=0.8, 9.2 hz, 1 h), 7.70 (dd, j=1.6, 9.2 hz, 1 h), 2.82 (t, j=7.2 hz, 2 h), 2.55 (t, j=7.2 hz, 2 h), 1.97-1.90 (m, 2 h). ms m/z 230.3 (m+1)+. synthesis of n-(5-(5-(aminomethyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (26) [ftimg=68000081] to a stirring suspension of tert-butyl 3-(3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)methyl(methyl) carbamate (f54) (90 mg, 0.195 mmol) in acetonitrile (1 ml) was added 4n hcl in dioxane (1 ml) and water (0.5 ml). the reaction mixture was stirred at room temperature for 45 minutes. then, the solvent was concentrated and the crude product was dried under high vacuum. the crude product n-(5-(5-(aminomethyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (26) was used in the next step without further purification. 1h nmr (400 mhz, d6-dms) delta 10.04 (s, 1 h), 9.46-9.44 (m, 1 h), 8.74 (s, 2 h), 8.63 (s, 1 h), 8.15 (d, j=2.0 hz, 1 h), 7.86-7.80 (m, 2 h), 7.59-7.54 (m, 1 h), 7.55 (d, j=8.4 hz, 1 h), 7.23-7.20 (m, 1 h), 4.62 (s, 2 h), 2.39 (s, 3 h). ms m/z 349.4 (m+1)+. synthesis of methyl 3-(3-(3-amino-4-methylphenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (31) [ftimg=68000082][ftimg=68000083]a stirring mixture of 4-methyl-3-nitrobenzonitrile (2 g, 12.33 mmol), hydroxylamine hydrogen chloride (1 g, 14.80 mmol) and n-diisopropylethylamine (3.2 ml, 18.50 mmol) in etoh (20 ml) was heated at 78 degrees centigrade for 3 hours. then, the solvent was concentrated and the crude product was dried under high vacuum. the crude product was taken in water and the solid was collected by vacuum filtration. the crude product (27) was used in the next step without further purification. ms m/z 196.3 (m+1)+. to a stirring solution of boc-azetidine-3-carboxylic acid (1.9 g, 9.22 mmol) in anhydrous nmp (12 ml) was added 1,1'-carbonyldiimidazole (cdi) (1.5 g, 9.22 mmol). the reaction was stirred for 5 minutes. then, n'-hydroxy-4-methyl-3-nitrobenzimidamide (27) (1.2 g, 6.1 mmol) was added and the reaction was stirred for 25 minutes. next, the reaction was heated in the microwave at 115 degrees centigrade for 12 minutes. the crude product was extracted with ethyl acetate. the organic was washed with water/brine mixture followed by brine and dried over anhydrous sodium sulfate. the solvent was concentrated and the crude product tert-butyl 3-(3-(4-methyl-3-nitrophenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (28) was taken in dichloromethane and minimal tetrahydrofuran and purified by silica chromatography. ms m/z 361.4 (m+1)+. to stirring suspension of tert-butyl 3-(3-(4-methyl-3-nitrophenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (28) (1 g, 2.78 mmol) in acetonitrile (2 ml) was added 4 n hcl in dioxane (5 ml). the reaction was stirred at room temperature for 1 hour. the solvent was concentrated and the crude product was dried under high vacuum to yield 5-(azetidin-3-yl)-3-(4-methyl-3-nitrophenyl)-1,2,4-oxadiazole hydrochloride (29). ms m/z 261.4 (m+1)+. to a stirring suspension of 5-(azetidin-3-yl)-3-(4-methyl-3-nitrophenyl)-1,2,4-oxadiazole hydrochloride (29) (825 mg, 2.78 mmol) in anhydrous dichloromethane (20 ml) at 0 degrees centigrade was added n,n-diisopropylethylamine (1.2 ml, 6.95 mmol) and methyl chloroformate (215 micro l, 2.78 mmol) dropwise. the reaction was stirred to room temperature for 25 minutes. the crude product was purified by silica chromatography to yield 3-(3-(4-methyl-3-nitrophenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (30). ms m/z 425.39 (m+1)+. to a stirring suspension of methyl 3-(3-(4-methyl-3-nitrophenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (30) (795 mg, 2.50 mmol) in etoh (20 ml) was added stannous chloride dihydrate (2.3 g, 9.99 mmol). the reaction mixture was heated at 78 degrees centigrade for 3 hours. then, the reaction was cooled to room temperature and the solvent was partially concentrated. the ph was adjusted to slightly basic ph with a saturated solution of sodium bicarbonate. the resulting white suspension was filtered and washed with water and ethyl acetate. the aqueous was extracted with ethyl acetate and washed with water, brine and dried over anhydrous sodium sulfate. the solvent was concentrated to give methyl 3-(3-(3-amino-4-methylphenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (31). 1h nmr (400 mhz, d6-dms) delta 7.32 (d, j=1.6 hz, 1 h), 7.12 (dd, j=1.6, 7.6 hz, 1 h), 7.30 (d, j=7.6 hz, 1 h), 5.19 (s, 2 h), 4.38-4.31 (m, 2 h), 4.27-4.20 (m, 1 h), 4.19-4.16 (m, 2 h), 3.60 (s, 3 h), 2.10 (s, 3 h). ms m/z 289.12 (m+1)+. synthesis of n-(5-(5-(chloromethyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (38) [ftimg=68000084]a mixture of n-(5-(n'-hydroxycarbamidoyl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (9) (500 mg, 1.62 mmol) and 2-chloroacetic anhydride (553 mg, 3.23 mmol) in anhydrous nmp (10 ml) was heated in the microwave at 110 degrees centigrade for 12 minutes. the crude was diluted with water and extracted with ethyl acetate. the organic was washed with water/brine mixture and dried over anhydrous sodium sulfate. the solvent was concentrated and the crude product was purified by silica chromatography to yield n-(5-(5-(chloromethyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (38). ms m/z 378.9 (m+1)+. synthesis of (z)-6-fluoro-n-(5-(n'-hydroxycarbamidoyl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (40) [ftimg=68000085]oxalyl chloride (10 ml, 110 mmol) was added dropwise to a stirred suspension of 6-fluoroimidazo[1,2-a]pyridine-3-carboxylic acid (24b) (2 g, 11 mmol) and catalytic amounts of dmf in dichloromethane (20 ml). after 5 hours, the solvent was evaporated and the solid was suspended in dry dce (20 ml) and added to a stirred solution of 3-amino-4-methylbenzonitrile (1.45 g, 11 mmol) and diea (6 mmol) in dce (10 ml) at 0 degrees centigrade after the addition, the reaction was heated at 60 degrees centigrade for 5 hours. the mixture was subjected to standard aqueous work and silica purification to give n-(5-cyano-2-methylphenyl)-6-fluoroimidazo[1,2-a]pyridine-3-carboxamide (39) as a solid. 1h nmr (400 mhz, d6-dms) delta 10.14 (s, 1 h), 9.45 (dd, j=5.2, 2.0 hz, 1 h), 8.62 (s, 1 h), 7.90-7.87 (m, 2 h), 7.68-7.63 (m, 1 h), 7.53 (d, j=8.0 hz, 1 h), 2.37 (s, 3 h). ms m/z 295.1 (m+1)+.nh2oh (5 ml, 16.1 mmol) was added in one portion to a stirred suspension of n-(5-cyano-2-methylphenyl)-6-fluoroimidazo[1,2-a]pyridine-3-carboxamide (39) (0.95 g, 3.23 mmol). the resulting suspension was heated at 60 degrees centigrade overnight and then cooled to 0 degrees centigrade the product, (z)-6-fluoro-n-(5-(n'-hydroxycarbamidoyl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (40) was collected by filtration. ms m/z 328.1 (m+1)+. synthesis of methyl 3-(3-(3-(7-bromoimidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (42) [ftimg=68000086] to a stirring suspension of 7-bromoimidazo[1,2-a]pyridine-3-carboxylic acid (24f) (400 mg, 1.67 mmol), in anhydrous dichloromethane (2 ml) at 0 degrees centigrade under argon was added dropwise oxalyl chloride (325 micro l, 3.72 mmol). then, a drop of anhydrous dmf was added and the reaction mixture was stirred at room temperature for 1.5 hour. the solvent was concentrated and the crude solid was added portion-wise to a stirring solution of methyl 3-(3-(3-amino-4-methylphenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (31) (429 mg, 1.49 mmol) in anhydrous pyridine (1 ml) at 0 degrees centigrade the reaction was stirred to room temperature under argon for 30 minutes. then, the reaction was quenched with water. the solvent was concentrated and the crude product was purified by silica chromatography to yield methyl 3-(3-(3-(7-bromoimidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (42). ms m/z 511.1 (m+1)+.the following compounds were prepared according to the protocol described for methyl 3-(3-(3-(7-bromoimidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (42).intermediatenumberstructurephysical data42g [ftimg=68000087]1h nmr (400 mhz, d6-dms) delta 10.12 (s, 1 h), 9.38 (dd, j= 0.8, 7.2 hz, 1h), 8.59 (s, 1h), 8.14 (dd, j= 0.8, 2.4 hz, 1h), 8.09 (d, j= 1.6 hz, 1h), 7.85 (dd, j= 2.0, 8.0 hz, 1h), 7.51 (d, j= 8.0 hz, 1h), 7.35 (dd, j= 2.0, 7.6 hz, 1h), 4.16-4.42 (m, 5h), 3.60 (s, 3h), 2.37 (s, 3h). ms m/z 511.0, 513.0 (m + 1)+.42j[ftimg=68000088]ms m/z 511.0, 513.0 (m + 1)+. synthesis of 3-(3-(3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)methyl methanesulfonate (44) [ftimg=68000089]carbonyl diimidazole (cdi) (324 mg, 2.0 mmol) was added to a stirred solution of 2-acetoxycetic acid (236 mg, 2.0 mmol) in nmp. after 20 minutes, n-(5-(n'-hydroxycarbamidoyl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (9) (310 mg, 1.0 mmol) was added in one portion and the resulting solution was stirred for 1 hour before it was heated at 125 degrees centigrade for 15 minutes in a microwave reactor. the reaction solution was subjected to standard aqueous work up to afford a residue which was hydrolyzed by lithium hydroxide monohydrate (252 mg, 6.0 mmol) in thf:meoh/h2o (3:2:1). after removal of all solvents 2m nahco3 (10 ml) was added. the precipitate was filtered and dried in air to afford n-(5-(5-(hydroxymethyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (43). 1h nmr (400 mhz, d6-dms) delta 10.02 (s, 1 h), 9.46 (d, j=6.8 hz, 1 h), 8.59 (s, 1 h), 8.11 (s, 1 h), 7.82 (m, 2 h), 7.53 (m, 2 h), 7.18 (m, 1 h), 6.08 (m, 1 h), 4.80 (d, j=6.0 hz, 2 h), 2.37 (s, 3 h). ms m/z 350.1 (m+1)+. to a solution of n-(5-(5-(hydroxymethyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (43) (210 mg, 0.6 mmol) and diea (0.32 ml, 1.8 mmol) in dcm (5 ml) was added mscl (138 mg, 1.2 mmol). the mixture was stirred at room temperature for 10 minutes then subjected to standard aqueous work up. the crude product was purified by silica chromatography to yield 3-(3-(3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)methyl methanesulfonate (44) (180 mg, 70 percent yield). ms m/z 428.1 (m+1)+.the following compounds were prepared according to the protocol described for 3-(3-(3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)methyl methanesulfonate (44).intermediatenumberstructurephysical data44a [ftimg=68000090]ms m/z 442.1 (m + 1)+.44b[ftimg=68000091]ms m/z 442.1 (m + 1)+.44c[ftimg=68000092]ms m/z 432.1 (m + 1)+.44d[ftimg=68000093]ms m/z 446.1 (m + 1)+. synthesis of n-(5-(5-(3-aminooxetan-3-yl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (47) [ftimg=68000094]a mixture of 3-aminooxetane-3-carboxylic acid (117.0 mg, 1.0 mmol) and nme4oh.5h2o (tmah) (181.0 mg, 1.0 mmol) in ch3cn (10 ml) was stirred at room temperature for 30 minutes. then (boc)2o (327.3 mg, 1.5 mmol) was added and the resulting mixture was stirred overnight. water (10 ml) was added and the mixture was extracted with ether (20 ml). the aqueous layer was acidified to ph=2 by addition of citric acid (solid) and extracted with etoac (2x20 ml). the organic layers were combined, dried over na2so4, filtered and concentrated to yield crude 3-((tert-butoxycarbonyl)amino)oxetane-3-carboxylic acid (45) which was used without further purification. ms m/z 218.1 (m+1)+.carbonyl diimidazole (cdi) (162.2 mg, 1.0 mmol) was added to a stirred solution of 3-((tert-butoxycarbonyl)amino)oxetane-3-carboxylic acid (45) (217.1 mg, 1.0 mmol)] in nmp (1.0 ml). after 20 minutes, n-(5-(n'-hydroxycarbamidoyl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (9) (150.0 mg, 0.5 mmol) was added in one portion and the resulting solution was stirred for 1 hour before it was heated at 125 degrees centigrade for 15 minutes in a microwave reactor. the reaction solution was subjected to standard aqueous work up to afford a residue which was purified by silica chromatography to yield tert-butyl 3-(3-(3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)oxetan-3-yl) carbamate (46) (159 mg, 65 percent yield). ms m/z 491.2 (m+1)+.3-(3-(3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl) oxetan-3-yl)carbamate (46) (29.5 mg, 0.06 mmol) was dissolved in tfa (0.5 ml) and stirred at room temperature for 10 minutes. then tfa was removed under vacuum to yield crude n-(5-(5-(3-aminooxetan-3-yl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (47) as a tfa salt which was used without further purification. ms m/z 391.1 (m+1)+. synthesis of n-(2-fluoro-5-(n'-hydroxycarbamidoyl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (50) [ftimg=68000095]a mixture of 4-fluoro-3-nitrobenzonitrile (5.0 g, 30.1 mmol) and fe powder (5.05 g, 90.3 mmol) in acoh (100 ml) was heated at 80 degrees centigrade for 1 hour under n2. then the solvent was removed under vacuum and water (200 ml) was added to the residue. the solution was adjusted to ph 6 by addition of na2co3 and extracted with dcm (2x200 ml). the organic layers were combined, dried over na2so4, filtered and concentrated to yield 3-amino-4-fluorobenzonitrile (48), which was used without further purification. ms m/z 137.0 (m+1)+. to a stirring suspension of imidazo[1,2-a]pyridine-3-carboxylic acid (1) (3.0 g, 18.5 mmol) in anhydrous dichloromethane (50 ml) at 0 degrees centigrade was added dropwise oxalyl chloride (4.84 ml, 55.5 mmol). then, three drops of anhydrous dmf was added and the reaction mixture was stirred at room temperature for 15 minutes. the solvent was concentrated and the crude solid was added to a stirring solution of 3-amino-4-fluorobenzonitrile (48) (2.5 g, 18.5 mmol) in anhydrous pyridine (50 ml) at room temperature. the reaction was stirred for 20 minutes and quenched with water (200 ml) with stirring for another 10 minutes. then the precipitate was filtered and dried in air to yield n-(5-cyano-2-fluorophenyl)imidazo[1,2-a]pyridine-3-carboxamide (49). 1h nmr (400 mhz, d6-dms) delta 10.40 (s, 1h), 9.43 (td, j=1.2, 6.8 hz, 1h), 8.63 (s, 1h), 8.21 (dd, j=2.0, 7.2 hz, 1h), 7.78-7.84 (m, 2h), 7.54-7.63 (m, 2h), 7.22 (dt, j=1.2, 6.8, 1h). ms m/z 281.1 (m+1)+.nh2oh (10 ml, 32.1 mmol) was added in one portion to a stirred suspension of n-(5-cyano-2-fluorophenyl)imidazo[1,2-a]pyridine-3-carboxamide (49) (3.6 g, 12.85 mmol) in etoh (100 ml). the resulting suspension was heated at 70 degrees centigrade for 3 hours and then the solvent was removed to yield n-(2-fluoro-5-(n'-hydroxycarbamidoyl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (50). 1h nmr (400 mhz, d6-dms) delta 10.21 (s, 1h), 9.70 (s, 1h), 9.45 (td, j=1.2, 7.2 hz, 1h), 8.61 (s, 1h), 7.95 (dd, j=2.4, 7.6 hz, 1h), 7.79 (td, j=1.2, 8.8 hz, 1h), 7.51-7.60 (m, 2h), 7.31-7.37 (m, 1h), 7.19 (dt, j=1.2, 6.8, 1h), 5.88 (s, 2h). ms m/z 314.1 (m+1)+.the following compounds were prepared according to the protocol described for n-(2-fluoro-5-(n'-hydroxycarbamidoyl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (50).intermediatenumberstructurephysical data50a[ftimg=68000096]1h nmr (400 mhz, d6-dms) delta 9.96 (s, 1h), 9.65 (s, 1h), 9.44 (td, j= 0.8, 6.8 hz, 1h), 8.55 (s, 1h), 7.78 (td, j= 1.2, 9.2 hz, 1h), 7.52 (m, 2h), 7.21 (d, j= 11.6 hz, 1h), 7.17 (dt, j= 1.2, 6.8, 1h), 5.81 (s, 2h), 2.28 (s, 3h). ms m/z 328.1 (m + 1)+.50b[ftimg=68000097]ms m/z 422.1 (m + 1)+.50c[ftimg=68000098]1h nmr (400 mhz, d6-dms) delta 9.89 (s, 1h), 9.44 (td, j= 6.8, 1.2 hz, 1h), 9.33 (s, 1h), 8.55 (s, 1h), 7.76 (td, j= 9.2, 1.2 hz, 1h), 7.49-7.52 (m, 1h), 7.28 (s, 1h), 7.17 (d, j= 11.6 hz, 1h), 5.72 (s, 2h), 2.34 (s, 3h), 2.24 (s, 3h). ms m/z 324.1 (m + 1)+.50d[ftimg=68000099]1h nmr (400 mhz, d6-dms) delta 9.84 (s, 1h), 9.43 (d, j= 6.8 hz, 1h), 8.59 (s, 1h), 7.78 (d, j= 8.8 hz, 1h), 7.50 (d, j= 8.0 hz, 1h), 7.17 (m, 3h), 5.76 (s, 2h), 2.25 (s, 3h), 2.24 (s, 3h). ms m/z 324.1 (m + 1)+.50e[ftimg=68000100]1h nmr (400 mhz, d6-dms) delta 9.90 (s, 1h), 9.60 (s, 1h), 9.32 (d, j= 7.2 hz, 1h), 8.50 (s, 1h), 7.69 (d, j= 2.20 hz, 1h), 7.56 (m, 1h), 7.50 (dd, j= 1.6, 8.0 hz, 1h), 7.29 (d, j= 8.0 hz, 1h), 7.02 (dd, j= 1.6, 7.2 hz, 1h), 5.80 (s, 2h), 2.42 (s, 3h), 2.27 (s, 3h). ms m/z 324.1 (m + 1)+.50f[ftimg=68000101]1h nmr (400 mhz, d6-dms) delta 10.09 (s, 1h), 9.63 (m, 1h), 9.60 (s, 1h), 8.58 (s, 1h), 7.78 (dd, j= 0.8, 9.6 hz, 1h), 7.69 (d, j= 1.6 hz, 1h), 7.66 (dd, j= 2.0, 9.2 hz, 1h), 7.52 (dd, j= 1.6, 8.0 hz, 1h), 7.31 (d, j= 8.0 hz, 1h), 5.81 (s, 2h), 2.27 (s, 3h). ms m/z 388.0, 390.0 (m + 1)+. synthesis of 5-amino-2-fluoro-4-methylbenzonitrile (51) [ftimg=68000102]a mixture of 5-bromo-4-fluoro-2-methylaniline (2.04 g, 10.0 mmol), cucn (889 mg, 10.0 mmol) and cui (1.9 g, 10.0 mmol) in nmp was purged with n2 for 5 minutes and then sealed and heated at 195 degrees centigrade for 30 minutes under microwave condition. the mixture was subjected to standard aqueous workup to give a residue which was purified by silica chromatography to yield 5-amino-2-fluoro-4-methylbenzonitrile (51) (540 mg, 36 percent yield). ms m/z 151.0 (m+1)+. synthesis of n-(5-(5-(azetidin-3-ylmethyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (55) [ftimg=68000103]carbonyl diimidazole (cdi) (52.0 mg, 0.32 mmol) was added to a stirred solution of 2-(1-(tert-butoxycarbonyl)azetidin-3-yl)acetic acid (69.0 mg, 0.32 mmol) in nmp (1.0 ml). after 20 minutes, n-(5-(n'-hydroxycarbamidoyl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (9) (49.5 mg, 0.16 mmol) was added in one portion and the resulting solution was stirred for 30 minutes before it was heated at 125 degrees centigrade for 15 minutes in a microwave reactor. the reaction mixture was added dropwise to water (20 ml) with stirring. the precipitate was filtered and dried to give tert-butyl 3-(3-(3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)methyl)azetidine-1-carboxylate (54). ms m/z 489.2 (m+1)+.3-(3-(3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)methyl)azetidine-1-carboxylate (54) (29.3 mg, 0.06 mmol) was dissolved in tfa (0.5 ml) and stirred at room temperature for 10 minutes. then tfa was removed under

vacuum to yield crude n-(5-(5-(azetidin-3-ylmethyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (55) which was used without further purification. ms m/z 389.2 (m+1)+. synthesis of 2-(3-(3-difluoropyrrolidin-1-yl)-3-methoxypropanoic acid (58) [ftimg=68000104]a mixture of methyl 2-bromo-3-methoxypropanoate (132.0 mg, 0.66 mmol), 3,3-difluoropyrrolidine (70.6 mg, 0.66 mmol) and k2co3 (91.2 mg, 0.66 mmol) in dmf (2 ml) was heated at 90 degrees centigrade for 3 hours. the mixture was subjected to standard aqueous workup to afford a residue which was dissolved in thf/meoh/h2o (3:2:1, 5 ml). lioh (6n, 3.3 mmol) was added and the resulting mixture was stirred at room temperature for 30 minutes. the solution was acidified to ph5 by addition of 6n hcl. all solvents were removed under vacuum to give a crude 2-(3-(3-difluoropyrrolidin-1-yl)-3-methoxypropanoic acid (58) which was used without purification. ms m/z 210.1 (m+1)+. synthesis of 6-(((triosopropylsilyl)oxy)methyl)imidazo[1,2-a]pyridine-3-carboxylic acid (61) [ftimg=68000105]to a stirring suspension of (6-aminopyridin-3-yl)methanol (1.24 mg, 10.0 mmol) and ethyl 2-chloro-3-hydroxyacrylate, potassium salt (29) (3.76 g, 20.0 mmol) in etoh (10 ml) at room temperature was added conc sulfuric acid (10.0 mmol) dropwise. the reaction mixture was stirred at room temperature for 15 minutes and pyridine (0.92 g, 12.0 mmol) was added. the resulting mixture was heated at 85 degrees centigrade overnight. the reaction was cooled to room temperature and the solvent was concentrated. the residue was taken in water and the solution was adjusted to ph 8 with saturated sodium bicarbonate. the crude product was extracted with ethyl acetate. the organic layer was washed with brine and dried over anhydrous sodium sulfate. the crude product ethyl 6-(hydroxymethyl)imidazo[1,2-a]pyridine-3-carboxylate (59) was purified by silica chromatography. 1h nmr (400 mhz, d6-dmsol) delta 9.16 (d, j=6.8 hz, 1h), 8.26 (s, 1h), 7.67 (s, 1h), 7.19 (dd, j=1.6, 6.8 hz, 1h), 5.57 (t, j=6.4 hz, 1h), 4.63 (d, j=6.0, 2h), 4.36 (q, j=7.2 hz, 2h), 1.35 (t, j=6.8 hz, 3h). ms m/z 221.1 (m+1)+. to a suspension of ethyl 6-(hydroxymethyl)imidazo[1,2-a]pyridine-3-carboxylate (59) (497.0 mg, 2.26 mmol), dmap (12.2 mg, 0.1 mmol) and 1h-imidazole (154.0 mg, 2.26 mmol) in dichloromethane (10 ml), was added tipsci (523.0 mg, 2.71 mmol). the resulting mixture was stirred overnight at room temperature. the solvent was removed under vacuum to yield crude ethyl 6-(((triosopropylsilyl)oxy)methyl)imidazo[1,2-a]pyridine-3-carboxylate (60). ms m/z 377.2 (m+1)+. the crude ethyl 6-(((triosopropylsilyl)oxy)methyl)imidazo[1,2-a]pyridine-3-carboxylate (60) obtained above was dissolved in thf/meoh/h2o (3:2:1, 5 ml). 6n lioh (2.27 ml, 13.6 mmol) was added and the reaction mixture was stirred at room temperature for 2 hours. all solvents were removed and 6n hcl was added until ph 5-6. etoac (5 ml) was added and the mixture was stirred for 1 hour. the precipitate was filtered and dried to give 6-(((triosopropylsilyl)oxy)methyl)imidazo[1,2-a]pyridine-3-carboxylic acid (61). 1h nmr (400 mhz, d6-dmsol) delta 9.37 (s, 1h), 8.21 (s, 1h), 7.76 (dd, j=1.2, 9.2 hz, 1h), 7.46 (dd, j=2.0, 9.2 hz, 1h), 4.94 (s, 2h), 1.20 (m, 3h), 1.08 (d, j=6.8 hz, 18h). ms m/z 349.2 (m+1)+. synthesis of 7-(1h-pyrazol-3-yl)imidazo[1,2-a]pyridine-3-carboxylic acid (63) [ftimg=68000106]to a solution of 5-ethyl 7-bromoimidazo[1,2-a]pyridine-3-carboxylate 24 g (202 mg, 0.75 mmol) in dmf (2 ml) was added (1h-pyrazol-3-yl)boronic acid (101 mg, 0.903 mmol), 1.8 m k2co3 (1.3 ml, 2.26 mmol) and pd(pph3)4 (87 mg, 0.075 mmol). the reaction was evacuated and backfilled with nitrogen twice then heated at 160 degrees centigrade for 10 minutes in a microwave oven. after the reaction mixture was filtered through a pad of celite, the mixture was diluted with a saturated solution of nh4cl and extracted with ethyl acetate. the organic layer was washed with brine, dried over na2so4 and concentrated to give ethyl 7-(1h-pyrazol-3-yl)imidazo[1,2-a]pyridine-3-carboxylate (62). ms (m/z) 257.1 (m+1)+. to a stirring solution of ethyl 7-(1h-pyrazol-3-yl)imidazo[1,2-a]pyridine-3-carboxylate (62) (103 mg, 0.4 mmol) in thf:meoh:h2o (3:2:1, 1.6 ml) was added 6n lioh (0.035 ml). the reaction was stirred at room temperature for 20 minutes. the ph was adjusted between 4-5 with 3n hcl. the resulting mixture was concentrated to yield 7-(1h-pyrazol-3-yl)imidazo[1,2-a]pyridine-3-carboxylic acid (63). ms (m/z) 229.2 (m+1)+. synthesis of n-(5-amino-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (67) [ftimg=68000107]oxaly chloride (10 ml) was added dropwise to a stirred solution of imidazo[1,2-a]pyridine-3-carboxylic acid (1) (3 g, 18.5 mmol) in dry dichloromethane (100 ml) and a few drops of dmf. the resulting solution was stirred at room temperature for 5 hours before it was evaporated to dryness and fresh dichloromethane was added to the resulting acid chloride to make a suspension. in a separate flask, tert-butyl 3-amino-4-methylphenylcarbamate (65) (4.5 g, 20.3 mmol) and diea (10 ml) was dissolved in dichloromethane (100 ml) and the above acid chloride solution was added slowly. the resulting solution was stirred overnight at room temperature. saturated nh4cl was added to the reaction solution and the phases were separated. the organic layer was dried over na2so4 and filtered. after evaporation, the residue was purified over silica gel column using hexane and etoac to give tert-butyl 3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenylcarbamate (66) as a slightly yellow solid. tfa (50 ml) was added to a stirred suspension of tert-butyl 3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenylcarbamate (66) in me2s (5 ml) and dichloromethane (10 ml). after 2 hours the solution was evaporated and partitioned with dichloromethane and saturated nahco3. the aqueous layer was extracted several times with dichloromethane and the combined organic layers were dried over na2so4. n-(5-amino-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (67) was isolated and used without further purification. 1h nmr (400 mhz, cdcl3) delta 9.44 (d, j=6.8 hz, 1 h), 8.05 (s, 1 h), 7.67 (d, j=8.8 hz, 1 h), 7.38-7.33 (m, 2 h), 6.98-6.94 (m, 2 h), 2.19 (s, 3 h). ms m/z 267.1 (m+1)+. synthesis of (e)-n-(5-(2-hydroxyguanidino)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (69) [ftimg=68000108]to n-(5-amino-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (67) (4.53 g, 15 mmol) in meoh (100 ml) was added koac (4.41 g, 45 mmol) and the mixture was stirred at room temperature for 5 minutes then cooled to 0 degrees centigrade before a solution of brcn (1.62 g, 15 mmol) in meoh (30 ml) was added dropwise. the resulting mixture was slowly warmed to room temperature and stirred overnight. the solvent was evaporated and to the residue was added water (150 ml). the mixture was stirred at room temperature for 1 hour, filtered and washed with water (2x20 ml), then air dried to give n-(5-cyanamido-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (68) as a white solid. to a suspension of n-(5-cyanamido-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (68) 3.52 g (12.1 mmol) in 200 ml of etoh was added 0.75 ml nh2oh (50 wt percent in water, 12.1 mmol). the resulting mixture was stirred at room temperature overnight. the precipitate was filtered, washed with etoh (10 ml) and air dried to give n-(5-(2-hydroxyguanidino)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (69) as a white solid, which was used directly in the next step without further purification. 1h nmr (400 mhz, d6-dmsol) delta 9.44 (s, 1 h), 9.46 (dd, j=6.8, 0.8 hz, 1 h), 8.54 (s, 1 h), 8.34 (s, 1 h), 7.76 (dd, j=7.2, 2.2 hz, 1 h), 7.59 (s, 1 h), 7.52-7.43 (m, 2 h), 7.18-7.06 (m, 2 h), 2.13 (s, 3 h). ms m/z 325.1 (m+1)+. synthesis of 6-(3-(tert-butoxy)-3-oxopropyl)imidazo[1,2-a]pyridine-3-carboxylic acid (72) [ftimg=68000109]a stirring mixture of ethyl 6-bromoimidazo[1,2-a]pyridine-3-carboxylate (24s) (500 mg, 1.86 mmol), tert-butyl acrylate (408 ul, 2.79 mmol), tris(dibenzylideneacetone)dipalladium(0) (51 mg, 0.056 mmol), [(t-bu)3ph]bf4 (27 mg, 0.093 mmol) and n,n-dicyclohexylmethylamine (738 ul, 3.48 mmol) in anhydrous 1,4-dioxane (5 ml) was heated at 95 degrees centigrade overnight. the reaction was cooled to room temperature and filtered. the solvent was concentrated and the crude product was purified by silica chromatography to yield ethyl 6-(3-(tert-butoxy)-3-oxoprop-1-en-1-yl)imidazo[1,2-a]pyridine-3-carboxylate (70). ms m/z 317.14 (m+1)+. a stirring mixture of ethyl 6-(3-(tert-butoxy)-3-oxoprop-1-en-1-yl)imidazo[1,2-a]pyridine-3-carboxylate (70) (460 mg, 1.80 mmol) and 10 wt percent pd/c (wet) in ethanol:ethylacetate (1:1, 10 ml) was hydrogenated overnight. the reaction was filtered over celite and the solvent was concentrated. crude ethyl 6-(3-(tert-butoxy)-3-oxopropyl)imidazo[1,2-a]pyridine-3-carboxylate (71) was used in the next step without further purification. ms m/z 319.16 (m+1)+. a stirring mixture of ethyl 6-(3-(tert-butoxy)-3-oxopropyl)imidazo[1,2-a]pyridine-3-carboxylate (71) (400 mg, 1.26 mmol) and 2n lioh (1 ml) in thf:meoh (4:1, 4 ml) was heated at 60 degrees centigrade for 30 minutes. the reaction was cooled to room temperature and the ph was adjusted between 3-5 with 10 percent citric acid. the solvent was partially reduced. the resulting solid was collected by vacuum filtration and washed with excess water. crude 6-(3-(tert-butoxy)-3-oxopropyl)imidazo[1,2-a]pyridine-3-carboxylic acid (72) was dried and used in the next step without further purification. 1h nmr (400 mhz, d6-dmsol) delta 9.11 (s, 1 h), 8.20 (s, 1 h), 7.72 (dd, j=0.8, 9.2 hz, 1 h), 7.50 (dd, j=1.6, 9.2 hz, 1h), 2.91 (t, j=6.8 hz, 2 h), 2.60 (t, j=7.2, 2 h), 1.33 (s, 9 h). ms m/z 291.13 (m+1)+. synthesis of 6(2-cyanoethyl)imidazo[1,2-a]pyridine-3-carboxylic acid (75) [ftimg=68000110]a stirring mixture of ethyl 6-bromoimidazo[1,2-a]pyridine-3-carboxylate (24s) (250 mg, 0.929 mmol), acrylonitrile (92 ul, 1.39 mmol), tris(dibenzylideneacetone)dipalladium(0) (26 mg, 0.0279 mmol), [(t-bu)3ph]bf4 (13 mg, 0.0465 mmol) and n,n-dicyclohexylmethylamine (217 ul, 1.02 mmol) in anhydrous 1,4-dioxane (4 ml) was heated at 95 degrees centigrade overnight. the reaction was cooled to room temperature and filtered. the solvent was concentrated and crude 6-(2-cyanovinyl)imidazo[1,2-a]pyridine-3-carboxylate (73) was purified by silica chromatography. ms m/z 242.09 (m+1)+. a stirring mixture of ethyl 6-(2-cyanovinyl)imidazo[1,2-a]pyridine-3-carboxylate (73) (115 mg, 0.451 mmol) and 10 wt percent pd/c (wet) in ethanol:ethylacetate (1:1, 5 ml) was hydrogenated overnight. the reaction was filtered over celite and the solvent was removed. crude ethyl 6-(2-cyanoethyl)imidazo[1,2-a]pyridine-3-carboxylate (74) was used in the next step without further purification. ms m/z 244.10 (m+1)+. a stirring mixture of ethyl 6-(2-cyanoethyl)imidazo[1,2-a]pyridine-3-carboxylate (74) (100 mg, 0.411 mmol) and 2n lioh (0.2 ml) in thf:meoh (4:1, 3 ml) was heated at 50 degrees centigrade for 45 minutes. the reaction was cooled to room temperature and the ph was adjusted between 3-5 with 10 percent citric acid. the solvent was partially reduced. the resulting solid was collected by vacuum filtration and washed with excess water. crude 6-(2-cyanoethyl)imidazo[1,2-a]pyridine-3-carboxylic acid (75) was dried and used in the next step without further purification. ms m/z 416.07 (m+1)+. synthesis of 6-(3-(oxobutyl)imidazo[1,2-a]pyridine-3-carboxylic acid (78) [ftimg=68000111]a stirring mixture of ethyl 6-bromoimidazo[1,2-a]pyridine-3-carboxylate (24s) (250 mg, 0.929 mmol), methyl vinyl ketone (151 ul, 1.86 mmol), tris(dibenzylideneacetone)dipalladium(0) (26 mg, 0.0279 mmol), [(t-bu)3ph]bf4 (13 mg, 0.0465 mmol) and n,n-dicyclohexylmethylamine (217 ul, 1.02 mmol) in anhydrous 1,4-dioxane (4 ml) was heated at 95 degrees centigrade overnight. the reaction was cooled to room temperature and filtered. the solvent was concentrated and crude 6-(3-oxobut-1-enyl)imidazo[1,2-a]pyridine-3-carboxylate (76) was purified by silica chromatography. ms m/z 259.10 (m+1)+. a stirring mixture of ethyl 6-(3-oxobut-1-enyl)imidazo[1,2-a]pyridine-3-carboxylate (76) (200 mg, 0.774 mmol) and 10 wt percent pd/c (wet) in ethanol:ethylacetate (1:1, 8 ml) was hydrogenated overnight. the reaction was filtered over celite and the solvent was concentrated. crude 6-(3-oxobutyl)imidazo[1,2-a]pyridine-3-carboxylate (77) was used in the next step without further purification. ms m/z 261.12 (m+1)+. a stirring mixture of ethyl 6-(3-oxobutyl)imidazo[1,2-a]pyridine-3-carboxylate (77) (190 mg, 0.730 mmol) and 2n lioh (0.2 ml) in thf:meoh (4:1, 3 ml) was heated at 50 degrees centigrade for 45 minutes. the reaction was cooled to room temperature and the ph was adjusted between 3-5 with 10 percent citric acid. the solvent was partially reduced. the resulting solid was collected by vacuum filtration and washed with excess water. crude 6-(3-oxobutyl)imidazo[1,2-a]pyridine-3-carboxylic acid (78) was dried and used in the next step without further purification. ms m/z 233.08 (m+1)+. synthesis of 6-(3-(oxobutyl)imidazo[1,2-a]pyridine-3-carboxylic acid (80) [ftimg=68000112]a mixture of ethyl 7-hydroxyimidazo[1,2-a]pyridine-3-carboxylate (24t) (500 mg, 2.43 mmol) and sodium chlorodifluoroacetate (444 mg, 2.91 mmol) in anhydrous acetonitrile (8 ml) was heated in the microwave at 125 degrees centigrade for 12 minutes. the solvent was concentrated and the crude product ethyl 7-(difluoromethoxy)imidazo[1,2-a]pyridine-3-carboxylate (79) was purified by silica chromatography. ms m/z 257.07 (m+1)+. a stirring mixture of ethyl 7-(difluoromethoxy)imidazo[1,2-a]pyridine-3-carboxylate (79) (150 mg, 0.585 mmol) and 2n lioh (1 ml) in thf:meoh (4:1, 5 ml) was heated at 60 degrees centigrade for 45 minutes. the reaction was cooled to room temperature and the ph was adjusted between 4-5 with 1n hcl. the solvent was partially reduced and the crude product was purified by reverse phase preparative hplc to yield 6-(3-(oxobutyl)imidazo[1,2-a]pyridine-3-carboxylic acid (80). ms m/z 229.03 (m+1)+. synthesis of n-(5-(5-(1-(n-hydroxycarbamimidoyl)azetidin-3-yl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (82) [ftimg=68000113]to a stirring mixture of n-(5-(5-(azetidin-3-yl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide hydrochloride (21) (200 mg, 0.487 mmol), potassium carbonate (202 mg, 1.46 mmol) and cyanogen bromide (103 mg, 0.974 mmol) in dichloromethane:water (1:1, 15 ml) were heated at 45 degrees centigrade for 1.5 hours. the reaction was cooled to room temperature and the layers were separated. the aqueous layer was washed with 3 times with dcm and dried over anhydrous sodium sulfate. the combined organics were concentrated. the resulting solid was washed with hexanes to give n-(5-(5-(1-cyanoazetidin-3-yl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (82). ms m/z 400.14 (m+1)+. a stirring mixture of n-(5-(5-(1-cyanoazetidin-3-yl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (82) (50 mg, 0.125 mmol), hydroxylamine hcl (13 mg, 0.188 mmol) and diea (44 ul, 0.250 mmol) in ethanol was heated at 78 degrees centigrade for 2 hours. the solvent was concentrated and dried under high vacuum. crude n-(5-(5-(1-(n-hydroxycarbamimidoyl)azetidin-3-yl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (83) was used in the next step without further purification. ms m/z 433.17 (m+1)+. synthesis of 7-(3-(oxobutyl)imidazo[1,2-a]pyridine-3-carboxylic acid (86) [ftimg=68000114]a stirring mixture of ethyl 7-bromoimidazo[1,2-a]pyridine-3-carboxylate (24g) (500 mg, 1.86 mmol), methyl vinyl ketone (301 ul, 3.72 mmol), tris(dibenzylideneacetone)dipalladium(0) (51 mg, 0.056 mmol), [(t-bu)3ph]bf4 (27 mg, 0.093 mmol) and n,n-dicyclohexylmethylamine (433 ul, 2.04 mmol) in anhydrous 1,4-dioxane (10 ml) was heated at 95 degrees centigrade overnight. the reaction was cooled to room temperature and filtered. the solvent was concentrated and crude ethyl 7-(3-oxobut-1-enyl)imidazo[1,2-a]pyridine-3-carboxylate (84) was purified by silica chromatography. ms m/z 259.10 (m+1)+. a stirring mixture of ethyl 7-(3-oxobut-1-enyl)imidazo[1,2-a]pyridine-3-carboxylate (84) (92 mg, 0.356 mmol) and 10 wt percent pd/c (wet) in ethanol:ethylacetate (1:1, 8 ml) was hydrogenated overnight. the reaction was filtered over celite and the solvent was concentrated. crude ethyl 7-(3-(oxobutyl)imidazo[1,2-a]pyridine-3-carboxylate (85) was used in the next step without further purification. ms m/z 261.12 (m+1)+. a stirring mixture of ethyl 7-(3-(oxobutyl)imidazo[1,2-a]pyridine-3-carboxylate (85) (90 mg, 0.346 mmol) and 2n lioh (0.5 ml) in thf:meoh (4:1, 3 ml) was heated at 60 degrees centigrade for 45 minutes. the reaction was cooled to room temperature and the ph was adjusted between 3-5 with 10 percent citric acid. the solvent was partially concentrated and the crude product was purified by reverse phase preparative hplc to yield 7-(3-(oxobutyl)imidazo[1,2-a]pyridine-3-carboxylic acid (86). ms m/z 233.08 (m+1)+. synthesis of 7-meth-1-d3-imidazo[1,2-a]pyridine-3-carboxylic acid (95) [ftimg=68000115]to a stirring solution of ethyl 7-bromoimidazo[1,2-a]pyridine-3-carboxylate (24g) (500 mg, 1.86 mmol), peppsi (63.2 mg, 0.093 mmol) and 2-iodopropane (928 ul, 9.3 mmol) in anhydrous thf (3 ml) at 0 degrees centigrade under a stream of nitrogen was added methyl-d3-magnesium iodide (5.6 ml, 5.57 mmol). the reaction was stirred to room temperature for 5 hours. then, the reaction was quenched with nh4cl. the crude product was extracted with ether, washed with water and brine and dried over sodium sulfate. the product was purified on silica gel using 10 percent meoh in dichloromethane to yield ethyl 7-methyl-d3-imidazo[1,2-a]pyridine-3-carboxylate (94). 1h nmr (400 mhz, d6-dmsol) delta 8.85 (dd, j=0.4, 7.0 hz, 1h), 7.98 (s, 1h), 7.36 (s, 1h), 6.86 (dd, j=1.6, 7.2 hz, 1h), 4.10 (q, j=7.2 hz, 2h), 1.09 (t, j=7.2 hz, 3h). ms m/z 208.1 (m+1)+. to a stirring suspension of ethyl 7-methyl-d3-imidazo[1,2-a]pyridine-3-carboxylate (94) (142 mg, 0.69 mmol) in thf:meoh: h2o (3:2:1, 3 ml) was added 6n lioh (0.34 ml). the reaction was stirred at room temperature for 2 hours then neutralized with sodium bisulfate monohydrate and concentrated to afford 7-methyl-d3-imidazo[1,2-a]pyridine-3-carboxylic acid (95), which was immediately used without purification. ms (m/z) 180.1 (m+1)+. synthesis of 6((2-(2,2-trifluoroethoxy)methyl)imidazo[1,2-a]pyridine-3-carboxylic acid (98) [ftimg=68000116]to a solution of ethyl 6-(hydroxymethyl)imidazo[1,2-a]pyridine-3-carboxylate (59) (460 mg, 2.2 mmol) and diea (0.78 ml, 4.4 mmol) in dcm (5 ml) was added mscl (303 mg, 2.64

mmol). the mixture was stirred at room temperature for 10 minutes then subjected to standard aqueous work up to give a residue. the crude product was dissolved in 2,2,2-trifluoroethanol (2 ml) and was added k2co3 (608 mg, 4.4 mmol). the reaction mixture was heated at 80 degrees centigrade for 2 hours. once complete, the reaction mixture was diluted and extracted with etoac. the organic layers were combined, dried over na2so4, filtered and concentrated to afford a residue which was purified by silica chromatography to yield ethyl 6-((2-(2,2-trifluoroethoxy)methyl)imidazo[1,2-a]pyridine-3-carboxylate (97). 1h nmr (400 mhz, cdcl3) delta 9.33 (m, 1h), 8.32 (s, 1h), 7.76 (dd, j=0.8, 9.2 hz, 1h), 7.47 (dd, j=2.0, 9.2 hz, 1h), 4.76 (s, 2h), 4.44 (q, j=7.2 hz, 2h), 3.92 (q, j=8.4 hz, 2h), 1.45 (t, j=7.2 hz, 3h). ms m/z 303.1 (m+1)+. a solution of ethyl 6-((2,2,2-trifluoroethoxy)methyl)imidazo[1,2-a]pyridine-3-carboxylate (97) (280 mg, 0.92 mmol) in thf/meoh/h2o (3:2:1, 5 ml) was treated with 6n lih (0.92 ml, 5.52 mmol) and stirred at room temperature for 1 hour. all solvents were removed and 6n hcl was added to adjust ph 5-6. then the mixture was purified by hplc to give 6-((2,2,2-trifluoroethoxy)methyl)imidazo[1,2-a]pyridine-3-carboxylic acid (98). 1h nmr (400 mhz, d6-dmsol) delta 9.34 (m, 1h), 8.40 (s, 1h), 7.88 (dd, j=0.8, 9.2 hz, 1h), 7.65 (dd, j=1.6, 9.2 hz, 1h), 4.83 (s, 2h), 4.18 (q, j=9.6 hz, 2h). ms m/z 275.1 (m+1)+. synthesis of 6-(3-(methoxy)methyl)-1h-1,2,4-triazol-5-yl)imidazo[1,2-a]pyridine-3-carboxylic acid (99) [ftimg=68000117]to a solution of ethyl 6-cyanoimidazo[1,2-a]pyridine-3-carboxylate (24q) (265 mg, 1.23 mmol) and 2-methoxyacetylhydrazide (193 mg, 1.85 mmol) in 2-ethoxyethanol (5 ml) was added naome (0.5 m in meoh, 3.7 ml). the mixture was heated at 110 degrees centigrade in a sealed vial overnight. the reaction mixture was purified by hplc to give 6-(3-(methoxy)methyl)-1h-1,2,4-triazol-5-yl)imidazo[1,2-a]pyridine-3-carboxylic acid (99). ms m/z 274.1 (m+1)+. synthesis of 5-(5-(azetidin-1-yl)-1,2,4-oxadiazol-3-yl)-2-methylaniline (109) [ftimg=68000118]to a solution of (z)-n'-hydroxy-4-methyl-3-nitrobenzimidazole (27) (30 g, 153.71 mmol, 1.00 equiv) and diea (39.7 g, 307.18 mmol, 2.00 equiv) in tetrahydrofuran (300 ml) was added dropwise to a solution of triphosgene (18.2 g) in tetrahydrofuran (50 ml). the reaction was stirred for 1 hour at room temperature then heated to reflux for an additional hour. the resulting solution was poured into 500 ml of water and extracted with 3x300 ml of ethyl acetate. the combined organic layers were washed with brine (3x200 ml), dried over anhydrous sodium sulfate, concentrated under vacuum, and purified by flash chromatography (dcm/meoh=20:1) to afford of 3-(4-methyl-3-nitrophenyl)-1,2,4-oxadiazol-5(4h)-one as a pale yellow solid (106). ms m/z 222.1 (m+1)+. to a solution of 3-(4-methyl-3-nitrophenyl)-1,2,4-oxadiazol-5(4h)-one (106) (12 g, 54.26 mmol) in pochl3 (120 ml) was added n,n-dimethylformamide (12 ml). the resulted solution was heated to reflux for 72 hours then concentrated under vacuum. the residue was dissolved in water (250 ml) and extracted with ethyl acetate (3x250 ml). the combined organic layers were washed with brine (3x250 ml), dried over anhydrous sodium sulfate and concentrated under vacuum. the residue was purified by flash chromatography (pe/ea=10:1) to afford 5-chloro-3-(4-methyl-3-nitrophenyl)-1,2,4-oxadiazole (107) as a white solid. 1h nmr (300 mhz, cdcl3) delta 8.64 (dd, j=1.5, 8.4 hz, 1h), 8.18 (dd, j=1.5, 7.8 hz, 1h), 7.56 (d, j=8.1 hz, 1h), 2.70 (s, 3h). ms m/z 240.7 (m+1)+. to a solution of 5-chloro-3-(4-methyl-3-nitrophenyl)-1,2,4-oxadiazole (107) (3.6 g, 15.02 mmol, 1.00 equiv) in ch3cn (40 ml) was added triethylamine (3.03 g, 29.94 mmol) and azetidine hydrochloride (1.68 g, 17.96 mmol). the resulting solution was stirred for 1 hour at room temperature, concentrated under vacuum and purified by prep-hplc to afford 5-(azetidin-1-yl)-3-(4-methyl-3-nitrophenyl)-1,2,4-oxadiazole (108) as a white solid. ms m/z 261.1 (m+1)+. to a stirred solution of 5-(azetidin-1-yl)-3-(4-methyl-3-nitrophenyl)-1,2,4-oxadiazole (108) (1.4 g, 5.38 mmol) in ethanol (25 ml) was added sncl2.2h2o (6.07 g, 26.90 mmol). the resulting solution was stirred for 20 min at reflux then cooled to room temperature and concentrated under vacuum. the residue was poured into saturated sodium hydroxide (50 ml) and extracted with ethyl acetate (3x50 ml). the combined organic layers were washed with brine (3x250 ml), dried over anhydrous sodium sulfate, concentrated under vacuum and purified by flash chromatography (pe/ea=10:1) to afford 5-(5-(azetidin-1-yl)-1,2,4-oxadiazol-3-yl)-2-methylaniline (109) (0.8 g, 65 percent yield) as a white solid. 1h nmr (300 mhz, cdcl3) delta 7.28-7.36 (m, 2h), 7.12 (d, j=7.8 hz, 1h), 4.32 (t, j=7.5 hz, 4h), 3.69 (brs, 2h), 2.47-2.57 (m, 2h), 2.21 (s, 3h). ms m/z 231.1 (m+1)+. synthesis of 6-carbamoylimidazo[1,2-a]pyridine-3-carboxylic acid (110) [ftimg=68000119]to a stirring solution of ethyl 6-cyanoimidazo[1,2-a]pyridine-3-carboxylate (24q) (500 mg, 2.32 mmol) in thf:meoh (4:1, 5 ml) was added 2n lih (4 ml). the reaction was heated at 60 degrees centigrade for 2 h then acidified with 10 percent citric acid. the solvent was partially concentrated and the resulting solid was collected by vacuum filtration and was washed with excess water. the product was purified from the crude solid to afford 6-carbamoylimidazo[1,2-a]pyridine-3-carboxylic acid (110). 1h nmr (400 mhz, d6-dmsol) delta 9.80 (s, 1h), 8.33-8.31 (m, 1h), 8.29 (s, 1h), 7.95 (dd, j=2.0, 9.6 hz, 1h), 7.83 (dd, j=0.8, 9.2 hz, 1h), 7.69 (s, 1h). ms m/z 205.05 (m+1)+. synthesis of 6-(2-(4-methylpiperazin-1-yl)ethyl)imidazo[1,2-a]pyridine-3-carboxylic acid (114) [ftimg=68000120]to a stirring mixture of ethyl 6-bromoimidazo[1,2-a]pyridine-3-carboxylate (24s) (1 g, 3.72 mmol) and tetrakis(triphenylphosphine)palladium(0) (215 mg, 0.19 mmol) in anhydrous toluene (10 ml) under argon was added tributyl[2-ethoxyethyl]stannane (1.7 g, 4.65 mmol). the reaction mixture was heated in a microwave sealed tube overnight at 90 degrees centigrade the reaction was cooled to room temperature and was filtered through celite. the solvent was concentrated and the crude product was purified by silica chromatography to afford (e)-ethyl 6-(2-ethoxyvinyl)imidazo[1,2-a]pyridine-3-carboxylate (111). ms m/z 261.3 (m+1)+. a stirring solution of ethyl 6-(2-ethoxyvinyl)imidazo[1,2-a]pyridine-3-carboxylate (111) (240 mg, 1.15 mmol) in thf:h2o (1:1, 4 ml) was heated at 50 degrees centigrade overnight. the reaction was cooled to room temperature and neutralized with saturated solution of sodium bicarbonate. the crude product was extracted with ethyl acetate. the organic layer was washed with water, brine and dried over anhydrous sodium sulfate. the solvent was concentrated and crude ethyl 6-(2-oxoethyl)imidazo[1,2-a]pyridine-3-carboxylate (112) was used in the next step without further purification. ms m/z 233.3 (m+1)+. to a stirring solution of crude ethyl 6-(2-oxoethyl)imidazo[1,2-a]pyridine-3-carboxylate (112) (214 mg, 0.92 mmol) in dcm (5 ml) and 1-methylpiperazine (231 micro l, 2.30 mmol) at room temperature was added portion-wise sodium triacetoxylborohydride (586 mg, 2.77 mmol). the reaction was stirred at room temperature overnight. the solvent was concentrated. the crude was taken in 10 percent sodium bicarbonate and ethyl acetate. the organic was washed with water, brine and dried over anhydrous sodium sulfate. the solvent was concentrated and the crude product was purified by silica chromatography to afford methyl 6-(2-(4-methylpiperazin-1-yl)ethyl)imidazo[1,2-a]pyridine-3-carboxylate (113). ms m/z 304.4 (m+1)+. to a stirring solution of methyl 6-(2-(4-methylpiperazin-1-yl)ethyl)imidazo[1,2-a]pyridine-3-carboxylate (113) (215 mg, 0.68 mmol) in thf:meoh (4:1, 4 ml) was added 2n lih (3 ml). the reaction was heated at 60 degrees centigrade for 45 minutes. the ph was adjusted between 4-5 with 1n hcl and concentrated. the crude product was purified by preparative hplc to afford 6-(2-(4-methylpiperazin-1-yl)ethyl)imidazo[1,2-a]pyridine-3-carboxylic acid (114). 1h nmr (400 mhz, d6-dmsol) delta 9.25 (s, 1h), 8.35 (s, 1h), 7.83 (d, j=9.2 hz, 1h), 7.61 (dd, j=1.6, 9.2 hz, 1h), 4.65-4.19 (m, 8h), 3.49-3.30 (m, 2h), 3.04-2.99 (m, 2h), 2.81 (s, 3h). ms m/z 316.1 (m+1)+. synthesis of tert-butyl 3-(3-(3-imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)azetidin-1-ylsulfonycarbamate (128) [ftimg=68000121]to a stirring solution of n-(5-(5-(azetidin-3-yl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (21) (50 mg, 0.133 mmol) in anhydrous pyridine (1.5 ml) at 0 degrees centigrade was added tert-butyl chlorosulfonylcarbamate (35 mg, 0.160 mmol). the reaction was stirred to room temperature for 1 hour. the reaction was quenched with water and the solvent was concentrated. the crude product tert-butyl 3-(3-(3-imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)azetidin-1-ylsulfonycarbamate (128) was purified by preparative hplc. 1h nmr (400 mhz, d6-dmsol) delta 11.27 (s, 1h), 10.25 (s, 1h), 9.55-9.53 (m, 1h), 8.76 (s, 1h), 8.07 (d, j=1.6 hz, 1h), 7.93-7.90 (m, 1h), 7.84 (dd, j=1.6, 8.0 hz, 1h), 7.75-7.71 (m, 1h), 7.52 (dd, j=8.4 hz, 1h), 7.37-7.34 (m, 1h), 4.37-4.33 (m, 5h), 2.38 (s, 3h), 1.38 (s, 9h). ms m/z 554.17 (m+1)+. synthesis of methyl 3-(3-(4-methyl-3-(6-(((triisopropylsilyl)oxy)methyl)imidazo[1,2-a]pyridine-3-carboxamido)phenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (133) [ftimg=68000122]to a stirring suspension of 6-(((triisopropylsilyl)oxy)methyl)imidazo[1,2-a]pyridine-3-carboxylic acid (61) (70 mg, 0.20 mmol) in anhydrous dichloromethane (5 ml) at room temperature oxalyl chloride was added dropwise (0.05 ml, 2.22 mmol). then, one drop of anhydrous dmf was added and the reaction mixture was stirred at room temperature for 15 minutes. the solvent was concentrated and the crude solid was added to a stirring solution of methyl 3-(3-(3-amino-4-methylphenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (31) (51.1 mg, 0.18 mmol) in anhydrous pyridine (5 ml) at room temperature. the reaction was stirred for 20 minutes. water (20 ml) was added to the reaction mixture and extraction with etoac afforded a residue after removing organic solvents. to the above residue, was added thf (0.5 ml) and tbaif (1m in thf, 0.30 ml) and the resulting mixture was stirred for 30 minutes. thf was removed and the residue was dissolved in etoac (20 ml) and washed with water twice. the organic layers were combined, dried over na2so4, filtered and concentrated to give a crude residue which was dissolved in dcm (1 ml) and followed by addition of diea (52 mg, 0.40 mmol) and msc1 (46 mg, 0.4 mmol). the reaction was stirred for 10 minutes. the mixture was diluted with dcm (10 ml) and washed with water. the organic layers were combined, dried over na2so4, filtered and concentrated to give methyl 3-(3-(4-methyl-3-(6-(((methylsulfonyl)oxy)methyl)imidazo[1,2-a]pyridine-3-carboxamido)phenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (133) which was used without further purification. ms m/z 541.1 (m+1)+. synthesis of 5-(4-methyl-1h-imidazol-1-yl)pyridin-2-amine (134) [ftimg=68000123]to a microwave tube with a magnetic stirring bar was charged cui (382 mg, 2.0 mmol), cs2co3 (6.5 g, 20.0 mmol), 4-methyl-1h-imidazole (1.15 g, 14.0 mmol), 5-bromopyridin-2-amine (1.75 g, 10.0 mmol), and dmf (10 ml) under n2. the system was sealed and then evacuated twice and back filled with n2. the reaction mixture was stirred for 30 min at room temperature, and then heated at 120 degrees centigrade for 48 h. the reaction mixture was then cooled to ambient temperature, diluted with 30 ml of ethyl acetate, washed with water. the combined organic layers were concentrated, and the resulting residue was purified by column chromatography on silica gel to provide 5-(4-methyl-1h-imidazol-1-yl)pyridin-2-amine (134). 1h nmr (400 mhz, d6-dmsol) delta 8.09 (m, 1h), 7.85 (d, j=1.6 hz, 1h), 7.56 (dd, j=2.8, 8.8 hz, 1h), 7.22 (t, j=1.2 hz, 1h), 6.51 (dd, j=0.8, 8.8 hz, 1h), 6.15 (s, 2h), 2.14 (d, j=1.2 hz, 3h). ms m/z 175.1 (m+1)+. synthesis of 6-bromo-n-(5-(5-(3-cyanoazetidin-1-yl)methyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (143) [ftimg=68000124]carbonyl diimidazole (cdi) (2.3 g, 14.24 mmol) was added to a stirred solution of 2-acetoxyacetic acid (1.68 g, 14.24 mmol) in nmp (10 ml). after 30 minutes, 6-bromo-n-(5-(n-hydroxycarbamidoyl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (50f) (1.38 g, 3.56 mmol) was added in one portion and the resulting solution was stirred for 30 minutes before it was heated at 125 degrees centigrade for 15 minutes in a microwave reactor. the reaction solution was subjected to standard aqueous work up to afford a residue which was hydrolyzed by lithium hydroxide monohydrate (897 mg, 21.36 mmol) in thf/meoh/h2o (3:2:1). after removal of all solvents 2n nahco3 (10 ml) was added. the precipitate was filtered and dried in air to afford 6-bromo-n-(5-(5-(hydroxymethyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (142). 1h nmr (400 mhz, d6-dmsol) delta 10.14 (s, 1h), 9.64 (d, j=1.2 hz, 1h), 8.60 (s, 1h), 8.11 (d, j=1.6 hz, 1h), 7.83 (dd, j=1.6, 8.0 hz, 1h), 7.79 (dd, j=0.8, 9.6 hz, 1h), 7.67 (dd, j=2.0, 9.6 hz, 1h), 7.51 (d, j=8.0 hz, 1h), 6.09 (s, 1h), 4.81 (s, 2h), 2.37 (s, 3h). ms m/z 427.9, 429.9 (m+1)+. to a solution of 6-bromo-n-(5-(5-(hydroxymethyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (142) (200 mg, 0.47 mmol) and diea (0.25 ml, 1.41 mmol) in dichloromethane (5 ml) was added msc1 (108.1 mg, 0.94 mmol). the mixture was stirred at room temperature for 10 minutes and then diluted with dichloromethane (10 ml) and washed with water. the organic layers were dried over na2so4, filtered and concentrated to give a residue which was dissolved in dmf (2 ml). then azetidine-3-carbonitrile (116 mg, 1.41 mmol) was added and the reaction mixture was heated at 80 degrees centigrade for 1 hour. the reaction mixture was diluted with water (50 ml) and extracted with etoac. the organic layers were dried over na2so4, filtered and concentrated to give the crude product which was purified by silica chromatography to yield 6-bromo-n-(5-(5-(3-cyanoazetidin-1-yl)methyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (143). 1h nmr (400 mhz, d6-dmsol) delta 10.15 (s, 1h), 9.62 (dd, j=0.8, 2.0 hz, 1h), 8.60 (s, 1h), 8.07 (d, j=1.6 hz, 1h), 7.83 (dd, j=1.6, 8.0 hz, 1h), 7.79 (dd, j=0.8, 9.6 hz, 1h), 7.68 (dd, j=2.0, 9.6 hz, 1h), 7.51 (d, j=8.4 hz, 1h), 4.06 (s, 2h), 3.67 (m, 2h), 3.51-3.60 (m, 3h), 2.37 (s, 3h). ms m/z 492.0, 494.0 (m+1)+. synthesis of 6-(2,4-dimethylthiazol-5-yl)imidazo[1,2-a]pyridine-3-carboxylic acid (146) [ftimg=68000125]a mixture of ethyl 6-bromoimidazo[1,2-a]pyridine-3-carboxylate (24s) (500 mg, 1.86 mmol), bis(pinacolato)diboron (472 mg, 1.86 mmol), dichloro-bis(triphenylphosphine)palladium (65 mg, 0.093 mmol) and potassium acetate (456 mg, 4.65 mmol) in anhydrous dioxane (8 ml) was heated at 95 degrees centigrade for 4 hours. the reaction turned black. the reaction was cooled and filtered through celite. the solvent was concentrated. the oil was taken in etoac. the organic was washed with water/brine mixture, brine and dried over anhydrous sodium sulfate. the crude product was purified by silica chromatography. ms m/z 317 (m+1)+. a mixture of 5-bromo-2,4-dimethylthiazole (171 mg, 0.89 mmol), ethyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)imidazo[1,2-a]pyridine-3-carboxylate (144) (250 mg, 1.07 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(11) (39 mg, 0.05 mmol) and a solution of 2m sodium carbonate (300 ul) in anhydrous dioxane (4 ml) was heated in the microwave at 135 degrees centigrade for 25 minutes. the reaction was filtered through celite. the crude product was taken in water and ethylacetate. the organic was washed with water/brine mixture and dried over anhydrous sodium sulfate. the crude product was purified by silica chromatography. ms m/z 302.09 (m+1)+. a mixture of ethyl 6-(2,4-dimethylthiazol-5-yl)imidazo[1,2-a]pyridine-3-carboxylate (145) (190 mg, 0.630 mmol) and 2n lih (1 ml) in thf:meoh (4:1, 4 ml) was heated at 60 degrees centigrade for 30 minutes. the reaction was cooled to room temperature and the ph was adjusted between 4-5 with 10 percent citric acid. the solvent was partially reduced and the resulting solid was collected by vacuum filtration to give 6-(2,4-dimethylthiazol-5-yl)imidazo[1,2-a]pyridine-3-carboxylic acid (146). 1h nmr (400 mhz, d6-dmsol) delta 9.34 (s, 1h), 8.29 (s, 1h), 7.87 (dd, j=0.8, 9.2 hz, 1h), 7.62 (dd, j=2.0, 9.2 hz, 1h), 2.66 (s, 3h), 2.41 (s, 3h). ms m/z 274.06 (m+1)+. synthesis of n-(5-(5-(chloromethyl)-1,2,4-oxadiazol-3-o-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (151) [ftimg=68000126]a mixture of n-(5-(n'-hydroxycarbamidoyl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide 9 (500 mg, 1.62 mmol) and 2-chloroacetic anhydride (553 mg, 3.23 mmol) in anhydrous 1-methyl-2-pyrrolidinone (10 ml) was heated in the microwave at 110 degrees centigrade for 12 minutes. the crude was diluted with water and extracted with ethyl acetate. the organic was washed with water/brine mixture and dried over anhydrous sodium sulfate. the crude product was purified by silica chromatography. ms m/z 368.08 (m+1)+. synthesis of final compounds synthesis of n-(5-(5-(5-difluorotetrahydro-2h-pyran-2-yl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (f10) [ftimg=68000127] hatu (0.134 g, 0.355 mmol) was added in one portion to a stirred solution of 5,5-difluorotetrahydro-2h-pyran-2-carboxylic acid (17) (53 mg, 0.31 mmol) and diea (60 l, 0.355 mmol) in dry dmf (3 ml). after 10 minutes, n-(5-(n'-hydroxycarbamidoyl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (9) (0.1 g, 0.323 mmol) was added in one portion and continued to stir for another 30 minutes, then heated at 110 degrees centigrade for 30 minutes. the reaction was filtered and purified by preparative reverse phase hplc to afford n-(5-(5-(5-difluorotetrahydro-2h-pyran-2-yl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (f10) as a white solid. 1h nmr (400 mhz, d4-meoh) delta 9.73 (d, j=7.2 hz, 1h), 8.74 (s, 1h), 8.17 (m, 1h), 7.98-7.95 (m, 3h), 7.52-7.50 (m, 2h), 5.06 (dd, j=8.4, 2.8 hz, 1h), 4.07-4.00 (m, 1h), 3.91-3.81 (m, 1h), 2.44 (s, 3h), 2.40-2.21 (m, 4h). ms m/z 440.1 (m+1)+. synthesis of tert butyl 3-(3-(3-(imidazo[1,2-a]pyridine-3-carboxamido)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (f13) [ftimg=68000128]to a stirring solution of boc-azetidine-3-carboxylic acid (162 mg, 0.8 mmol) in anhydrous nmp (4 ml) was added cdi (131 mg, 0.8 mmol). the reaction was stirred for 2 minutes. n-(5-(n'-

hydroxycarbamimidoyl)-2-methylphenyl]imidazo[1,2-a]pyridine-3-carboxamide (9) (250 mg, 0.8 mmol) was added and the reaction was stirred for 15 minutes, then heated via microwave at 120 degrees centigrade for 15 minutes. the crude was purified by reverse phase hplc to afford tert-butyl 3-(3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (f13) as a white solid. 1h nmr (400 mhz, d6-dmsol) delta 10.17 (s, 1h), 9.51 (d, j=6.8 hz, 1h), 8.70 (s, 1h), 8.10 (d, j=2.0 hz, 1h), 7.86 (dt, j=12, 2.0 hz, 2h), 7.68 (t, j=8.0 hz, 1h), 7.51 (d, j=8 hz, 1h), 7.31 (td, j=6.8, 0.8 hz, 1h), 4.06-4.38 (m, 5h) 2.37 (s, 1h), 1.40 (s, 9h). ms m/z 476.2 (m+1)+. synthesis of methyl 3-(3-(3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (f15) [ftimg=68000129]to a stirring solution of n-(5-(5-(azetidin-3-yl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (21) (25 mg, 0.0667 mmol) in anhydrous pyridine (1 ml) was added methylchloroformate (5 micro l, 0.667 mmol). the reaction was stirred to room temperature for 10 minutes. the ph was adjusted to neutral with 10 percent citric acid. the crude was purified by reverse phase hplc to afford methyl 3-(3-(3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (f15) as a white solid. 1h nmr (400 mhz, d6-dmsol) delta 10.18 (s 1h), 9.52 (d, j=7.2 hz, 1h), 8.71 (s, 1h), 8.10 (s, 1h), 7.82-7.91 (m, 2h), 7.69 (t, j=8.0 hz, 1h), 7.51 (d, j=8.4 hz, 1h), 7.31 (td, j=7.2, 0.8 hz, 1h), 4.15-4.44 (m, 5h) 3.59 (s, 3h), 2.37 (s, 3h). ms m/z 433.3 (m+1)+. synthesis of n-(2-methyl-5-(5-(morpholinomethyl)-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (f22) [ftimg=68000130]a solution of (3-(3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl) methyl methanesulfonate (44) (21.4 mg, 0.05 mmol), diea (13.0 mg, 0.1 mmol) and morpholine (13.0 mg, 0.15 mmol) in dmf (1 ml) was heated at 80 degrees centigrade for 4 hours. the crude product was purified by preparative hplc to yield n-(2-methyl-5-(5-(morpholinomethyl)-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (f22). 1h nmr (400 mhz, cd2cl2) delta 9.60 (d, j=6.8 hz, 1h), 8.60 (d, j=1.6 hz, 1h), 8.45 (s, 1h), 8.06 (s, 1h), 7.89 (dd, j=2.0, 8.0 hz, 1h), 7.80 (d, j=8.8 hz, 1h), 7.54 (m, 1h), 7.43 (d, j=8.0 hz, 1h), 7.15 (m, 1h), 3.93 (s, 2h), 3.75 (m, 4h), 2.67 (m, 4h), 2.48 (s, 3h). ms m/z 419.2 (m+1)+. note: if hcl salt of morpholine (0.15 mmol) was used, agno3 (0.15 mmol) was needed to avoid replacement of oms group by cl. synthesis of n-(2-methyl-5-(5-(1-sulfamoylazetidin-3-yl)-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (f23) [ftimg=68000131]to a stirring solution of tert-butyl 3-(3-(3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)azetidin-1-ylsulfonycarbamate (128) (25 mg, 0.0452 mmol) in ch3cn (0.5 ml) was added hcl (4n in dioxane, 1 ml). the reaction was stirred for 30 minutes. the solvent was concentrated and the crude was purified by preparative hplc to give n-(2-methyl-5-(5-(1-sulfamoylazetidin-3-yl)-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (f23). 1h nmr (400 mhz, d6-dmsol) delta 10.14 (s, 1h), 9.51-9.48 (m, 1h), 8.67 (s, 1h), 8.11 (d, j=1.6 hz, 1h), 7.87-7.84 (m, 2h), 7.66-7.61 (m, 1h), 7.52 (d, j=8.0 hz, 1h), 7.29-7.25 (m, 1h), 7.13 (s, 2h), 4.24-4.18 (m, 1h), 4.16-4.12 (m, 2h), 4.05-4.01 (m, 2h), 2.37 (s, 3h). ms m/z 454.59 (m+1)+. synthesis of (3-(3-(3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)oxetan-3-yl)carbamate (f26) [ftimg=68000132]to a stirring solution of n-(5-(5-(3-aminoxetan-3-yl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (47) (8.0 mg, 0.02 mmol) and diea (5.2 mg, 0.04 mmol) in anhydrous dichloromethane (1 ml) was added methylchloroformate (2.3 mg, 0.024 mmol). the reaction was stirred to room temperature for 10 minutes. the solvent was removed and the crude was purified by preparative hplc to afford methyl methyl 3-(3-(3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)oxetan-3-yl)carbamate (f26). 1h nmr (400 mhz, cdcl3) delta 9.46 (m, 1h), 8.48 (s, 1h), 8.14 (s, 1h), 7.81 (dd, j=1.6, 8.0 hz, 1h), 7.69 (d, j=7.2 hz, 1h), 7.56 (s, 1h), 7.38 (m, 1h), 7.31 (d, j=8.0 hz, 1h), 6.98 (dt, j=0.8, 6.8 hz, 1h), 5.12 (m, 2h), 4.91 (m, 2h), 3.66 (s, 3h), 2.36 (s, 3h). ms m/z 449.1 (m+1)+. synthesis of 3-(3-(4-fluoro-3-(imidazo[1,2-a]pyridine-3-carboxamido)phenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (f27) [ftimg=68000133]to a stirring solution of boc-azetidine-3-carboxylic acid (162 mg, 0.8 mmol) in anhydrous nmp (4 ml) was added cdi (131 mg, 0.8 mmol). the reaction was stirred for 10 minutes. n-(2-fluoro-5-(n'-hydroxycarbamimidoyl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (50) (125 mg, 0.4 mmol) was added and the reaction was stirred for 15 minutes, then heated via microwave at 125 degrees centigrade for 15 minutes. the crude was purified via reverse phase hplc to afford tert-butyl 3-(3-(4-fluoro-3-(imidazo[1,2-a]pyridine-3-carboxamido)phenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (f27) as a white solid. ms m/z 479.21 (m+1)+. synthesis of n-(5-(5-(1-(ethylsulfonyl)azetidin-3-yl)-1,2,4-oxadiazol-3-yl)-2-fluorophenyl)imidazo[1,2-a]pyridine-3-carboxamide (f28) [ftimg=68000134]tert-butyl 3-(3-(4-fluoro-3-(imidazo[1,2-a]pyridine-3-carboxamido)phenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (f27) (14.4 mg, 0.03 mmol) was dissolved in tfa (0.5 ml) and stirred at room temperature for 10 minutes. then tfa was removed under vacuum. the residue was dissolved in anhydrous dichloromethane (1 ml) and diea (13.0 mg, 0.10 mmol) and ethanesulfonyl chloride (5.8 mg, 0.045 mmol) were added. the reaction was stirred at room temperature for 10 minutes. the solvent was removed and the crude was purified by preparative hplc to afford n-(5-(5-(1-(ethylsulfonyl)azetidin-3-yl)-1,2,4-oxadiazol-3-yl)-2-fluorophenyl)imidazo[1,2-a]pyridine-3-carboxamide (f28). 1h nmr (400 mhz, cdcl3) delta 9.50 (d, j=0.8 hz, 1h), 9.09 (dd, j=2, 7.2 hz, 1h), 8.21 (s, 1h), 7.87 (m, 1h), 7.79 (m, 1h), 7.71 (d, j=9.2 hz, 1h), 7.41 (m, 1h), 7.22 (dd, j=8.8, 10.4 hz, 1h), 7.02 (dt, j=8.8, 6.8 hz, 1h), 4.34 (m, 4h), 4.07 (m, 1h), 3.00 (q, j=7.6 hz, 2h), 1.35 (t, j=7.6 hz, 3h). ms m/z 471.1 (m+1)+. synthesis of methyl 3-(3-(4-methyl-3-(6-(trifluoromethyl)imidazo[1,2-a]pyridine-3-carboxamido)phenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (f52) [ftimg=68000135]to a stirring suspension of 6-(trifluoromethyl)imidazo[1,2-a]pyridine-3-carboxylic acid (24a) (50 mg, 0.217 mmol) in anhydrous dichloromethane (2 ml) at 0 degrees centigrade under argon was added dropwise oxalyl chloride (19 micro l, 0.228 mmol). then, a drop of anhydrous dmf was added and the reaction mixture was stirred at room temperature for 1.5 hours. the solvent was concentrated and the crude solid was added portion-wise to a stirring solution of methyl 3-(3-(3-amino-4-methylphenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (31) (47 mg, 0.163 mmol) in anhydrous pyridine (1 ml) at 0 degrees centigrade the reaction was stirred at room temperature under argon for 10 minutes and quenched with water. the crude product was purified by preparative hplc to yield methyl 3-(3-(4-methyl-3-(6-(trifluoromethyl)imidazo[1,2-a]pyridine-3-carboxamido)phenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (f52). 1h nmr (400 mhz, d6-dmsol) delta 10.27 (s, 1h), 9.90-9.85 (m, 1h), 8.72 (s, 1h), 8.08 (d, j=1.6 hz, 1h), 8.02-7.99 (m, 1h), 7.86 (dd, j=2.0, 8.0 hz, 1h), 7.79 (dd, j=2.0, 9.2 hz, 1h), 7.52 (d, j=8.0 hz, 1h), 4.37-4.19 (m, 5h), 3.59 (s, 3h), 2.37 (s, 3h). ms m/z 501.43 (m+1)+. synthesis of methyl 3-(3-(4-methyl-3-(7-(1-methyl-1h-pyrazol-3-yl)imidazo[1,2-a]pyridine-3-carboxamido)phenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (f56) [ftimg=68000136]methyl 3-(3-(3-(7-bromoimidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (42) (40 mg, 0.078 mmol), 1-methyl-3-(4,4,5,5-tetramethyl-1,2,2-dioxaborolan-2-yl)-1h-pyrazole (19.6 mg, 0.094 mmol) and pd(pph3)4 (9 mg, 0.0078 mmol) were added to a flask equipped with a stir bar. the flask was evacuated and backfilled with nitrogen several times. dmf (1 ml) and 1.8 m k2co3 (0.094 mmol) were added by syringe. the flask was sealed and heated at 80 degrees centigrade for 12 hours. the reaction was filtered and directly purified by preparative reverse phase hplc to afford methyl 3-(3-(4-methyl-3-(7-(1-methyl-1h-pyrazol-3-yl)imidazo[1,2-a]pyridine-3-carboxamido)phenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (f56). ms m/z 513.2 (m+1)+. synthesis of methyl 3-(3-(4-methyl-3-(7-(trifluoromethyl)imidazo[1,2-a]pyridine-3-carboxamido)phenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (f57) [ftimg=68000137]to a stirring suspension of 7-(trifluoromethyl)imidazo[1,2-a]pyridine-3-carboxylic acid (24) (89 mg, 0.387 mmol) in anhydrous dichloromethane (3 ml) at 0 degrees centigrade under argon oxalyl chloride (34 ul, 0.407 mmol) was added dropwise. then, a drop of anhydrous dmf was added and the reaction mixture was stirred at 0 degrees centigrade for 1.5 hours. the solvent was concentrated and the crude solid was added to a stirring solution of methyl 3-(3-(3-amino-4-methylphenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (31) (19 mg, 0.0645 mmol) in anhydrous pyridine (1.5 ml) at 0 degrees centigrade the reaction was stirred at room temperature under argon for 20 minutes. the crude product was filtered and purified by preparative hplc to give methyl 3-(3-(4-methyl-3-(7-(trifluoromethyl)imidazo[1,2-a]pyridine-3-carboxamido)phenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (f57). 1h nmr (400 mhz, d6-dmsol) delta 10.25 (s, 1h), 9.64-9.61 (m, 1h), 9.75 (s, 1h), 8.33-8.30 (m, 1h), 8.10 (dd, j=1.6 hz, 1h), 7.86 (dd, j=1.6, 8.0 hz, 1h), 7.52 (d, j=8.4 hz, 1h), 7.46 (dd, j=2.0, 7.6 hz, 1h), 4.40-4.33 (m, 2h), 4.31-4.25 (m, 1h), 4.22-4.18 (m, 2h), 3.59 (s, 3h), 2.38 (s, 3h). ms m/z 501.43 (m+1)+. synthesis of methyl 3-(3-(6-(3-cyanopropyl)imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (f59) [ftimg=68000138]to a stirring suspension of 6-(3-cyanopropyl)imidazo[1,2-a]pyridine-3-carboxylic acid (25) (50 mg, 0.218 mmol) in anhydrous dichloromethane (2 ml) at 0 degrees centigrade under argon was added dropwise oxalyl chloride (20 micro l, 0.240 mmol). then, a drop of anhydrous dmf was added and the reaction mixture was stirred at 0 degrees centigrade for 1 hour. the solvent was concentrated and the crude solid was dried under vacuum. to a mixture of the acid chloride and methyl 3-(3-(3-amino-4-methylphenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (31) (31 mg, 0.109 mmol) cooled to degrees centigrade under argon was added anhydrous pyridine (2 ml). the reaction was stirred to room temperature under argon for 20 minutes. the solvent was concentrated. the crude product methyl 3-(3-(3-(6-(3-cyanopropyl)imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (f59) was purified by silica chromatography. 1h nmr (400 mhz, d6-dmsol) delta 10.13 (s, 1h), 9.38-9.36 (m, 1h), 8.66 (s, 1h), 8.11 (d, j=1.6 hz, 1h), 7.86-7.82 (m, 2h), 7.63-7.60 (m, 1h), 7.51 (d, j=8.0 hz, 1h), 4.39-4.34 (m, 2h), 4.31-4.24 (m, 1h), 4.21-4.18 (m, 2h), 3.59 (s, 3h), 2.81-2.77 (m, 2h), 2.60-2.52 (m, 2h), 2.38 (s, 3h), 1.97-1.90 (m 2h). ms m/z 500.52 (m+1)+. synthesis of methyl 3-(3-(4-methyl-3-(7-methylimidazo[1,2-a]pyridine-3-carboxamido)phenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (f61) [ftimg=68000139]to a stirring suspension of 7-methylimidazo[1,2-a]pyridine-3-carboxylic acid (24i) (100 mg, 0.568 mmol) in anhydrous dichloromethane (5 ml) at 0 degrees centigrade under argon was added dropwise oxalyl chloride (53 ul, 0.624 mmol). then, a drop of anhydrous n,n-dimethylformamide was added and the reaction mixture was stirred at 0 degrees centigrade for 1 hour. the solvent was concentrated. a stirring mixture of the acid chloride and methyl 3-(3-(3-amino-4-methylphenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (31) (82 mg, 0.283 mmol) in anhydrous pyridine (2 ml) was stirred at room temperature for 2 hour. the solvent was concentrated and the crude product was purified by silica chromatography to give methyl 3-(3-(4-methyl-3-(7-methylimidazo[1,2-a]pyridine-3-carboxamido)phenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (f61). 1h nmr (400 mhz, d6-dmsol) delta 9.97 (s, 1h), 9.33 (d, j=7.2 hz, 1h), 8.52 (s, 1h), 8.09 (d, j=1.6 hz, 1h), 7.83 (dd, j=1.6, 7.6 hz, 1h), 7.58 (s, 1h), 7.50 (d, j=8.0 hz, 1h), 7.03 (dd, j=1.6, 7.2 hz, 1h), 4.39-4.33 (m, 2h), 4.31-4.24 (m, 1h), 4.22-4.16 (m, 2h), 3.59 (s, 3h), 2.43 (s, 3h), 2.36 (s, 3h). ms m/z 447.17 (m+1)+. synthesis of methyl 3-(3-(4-methyl-3-(6-methylimidazo[1,2-a]pyridine-3-carboxamido)phenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (f62) [ftimg=68000140]to a stirring suspension of 6-methylimidazo[1,2-a]pyridine-3-carboxylic acid (24j) (35 mg, 0.196 mmol) in anhydrous dichloromethane (2 ml) at 0 degrees centigrade under argon was added dropwise oxalyl chloride (17 ul, 0.206 mmol). then, a drop of anhydrous n,n-dimethylformamide was added and the reaction mixture was stirred at 0 degrees centigrade for 1 hour. the solvent was concentrated. a stirring mixture of the acid chloride and methyl 3-(3-(3-amino-4-methylphenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (31) (28 mg, 0.098 mmol) in anhydrous pyridine (1.5 ml) was stirred at room temperature for 2 hours. the solvent was concentrated and the crude product was purified by silica chromatography to give methyl 3-(3-(4-methyl-3-(6-methylimidazo[1,2-a]pyridine-3-carboxamido)phenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (f62). 1h nmr (400 mhz, d6-dmsol) delta 10.15 (s, 1h), 9.36 (s, 1h), 8.67 (s, 1h), 8.11 (d, j=2.0 hz, 1h), 7.85 (dd, j=2.0, 8.0 hz, 1h), 7.81 (d, j=9.2 hz, 1h), 7.57 (dd, j=1.2, 9.2 hz, 1h), 7.51 (d, j=8.0 hz, 1h), 4.39-4.34 (m, 2h), 4.31-4.24 (m, 1h), 4.22-4.17 (m, 2h), 3.59 (s, 3h), 2.41 (s, 3h), 2.37 (s, 3h). ms m/z 447.17 (m+1)+. synthesis of methyl 3-(3-(3-(6-(2-cyanoethyl)imidazo[1,2-a]pyridine-3-carboxamido)phenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (f64) [ftimg=68000141]to a stirring suspension of 6-(2-cyanoethyl)imidazo[1,2-a]pyridine-3-carboxylic acid (75) (50 mg, 0.232 mmol) in anhydrous dichloromethane (2 ml) at 0 degrees centigrade under argon was added dropwise oxalyl chloride (22 ul, 0.256 mmol). then, a drop of anhydrous n,n-dimethylformamide was added and the reaction mixture was stirred at 0 degrees centigrade for 1 hour. the solvent was concentrated and the crude solid was dried under vacuo. methyl 3-(3-(3-amino-4-methylphenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (31) (33 mg, 0.116 mmol) and anhydrous pyridine (2 ml) were added to the acid chloride. the reaction was stirred to room temperature under argon for 20 minutes. the crude product was purified by reverse phase preparative hplc to give methyl 3-(3-(3-(6-(2-cyanoethyl)imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (f64). 1h nmr (400 mhz, d6-dmsol) delta 10.08 (s, 1h), 9.45 (s, 1h), 8.63 (s, 1h), 8.12 (d, j=1.6 hz, 1h), 7.85 (dd, j=2.0, 5.6 hz, 1h), 7.82 (d, j=6.8 hz, 1h), 7.60 (dd, j=1.6, 9.2 hz, 1h), 7.51 (d, j=8.0 hz, 1h), 4.38-4.33 (m, 2h), 4.31-4.24 (m, 1h), 4.21-4.18 (m, 2h), 3.59 (s, 3h), 3.01 (t, j=7.6 hz, 2h), 2.91 (t, j=6.4 hz, 2h), 2.38 (s, 3h). ms m/z 486.18 (m+1)+. synthesis of methyl 3-(3-(4-methyl-3-(6-(3-oxobutyl)imidazo[1,2-a]pyridine-3-carboxamido)phenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (f65) [ftimg=68000142]to a stirring suspension of 6-(3-oxobutyl)imidazo[1,2-a]pyridine-3-carboxylic acid (78) (50 mg, 0.215 mmol) in anhydrous dichloromethane (2 ml) at 0 degrees centigrade under argon was added dropwise oxalyl chloride (20 ul, 0.237 mmol). then, a drop of anhydrous n,n-dimethylformamide was added and the reaction mixture was stirred at 0 degrees centigrade for 1 hour. the solvent was concentrated and the crude solid was dried under vacuo. next, methyl 3-(3-(3-amino-4-methylphenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (31) (27 mg, 0.0796 mmol) and anhydrous pyridine (1 ml) were added to the acid chloride. the reaction was stirred to room temperature under argon for 20 minutes. the crude product was purified by reverse phase preparative hplc to give methyl 3-(3-(4-methyl-3-(6-(3-oxobutyl)imidazo[1,2-a]pyridine-3-carboxamido)phenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (f65). 1h nmr (400 mhz, d6-dmsol) delta 10.02 (s, 1h), 9.31 (s, 1h), 8.55 (s, 1h), 8.10 (d, j=1.6 hz, 1h), 7.83 (dd, j=2.0, 8.0 hz, 1h), 7.73 (d, j=9.2 hz, 1h), 7.50 (d, j=8.0 hz, 1h), 7.46 (dd, j=1.6, 9.2 hz, 1h), 4.39-4.34 (m, 2h), 4.31-4.25 (m, 1h), 4.22-4.18 (m, 2h), 3.59 (s, 3h), 2.85 (s, 4h), 2.37 (s, 3h), 2.10 (s, 3h). ms m/z 503.2 (m+1)+. synthesis of methyl 3-(3-(4-methyl-3-(6-(2-morpholinoethyl)imidazo[1,2-a]pyridine-3-carboxamido)phenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (f66) [ftimg=68000143]to a stirring suspension of 6-(2-morpholinoethyl)imidazo[1,2-a]pyridine-3-carboxylic acid (24i) (50 mg, 0.182 mmol) in anhydrous dichloromethane (2 ml) at 0 degrees centigrade under argon was added dropwise oxalyl chloride (17 ul, 0.200 mmol). then, a drop of anhydrous n,n-dimethylformamide was added and the reaction mixture was stirred at 0 degrees centigrade for 1 hour. the solvent was concentrated. a stirring mixture of the acid chloride and methyl 3-(3-(3-amino-4-methylphenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (31) (26 mg, 0.0908 mmol) in anhydrous pyridine (1.5 ml) was stirred at room temperature for 2 hours. the crude product was purified by reverse phase preparative hplc to give methyl 3-(3-(4-methyl-3-(6-(2-morpholinoethyl)imidazo[1,2-a]pyridine-3-carboxamido)phenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (f66). 1h nmr (400 mhz, d6-dmsol) delta 10.07 (s, 1h), 9.46 (s, 1h), 8.61 (s, 1h), 8.12 (d, j=1.6 hz, 1h), 7.86-7.83 (m, 2h), 7.52-7.49 (m, 2h), 4.39-4.36 (m, 2h), 4.31-4.26 (m, 1h), 4.21-4.17 (m, 2h), 4.03-4.00 (m, 2h), 3.69-3.63 (m, 2h), 3.59 (s, 3h), 3.54-3.44 (m, 4h), 3.14-3.10 (m, 4h), 2.38 (s, 3h). ms m/z 546.24 (m+1)+. synthesis of methyl 3-(3-(3-(6-(3-hydroxy-3-methylbutyl)imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (f67) [ftimg=68000144]to a stirring solution of methyl 3-(3-(4-methyl-3-(6-(3-oxobutyl)imidazo[1,2-a]pyridine-3-carboxamido)phenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (f65) (10 mg, 0.0199 mmol) in anhydrous thf (1 ml) at -78 degrees centigrade under a stream of argon was added methylmagnesium bromide (27 ul, 0.080 mmol). the reaction was stirred to

room temperature for 15 minutes then cooled to 0 degrees centigrade and quenched with 1n hcl. the crude product was purified by reverse phase preparative hplc to give methyl 3-(3-(6-(3-hydroxy-3-methylbutyl)imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (f67). 1h nmr (400 mhz, d6-dmsol) delta 10.10 (s, 1h), 9.34 (s, 1h), 8.63 (s, 1h), 8.10 (d, j=1.6 hz, 1h), 7.84 (dd, j=1.6, 8.0 hz, 1h), 7.78 (d, j=9.2 hz, 1h), 7.56-7.54 (m, 1h), 7.51 (d, j=8.4 hz, 1h), 4.39-4.34 (m, 2h), 4.31-4.25 (m, 1h), 4.22-4.17 (m, 2h), 3.59 (s, 3h), 2.76-2.72 (m, 2h), 2.37 (s, 3h), 1.71-1.67 (m, 2h), 1.15 (s, 6h). ms m/z 519.23 (m+1)+. synthesis of methyl 3-(3-(3-(7-(1h-pyrazol-3-yl)imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (f68) [ftimg=68000145]to a stirring solution of 7-(1h-pyrazol-3-yl)imidazo[1,2-a]pyridine-3-carboxylic acid (63) (31.7 mg, 0.14 mmol), and methyl 3-(3-amino-4-methylphenyl)-1,2,4-oxadiazol-5-yl)methylcarbamate (31) (52 mg, 0.18 mmol) in ethyl acetate (0.1 ml) was added propylphosphonic anhydride (50 wt percent in ethyl acetate 0.41 ml). the reaction was heated at 80 degrees centigrade for 12 hours. the resulting mixture was diluted in ethyl acetate and washed with 1n na2co3. after aqueous workup, the residue was purified by reverse phase hplc to afford methyl 3-(3-(3-(7-(1h-pyrazol-3-yl)imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (f68). ms (m/z) 499.1 (m+1)+. synthesis of methyl 3-(3-(3-(7-(3-hydroxy-3-methylbutyl)imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (f73) [ftimg=68000146]to a stirring suspension of 7-(3-oxobutyl)imidazo[1,2-a]pyridine-3-carboxylic acid (86) (40 mg, 0.172 mmol) in anhydrous dichloromethane (2 ml) at 0 degrees centigrade under argon was added dropwise oxalyl chloride (16 ul, 0.189 mmol). then, a drop of anhydrous n,n-dimethylformamide was added and the reaction mixture was stirred at 0 degrees centigrade for 1 hour. the solvent was concentrated and the crude solid was dried under vacuum. methyl 3-(3-(3-amino-4-methylphenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (31) (25 mg, 0.086 mmol) and anhydrous pyridine (1 ml) were added to the acid chloride. the reaction was stirred to room temperature under argon for 20 minutes. the crude product was purified by reverse phase preparative hplc to give methyl 3-(3-(4-methyl-3-(7-(3-oxobutyl)imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (f73). 1h nmr (400 mhz, d6-dmsol) delta 10.24 (s, 1h), 9.44-9.41 (m, 1h), 8.73 (s, 1h), 8.09 (d, j=1.6 hz, 1h), 7.85 (dd, j=1.6, 8.0 hz, 1h), 7.73 (s, 1h), 7.51 (d, j=8.4 hz, 1h), 7.32-7.29 (m, 1h), 4.39-4.35 (m, 2h), 4.31-4.24 (m, 1h), 4.21-4.17 (m, 2h), 3.59 (s, 3h), 2.98-2.91 (m, 4h), 2.37 (s, 3h), 2.13 (s, 3h). ms m/z 503.2 (m+1)+. synthesis of methyl 3-(3-(3-(7-(3-hydroxy-3-methylbutyl)imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (f74) [ftimg=68000147]to a stirring solution of methyl 3-(3-(4-methyl-3-(7-(3-oxobutyl)imidazo[1,2-a]pyridine-3-carboxamido)phenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (f194) (10 mg, 0.0199 mmol) in anhydrous thf (1 ml) at -78 degrees centigrade under a stream of argon was added methylmagnesium bromide (27 ul, 0.080 mmol). the reaction was stirred to room temperature for 15 minutes and quenched at 0 degrees centigrade with 1n hcl. the crude product was purified by reverse phase preparative hplc to give methyl 3-(3-(3-(6-(3-hydroxy-3-methylbutyl)imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (f74). 1h nmr (400 mhz, d6-dmsol) delta 10.11 (s, 1h), 9.41-9.38 (m, 1h), 8.64 (s, 1h), 8.10 (s, 1h), 7.84 (dd, j=1.2, 7.6 hz, 1h), 7.65 (s, 1h), 7.50 (d, j=8.0 hz, 1h), 7.21-7.17 (m, 1h), 4.39-4.35 (m, 2h), 4.31-4.24 (m, 1h), 4.22-4.18 (m, 2h), 3.59 (s, 3h), 2.82-2.77 (m, 2h), 2.37 (s, 3h), 1.74-1.69 (m, 2h), 1.17 (s, 6h). ms m/z 519.23 (m+1)+. synthesis of n-(2-methyl-5-(3-morpholino-1,2,4-oxadiazol-5-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (f75) [ftimg=68000148]a stirring suspension of 3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylbenzoic acid (4) (41 mg, 0.138 mmol) in anhydrous nmp (1 ml) was heated in the microwave at 105 degrees centigrade for 2 minutes to dissolve all solid. then, 1,1'-carbonyldiimidazole (22 mg, 0.138 mmol) was added and the reaction was stirred at room temperature for 15 minutes. n'-hydroxymorpholine-4-carboximidamide (20 mg, 0.138 mmol) was added and the reaction was stirred for 30 minutes. the reaction was heated in the microwave at 130 degrees centigrade for 15 minutes. the crude product was purified by reverse phase preparative hplc to give n-(2-methyl-5-(3-morpholino-1,2,4-oxadiazol-5-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (f75). 1h nmr (400 mhz, d6-dmsol) delta 10.18 (s, 1h), 9.52-9.48 (m, 1h), 8.68 (s, 1h), 8.11 (d, j=2.0 hz, 1h), 7.88-7.83 (m, 2h), 7.68-7.63 (m, 1h), 7.54 (d, j=8.0 hz, 1h), 7.31-7.27 (m, 1h), 3.72-3.69 (m, 4h), 3.41-3.38 (m, 4h), 2.39 (s, 3h). ms m/z 405.16 (m+1)+. synthesis of methyl 3-(3-(4-methyl-3-(5,6,7,8-d4)imidazo[1,2-a]pyridine-3-carboxamido)phenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (f76) [ftimg=68000149] oxalyl chloride (6 ml, 69 mmol) was added dropwise to a stirred suspension of 5,6,7,8-deutero-imidazo[1,2-a]pyridine-3-carboxylic acid (24n) (1.91 g, 11.5 mmol) and dmf (0.1 ml). the mixture was stirred overnight and the volatiles were evaporated. methyl 3-(3-(3-amino-4-methylphenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (31) (3.23 g, 11.2 mmol) in dry pyridine (50 ml) was added to the solid acid chloride at 0 degrees centigrade after the addition, the mixture was warmed to room temperature and stirred for 3 hours before it was heated (50 degrees centigrade) for 5 hours. the solvent was evaporated and the residue was stirred in saturated nh4cl and etoac. a precipitate formed and was filtered and washed with water, and etoac to give methyl 3-(3-(3-(4-methyl-3-(5,6,7,8-d4)imidazo[1,2-a]pyridine-3-carboxamido)phenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (f76) as a grey solid. 1h nmr (400 mhz, d4-meoh) 8.70 (s, 1h), 8.16 (s, 1h), 7.96 (dd, j=7.6, 1.6 hz, 1h), 7.49 (d, j=7.6 hz, 1h), 4.48-4.44 (m, 2h), 4.32-4.29 (m, 2h), 4.24-4.19 (m, 1h), 3.69 (s, 3h), 2.42 (s, 3h). ms m/z 438.1 (m+1)+. synthesis of n-(5-(5-(azetidin-1-yl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (f77) [ftimg=68000150]to a stirring suspension of imidazo[1,2-a]pyridine-3-carboxylic acid (1) (71 mg, 0.39 mmol) in anhydrous dichloromethane (2 ml) was added dropwise oxalyl chloride (173 ul, 1.98 mmol). then, a drop of anhydrous n,n-dimethylformamide was added and the reaction mixture was stirred at room temperature for 30 minutes. the solvent was concentrated, a stirring mixture of the acid chloride and 5-(azetidin-1-yl)-3-(4-methyl-3-nitrophenyl)-1,2,4-oxadiazole (109) (85 mg, 0.29 mmol) in anhydrous pyridine (2 ml) was stirred at room temperature for 30 minutes. the crude product was purified on silica gel using 10 percent meoh in dichloromethane to give n-(5-(5-(azetidin-1-yl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (f77). 1h nmr (400 mhz, cd2cl2) delta 10.10 (s, 1h), 9.51-9.48 (m, 1h), 8.65 (s, 1h), 7.94 (d, j=1.6 hz, 1h), 7.86-7.83 (m, 1h), 7.71 (dd, j=1.6, 7.6 hz, 1h), 7.64-7.60 (m, 1h), 7.43 (d, j=8.0 hz, 1h), 7.27-7.24 (m, 1h), 4.26-4.22 (m, 4h), 2.48-2.40 (m, 2h), 2.34 (s, 3h). ms m/z 374.15 (m+1)+. synthesis of methyl 3-(3-(5-(imidazo[1,2-a]pyridine-3-carboxamido)-2,4-dimethylphenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (f79) [ftimg=68000151]to a stirring solution of boc-azetidine-3-carboxylic acid (20 mg, 0.1 mmol) in anhydrous nmp (1 ml) was added cdi (16.3 mg, 0.1 mmol). the reaction was stirred for 10 minutes. then, n-(5-(n'-hydroxycarbamidoyl)-2,4-dimethylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (50c) (15 mg, 0.05 mmol) was added and the reaction was stirred for 15 minutes. the reaction was heated in the microwave at 125 degrees centigrade for 15 minutes. the reaction mixture was added dropwise to water (20 ml) and extracted with etoac. the organic layers were combined, dried over na2so4, filtered and concentrated to afford a residue which was dissolved in 0.5 ml of tfa and stirred for 10 minutes. then tfa was removed under vacuum and the residue was dissolved in dcm (1 ml) followed by addition of tea (15 mg, 0.15 mmol) and methyl chloroformate (6 mg, 0.06 mmol). the solvent was removed and the residue was purified by hplc to give methyl 3-(3-(5-(imidazo[1,2-a]pyridine-3-carboxamido)-2,4-dimethylphenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (f79). ms m/z 447.1 (m+1)+. synthesis of methyl 3-(3-(4-methyl-3-(7-methyl-d3-imidazo[1,2-a]pyridine-3-carboxamido)phenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (f80) [ftimg=68000152]to a stirring suspension of 7-methyl-d3-imidazo[1,2-a]pyridine-3-carboxylic acid (95) (71 mg, 0.39 mmol) in anhydrous dichloromethane (2 ml) was added dropwise oxalyl chloride (173 ul, 1.98 mmol). then, a drop of anhydrous n,n-dimethylformamide was added and the reaction mixture was stirred at room temperature for 30 minutes. the solvent was concentrated, a stirring mixture of the acid chloride and methyl 3-(3-(3-amino-4-methylphenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (31) (85 mg, 0.29 mmol) in anhydrous pyridine (2 ml) was stirred at room temperature for 30 minutes. the crude product was purified on silica gel using 10 percent meoh in dichloromethane to give methyl 3-(3-(4-methyl-3-(7-methyl-d3-imidazo[1,2-a]pyridine-3-carboxamido)phenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (f80). 1h nmr (400 mhz, cd2cl2) delta 9.71 (d, j=7.2 hz, 1h), 9.15 (s, 1h), 9.04 (s, 1h), 8.33 (s, 1h), 7.95 (dd, j=1.2, 8.2 hz, 1h), 7.93 (s, 1h), 7.46 (d, j=8.0 hz, 1h), 7.37 (d, j=7.2 hz, 1h), 4.48 (d, j=9.2 hz, 1h), 4.46 (d, j=8.4 hz, 1h), 4.39 (d, j=6.0 hz, 1h), 4.37 (d, j=6.0 hz, 1h), 4.16 (m, 1h), 3.72 (s, 3h), 2.77 (s, 3h). ms m/z 450.1 (m+1)+. synthesis of n-(5-(5-(azetidin-1-yl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (f77) [ftimg=68000153] to a stirring suspension of imidazo[1,2-a]pyridine-3-carboxylic acid (1) (71 mg, 0.39 mmol) in anhydrous dichloromethane (2 ml) was added dropwise oxalyl chloride (173 ul, 1.98 mmol). then, a drop of anhydrous n,n-dimethylformamide was added and the reaction mixture was stirred at room temperature for 30 minutes. the solvent was concentrated. a stirring mixture of the acid chloride and 5-(azetidin-1-yl)-3-(4-methyl-3-nitrophenyl)-1,2,4-oxadiazole (109) (85 mg, 0.29 mmol) in anhydrous pyridine (2 ml) was stirred at room temperature for 30 minutes. the crude product was purified on silica gel using 10 percent meoh in dichloromethane to give n-(5-(5-(azetidin-1-yl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (f77). 1h nmr (400 mhz, cd2cl2) delta 10.10 (s, 1h), 9.51-9.48 (m, 1h), 8.65 (s, 1h), 7.94 (d, j=1.6 hz, 1h), 7.86-7.83 (m, 1h), 7.71 (dd, j=1.6, 7.6 hz, 1h), 7.64-7.60 (m, 1h), 7.43 (d, j=8.0 hz, 1h), 7.27-7.24 (m, 1h), 4.26-4.22 (m, 4h), 2.48-2.40 (m, 2h), 2.34 (s, 3h). ms m/z 374.15 (m+1)+. synthesis of methyl 3-(3-(6-(2,2-difluoroethoxy)methyl)imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (f95) [ftimg=68000154]methyl 3-(3-(4-methyl-3-(6-(((methylsulfonyl)oxy)methyl)imidazo[1,2-a]pyridine-3-carboxamido)phenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (133) (15.0 mg, 0.028 mmol) and k2co3 (8.3 mg, 0.06 mmol) in 2,2-difluoroethanol (0.5 ml) was heated at 120 degrees centigrade for 5 minutes. the reaction mixture was purified by preparative hplc to afford methyl 3-(3-(3-(6-(((2,2-difluoroethoxy)methyl)imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (f95). ms m/z 527.1 (m+1)+. synthesis of methyl 3-(3-(3-(7-deuteroimidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (f97) [ftimg=68000155]method a: a mixture of methyl 3-(3-(3-(7-bromoimidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (42g) (0.185 g, 0.36 mmol) in anhydrous thf (5 ml) was degassed by bubbling argon for few minutes. then, pd(oac)2 (7.9 mg, 0.036 mmol, pph3 (38.0 mg, 0.144 mmol), tmeda (83.4 mg, 0.72 mmol) and finally nabd4 (60.6 mg, 1.44 mmol) were introduced in sequence. the mixture was heated at 65 degrees centigrade under argon for 2 hours. the residue was taken up in brine and extracted with ethyl acetate. the organic phase was separated, dried over na2so4, the solvent was evaporated and the residue was purified by flash chromatography to give methyl 3-(3-(3-(7-deuteroimidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (f97). 1h nmr (400 mhz, cd4od) delta 9.53 (dd, j=0.8, 7.2 hz, 1h), 8.49 (s, 1h), 8.16 (d, j=1.6 hz, 1h), 7.94 (dd, j=1.6, 8.0 hz, 1h), 7.75 (m, 1h), 7.49 (d, j=8.0 hz, 1h), 7.18 (dd, j=0.8, 7.2 hz, 1h), 4.47 (m, 2h), 4.33 (m, 2h), 4.24 (m, 1h), 3.70 (s, 3h), 2.43 (s, 3h). ms m/z 434.1 (m+1)+. representative compounds of formula (i) and formula (ii) with ic50 values in the range of 1 nm to 100 nm, and prepared following the procedures described above, are set forth in table 1. table 1c-kitcmpd(mo7e)no.structurephysical data micro mfi(ftimg=68000156)1h nmr (400 mhz, d6-dmsol) delta 10.13 (s, 1h), 9.50-9.48 (m, 1h), 8.66 (s, 1h), 8.10 (d, j = 1.6 hz, 1h), 7.86-7.82 (m, 2h), 7.65-7.61 (m, 1h), 7.53 (d, j = 8.4 hz, 1h), 7.28-7.25 (m, 1h), 4.06-4.02 (m, 4h), 2.44-2.36 (m, 2h), 2.39 (s, 3h). ms m/z 374.1 (m + 1)+.0.049f2[ftimg=68000157]1h nmr (400 mhz, d6-dmsol) delta 10.15 (s, 1h), 9.51-9.48 (m, 1h), 8.68 (s, 1h), 8.13 (d, j = 1.6 hz, 1h), 7.87-7.85 (m, 2h), 7.67-7.63 (m, 1h), 7.55 (d, j = 8.0 hz, 1h), 7.30-7.27 (m, 1h), 4.57-4.50 (m, 4h), 2.40 (s, 3h). ms m/z 410.1 (m + 1)+.0.013f3[ftimg=68000158]ms m/z 417.4 (m + 1)+.0.09f4[ftimg=68000159]1h nmr (400 mhz, d6-dmsol) delta 10.16 (s, 1h), 9.51-9.49 (m, 1h), 8.68 (s, 1h), 8.12 (d, j = 1.2 hz, 1h), 7.87-7.85 (m, 2h), 7.67-7.64 (m, 1h), 7.55 (d, j = 5.9 hz, 1h), 7.30-7.28 (m, 1h), 3.60-3.58 (m, 4h), 2.39 (s, 3h), 2.12-2.06 (m, 4h). ms m/z 438.16 (m + 1)+.0.035f5[ftimg=68000160]1h nmr (400 mhz, d6-dmsol) delta 10.19 (s, 1h), 9.52-9.51 (m, 1h), 8.71 (s, 1h), 8.11 (d, j = 1.2 hz, 1h), 7.90-7.88 (m, 1h), 7.85 (dd, j = 1.2, 5.2 hz, 1h), 7.71-7.68 (m, 1h), 7.55 (d, j = 5.2 hz, 1h), 7.33-7.31 (m, 1h), 4.96-4.85 (m, 1h), 3.61-3.57 (m, 2h), 3.45-3.41 (m, 2h), 2.39 (s, 3h), 2.02-1.93 (m, 2h), 1.81-1.74 (m, 2h). ms m/z 420.17 (m + 1)+.0.034f6[ftimg=68000161]1h nmr (400 mhz, d6-dmsol) delta 10.11 (s, 1h), 9.34 (s, 1h), 8.64 (s, 1h), 7.97 (d, j = 1.6 hz, 1h), 7.80 (d, j = 9.2 hz, 1h), 7.72 (dd, j = 1.6, 8.0 hz, 1h), 7.57-7.54 (m, 1h), 7.45 (d, j = 8.0 hz, 1h), 4.54-4.51 (m, 2h), 4.33-4.30 (m, 2h), 2.40 (s, 3h), 2.35 (s, 3h). ms m/z 472.15 (m + 1)+.0.026f7[ftimg=68000162]ms m/z 390.1 (m + 1)+.0.078f8[ftimg=68000163]1h nmr (400 mhz, d4-meoh) delta 9.73-9.76 (d, j = 7.2 hz, 1h), 8.78 (s, 1h), 8.15-8.13 (m, 1h), 8.06-8.00 (m, 2h), 7.95-7.91 (m, 1h), 7.58-7.48 (m, 2h), 4.72 (dd, j = 12.4, 2.8 hz, 1h), 4.14-4.09 (m, 1h), 3.63-3.57 (m, 1h), 2.35 (s, 3h), 2.06-1.86 (m, 4h), 1.72-1.55 (m, 2h). ms m/z 404.1 (m + 1)+.0.042f9[ftimg=68000164]1h nmr (400 mhz, d4-meoh) delta 9.77 (d, j = 7.2 hz, 1h), 8.78 (s, 1h), 8.14-8.13 (m, 1h), 8.04-8.03 (m, 2h), 7.95-7.93 (m, 1h), 7.57 (ddd, j = 6.8, 6.8, 1.2 hz, 1h), 7.50 (d, j = 8.0, 1h), 5.71 (d, j = 4.4 hz, 1h), 4.15-4.12 (m, 1h), 3.75 (s, 3h), 3.75-3.06 (m, 1h), 2.43 (s, 3h), 2.04-1.94 (m, 2h), 1.80-1.71 (m, 2h), 1.61-1.40 (m, 4h). ms m/z 461.1 (m + 1)+.0.035f10[ftimg=68000165]1h nmr (400 mhz, d4-meoh) delta 9.73 (d, j = 7.2 hz, 1h), 8.74 (s, 1h), 8.17 (m, 1h), 7.98-7.95 (m, 3h), 7.52-7.50 (m, 2h), 5.06 (dd, j = 8.4, 2.8 hz, 1h), 4.07-4.00 (m, 1h), 3.91-3.81 (m, 1h), 2.44 (s, 3h), 2.40-2.21 (m, 4h). ms m/z 440.1 (m + 1)+.0.023f11[ftimg=68000166]1h nmr (400 mhz, d4-meoh) delta 9.73 (d, j = 7.2 hz, 1h), 8.74 (s, 1h), 8.17 (m, 1h), 7.98-7.95 (m, 3h), 7.52-7.50 (m, 2h), 5.06 (dd, j = 8.4, 2.8 hz, 1h), 4.07-4.00 (m, 1h), 3.91-3.81 (m, 1h), 2.44 (s, 3h), 2.40-2.21 (m, 4h). ms m/z 440.1 (m + 1)+.0.023f12[ftimg=68000167]1h nmr (400 mhz, d4-meoh) delta 9.73 (d, j = 7.2 hz, 1h), 8.74 (s, 1h), 8.17 (m, 1h), 7.98-7.95 (m, 3h), 7.52-7.50 (m, 2h), 5.06 (dd, j = 8.4, 2.8 hz, 1h), 4.07-4.00 (m, 1h), 3.91-3.81 (m, 1h), 2.44 (s, 3h), 2.40-2.21 (m, 4h). ms m/z 440.1 (m + 1)+.0.032f13[ftimg=68000168]1h nmr (400 mhz, d6-dmsol) delta 10.17 (s, 1h), 9.51 (d, j = 6.8 hz, 1h), 8.70 (s, 1h), 8.10 (d, j = 2.0 hz, 1h), 7.86 (dd, j = 12, 2.0 hz, 2h), 7.68 (t, j = 8.0 hz, 1h), 7.51 (d, j = 8 hz, 1h), 7.31 (td, j = 6.8, 0.8 hz, 1h), 4.06-4.38 (m, 5h) 2.37 (s, 3h), 1.04 (s, 9h). ms m/z 476.2 (m + 1).0.623f14[ftimg=68000169]1h nmr (400 mhz, d6-dmsol) delta 10.17 (s, 1h), 9.52-9.50 (m, 1h), 8.69 (s, 1h), 8.10 (d, j = 1.6 hz, 1h), 7.88-7.85 (m, 2h), 7.68-7.64 (m, 1h), 7.52 (d, j = 8.0 hz, 1h), 7.31-7.27 (m, 1h), 4.36-4.30 (m, 3h), 4.22-4.19 (m, 2h), 3.11 (s, 3h), 2.37 (s, 3h). ms m/z 453.4 (m + 1)+.0.042f15[ftimg=68000170]1h nmr (400 mhz, d6-dmsol) delta 10.18 (s, 1h), 9.52 (d, j = 7.2 hz, 1h), 8.71 (s, 1h), 8.10 (s, 1h), 7.82-7.91 (m, 2h), 7.69 (t, j = 8.0 hz, 1h), 7.51 (d, j = 8.4 hz, 1h), 7.31 (td, j = 7.2, 0.8 hz, 1h), 4.15-4.44 (m, 5h) 3.59 (s, 3h), 2.37 (s, 3h) ms m/z 433.3 (m + 1).0.021f16[ftimg=68000171]1h nmr (400 mhz, d6-dmsol) delta 1h nmr (400 mhz, d6-dmsol) delta 10.07 (s, 1h), 9.43 (d, j = 7.0, 1h), 8.59 (s, 1h), 8.03 (s, 1h), 7.81-7.71 (m, 2h), 7.56 (s, 1h), 7.45 (d, j = 8.1 hz, 1h), 7.19 (s, 1h), 4.24 (d, j = 3.2 hz, 3h), 4.14 (s, 2h), 3.20-3.07 (m,3h), 2.31 (s,

3h), 1.66 (dd, j = 7.5 hz, 15.2, 2h), 0.92 (d, j = 7.5 hz, 2h). ms m/z 481.5 (m + 1)+0.035f17[ftimg=68000172]1h nmr (400 mhz, d6-dmso) delta 10.12 (s, 1h), 9.49 (d, j = 6.9 hz, 1h), 8.06 (s, 1h), 7.82 (d, j = 7.8 hz, 2h), 7.63-7.57 (m, 1h), 7.50 (d, j = 8.1 hz, 1h), 7.25 (s, 1h), 3.82 (s, 2h), 3.31 (t, j = 7.1 hz, 2h), 2.98 (d, j = 7.1 hz, 2h), 2.37 (s, 3h), 2.01-2.11 (m, 1h), 1.62 (s, 2h), 1.41-1.25 (m, 2h). ms m/z 418.4 (m + 1)+0.027f18[ftimg=68000173]1h nmr (400 mhz, d6-dmso) delta 10.15 (s, 1h), 9.51 (d, j = 6.9 hz, 1h), 8.68 (s, 1h), 8.07 (s, 1h), 7.96-7.75 (m, 2h), 7.66 (s, 1h), 7.50 (d, j = 8.1 hz, 1h), 7.29 (s, 1h), 4.30 (d, j = 5.1 hz, 1h), 3.83-3.73 (m, 1h), 3.72-3.51 (m, 1h), 3.09-3.28 (m, 2h), 2.37 (s, 3h), 2.02-2.14 (m, 1h), 1.81-1.91 (m, 2h), 1.61-1.78 (m, 2h). ms m/z 404.4 (m + 1)+0.064f19[ftimg=68000174]1h nmr (400 mhz, d6-dmso) delta 10.05 (s, 1h), 9.47-9.45 (m, 1h), 8.59 (s, 1h), 8.10-8.09 (d, j = 1.6 hz, 1h), 7.76-7.91 (m, 2h), 7.55-7.49 (m, 2h), 7.20-7.16 (m, 1h), 4.35-4.28 (m, 3h), 4.25-4.20 (m, 2h), 3.22 (q, j = 7.2 hz, 2h), 2.37 (s, 3h), 1.25 (t, j = 7.2 hz, 2h). ms m/z 467.5 (m + 1)+0.033f20[ftimg=68000175]1h nmr (400 mhz, d6-dmso) delta 10.06 (s, 1h), 9.46 (d, j = 7.0 hz, 1h), 8.63 (s, 1h), 8.09 (s, 1h), 7.82 (d, j = 8.7 hz, 2h), 7.58 (s, 1h), 7.51 (d, j = 8.1 hz, 1h), 7.22 (s, 1h), 3.91-4.01 (m, 2h), 3.53-3.65 (m, 5h), 3.47 (s, 3h), 3.32-3.20 (m, 2h), 3.12 (d, j = 7.4 hz, 4h), 2.37 (s, 3h), 2.21 (s, 2h). ms m/z 446.5 (m + 1)+0.095f21[ftimg=68000176]1h nmr (400 mhz, cdcl3) delta 9.47 (d, j = 7.2 hz, 1h), 8.51 (d, j = 1.2 hz, 1h), 8.13 (s, 1h), 7.81 (dd, j = 1.2, 7.6 hz, 1h), 7.68 (d, j = 9.2 hz, 1h), 7.54 (s, 1h), 7.38 (m, 1h), 7.32 (d, j = 8.0 hz, 1h), 6.99 (t, j = 7.2 hz, 1h), 4.10 (s, 2h), 3.82 (t, j = 12.0 hz, 4h). ms m/z 425.1 (m + 1)+0.044f22[ftimg=68000177]ms m/z 419.2 (m + 1)+0.073f23[ftimg=68000178]1h nmr (400 mhz, d6-dmso) delta 10.14 (s, 1h), 9.51-9.48 (m, 1h), 8.67 (s, 1h), 8.11 (d, j = 1.6 hz, 1h), 7.87-7.84 (m, 2h), 7.66-7.61 (m, 1h), 7.52 (d, j = 8.0 hz, 1h), 7.29-7.25 (m, 1h), 7.13 (s, 2h), 4.24-4.18 (m, 1h), 4.16-4.12 (m, 2h), 4.05-4.01 (m, 2h), 2.37 (s, 3h). ms m/z 454.5 (m + 1)+0.088f24[ftimg=68000179]1h nmr (400 mhz, d6-dmso) delta 10.15 (s, 1h), 9.51 (d, j = 6.9 hz, 1h), 8.68 (s, 1h), 8.10 (s, 1h), 7.86 (d, j = 9.0 hz, 2h), 7.65 (s, 1h), 7.52 (d, j = 8.1 hz, 1h), 7.28 (s, 1h), 5.50 (s, 1h), 4.02 (s, 4h), 2.76-2.64 (m, 1h), 2.37 (s, 3h), 1.22 (s, 9h). ms m/z 475.5 (m + 1)+0.08f25[ftimg=68000180]1h nmr (400 mhz, d6-dmso) delta 10.12 (s, 1h), 9.51-9.49 (m, 1h), 8.66 (s, 1h), 8.12 (d, j = 1.6 hz, 1h), 7.86-7.83 (m, 2h), 7.64-7.60 (m, 1h), 7.52 (d, j = 8.4 hz, 1h), 7.28-7.24 (m, 1h), 5.74 (t, j = 8.0 hz, 1h), 4.13 (q, j = 8.8 hz, 2h), 3.87 (q, j = 7.2 hz, 2h), 3.17 (s, 3h). ms m/z 453.5 (m + 1)+0.046f26[ftimg=68000181]1h nmr (400 mhz, cdcl3) delta 9.46 (m, 1h), 8.48 (s, 1h), 8.14 (s, 1h), 7.81 (dd, j = 1.6, 8.0 hz, 1h), 7.69 (d, j = 7.2 hz, 1h), 7.56 (s, 1h), 7.38 (m, 1h), 7.31 (d, j = 8.0 hz, 1h), 6.98 (dt, j = 0.8, 6.8 hz, 1h), 5.12 (m, 2h), 4.91 (m, 2h), 3.66 (s, 3h), 2.36 (s, 3h). ms m/z 499.0 (m + 1)+0.103f27[ftimg=68000182]ms m/z 479.2 (m + 1)+0.997f28 [ftimg=68000183]1h nmr (400 mhz, cdcl3) delta 9.50 (d, j = 2 hz, 1h), 9.09 (dd, j = 2, 7.2 hz, 1h), 8.21 (s, 1h), 7.87 (m, 1h), 7.79 (m, 1h), 7.71 (d, j = 9.2 hz, 1h), 7.41 (m, 1h), 7.22 (dd, j = 8.8, 10.4 hz, 1h), 7.02 (dt, j = 0.8, 6.8 hz, 1h), 4.34 (m, 4h), 4.07 (m, 1h), 3.00 (q, j = 7.6 hz, 2h), 1.35 (t, j = 7.6 hz, 2h). ms m/z 471.2 (m + 1)+0.12f29[ftimg=68000184]ms m/z 439.2 (m + 1)+0.016f30[ftimg=68000185]1h nmr (400 mhz, cd2cl2) delta = 9.71 (d, j = 6.9 hz, 1h), 9.37 (s, 1h), 9.01 (s, 1h), 8.10 (s, 1h), 8.00 (d, j = 8.8 hz, 1h), 7.89 (d, j = 7.3 hz, 1h), 7.75 (d, j = 7.9 hz, 1h), 7.41 (t, j = 6.9 hz, 1h), 7.29 (d, j = 8.0 hz, 1h), 4.42 (s, 2h), 3.36 (s, 3h), 2.31 (d, j = 9.8 hz, 8h). ms m/z 453.2 (m + 1)+0.02f31[ftimg=68000186]ms m/z 495.2 (m + 1)+0.054f32[ftimg=68000187]1h nmr (400 mhz, d6-dmso) delta 10.16 (s, 1h), 9.50 (d, j = 6.9 hz, 1h), 8.68 (s, 1h), 8.08 (d, j = 1.7 hz, 1h), 7.84 (dd, j = 5.5, 13.5 hz, 2h), 7.68-7.60 (m, 1h), 7.52 (d, j = 8.1 hz, 1h), 7.28 (t, j = 6.9 hz, 1h), 5.61-5.74 (m, 1h), 4.10 (dd, j = 11.7, 23.8 hz, 1h), 3.95 (dd, j = 11.7, 23.8 hz, 1h), 3.21 (s, 3h), 3.10-3.21 (m, 1h), 2.81-2.87 (m, 1h), 2.37 (s, 3h). ms m/z 503.4 (m + 1)+0.055f33[ftimg=68000188]1h nmr (400 mhz, d6-dmso) delta 10.17 (s, 1h), 8.69 (s, 1h), 8.06 (d, j = 1.6 hz, 1h), 7.92-7.78 (m, 2h), 7.72-7.61 (m, 1h), 7.50 (d, j = 8.1 hz, 1h), 7.30 (t, j = 6.9 hz, 1h), 3.60 (s, 3h), 3.37 (t, j = 11.0 hz, 1h), 3.05 (br s, 2h), 2.36 (s, 3h), 2.10 (d, j = 10.4 hz, 2h), 1.70 (dd, j = 11.3, 20.4 hz, 2h). ms m/z 461.5 (m + 1)+0.084f34[ftimg=68000189]1h nmr (400 mhz, d6-dmso) delta 10.12 (s, 1h), 9.48 (d, j = 6.9 hz, 1h), 8.64 (s, 1h), 8.06 (s, 1h), 7.83 (d, j = 8.0 hz, 2h), 7.60 (s, 1h), 2.85-3.15 (m, 4h), 2.36 (s, 3h), 2.22 (d, j = 9.5 hz, 2h), 1.87 (q, j = 9.5 hz, 2h). ms m/z 481.5 (m + 1)+0.095f35[ftimg=68000190]1h nmr (400 mhz, d6-dmso) delta 10.16 (s, 1h), 9.51 (d, j = 7.0 hz, 1h), 8.68 (s, 1h), 8.11 (d, j = 1.7 hz, 2h), 7.90-7.80 (m, 2h), 7.73-7.57 (m, 1h), 7.53 (d, j = 8.1 hz, 1h), 7.29 (t, j = 6.9 hz, 1h), 5.20 (dd, j = 3.1, 8.9 hz, 1h), 4.06 (d, j = 11.8 hz, 2h), 3.94-3.74 (m, 3h), 3.52-3.31 (m, 2h), 3.00 (s, 3h), 2.38 (s, 3h). ms m/z 483.5 (m + 1)+0.066f36[ftimg=68000191]1h nmr (400 mhz, d6-dmso) delta 10.16 (s, 1h), 9.51 (d, j = 6.9 hz, 1h), 8.68 (s, 1h), 8.07 (s, 1h), 7.91-7.73 (m, 2h), 7.65 (s, 1h), 7.51 (d, j = 8.1 hz, 1h), 7.28 (s, 1h), 5.32 (dd, j = 3.9, 8.5 hz, 1h), 3.50 (s, 3h), 3.01-3.21 (m, 2h), 2.37 (s, 3h), 2.21-1.87 (m, 4h). ms m/z 467.51 (m + 1)+0.093f37[ftimg=68000192]1h nmr (400 mhz, d6-dmso) delta 10.15 (s, 1h), 9.50 (d, j = 6.9 hz, 1h), 8.68 (s, 1h), 8.11 (d, j = 1.7 hz, 1h), 7.88-7.83 (m, 2h), 7.68-7.62 (m, 1h), 7.53 (d, j = 8.1 hz, 1h), 7.28 (t, j = 6.5 hz, 1h), 5.15-5.21 (m, 1h), 4.06 (d, j = 11.8 hz, 2h), 3.86-3.78 (m, 2h), 3.43-3.34 (m, 2h), 3.08 (d, j = 9.2 hz, 1h), 3.00 (s, 3h), 2.38 (s, 3h). ms m/z 483.51 (m + 1)+0.06f38 [ftimg=68000193]1h nmr (400 mhz, d6-dmso) delta 10.21 (s, 1h), 9.52 (d, j = 7.0 hz, 1h), 8.72 (s, 1h), 8.07 (d, j = 1.7 hz, 1h), 7.90 (d, j = 9.0 hz, 1h), 7.84 (dd, j = 1.7, 7.9 hz, 1h), 7.74-7.66 (m, 1h), 7.51 (d, j = 8.1 hz, 1h), 7.33 (t, j = 6.9 hz, 1h), 3.51-3.54 (m, 1h), 3.41-3.33 (m, 1h), 3.30-3.21 (m, 1h), 3.11-3.19 (m, 2h), 3.00-3.08 (m, 1h), 2.91 (s, 3h), 2.70-2.81 (m, 1h), 2.37 (s, 3h), 2.11-2.21 (m, 1h), 1.62-1.74 (m, 1h). ms m/z 481.54 (m + 1)+0.09f39 [ftimg=68000194]1h nmr (400 mhz, d6-dmso) delta 10.20 (s, 1h), 9.52 (dd, j = 3.5, 4.5 hz, 1h), 8.71 (s, 1h), 8.07 (d, j = 1.7 hz, 1h), 7.92-7.81 (m, 3h), 7.73-7.66 (m, 1h), 7.51 (d, j = 8.1 hz, 1h), 7.32 (dd, j = 5.9, 6.9 hz, 1h), 3.84 (d, j = 11.7 hz, 1h), 3.49-3.41 (m, 2h), 3.18-3.29 (m, 1h), 2.96-2.86 (m, 3h), 2.37 (s, 3h), 2.23-2.13 (m, 1h), 1.70-1.94 (m, 3h). ms m/z 481.54 (m + 1)+0.094f40[ftimg=68000195]1h nmr (400 mhz, d6-dmso) delta 10.18 (s, 1h), 9.52 (d, j = 6.9 hz, 1h), 8.70 (s, 1h), 8.06 (s, 1h), 7.92-7.76 (m, 2h), 7.72-7.64 (m, 1h), 7.51 (d, j = 8.1 hz, 1h), 7.31 (t, j = 6.9 hz, 1h), 4.27 (s, 2h), 3.34-3.21 (m, 4h), 2.37 (s, 3h), 1.94-2.04 (m, 1h), 1.72-1.88 (m, 3h). ms m/z 461.49 (m + 1)+0.094f41[ftimg=68000196]1h nmr (400 mhz, d6-dmso) delta 10.18 (s, 1h), 9.52 (d, j = 6.9 hz, 1h), 8.70 (s, 1h), 8.06 (s, 1h), 7.92-7.76 (m, 2h), 7.72-7.64 (m, 1h), 7.51 (d, j = 8.1 hz, 1h), 7.31 (t, j = 6.9 hz, 1h), 4.17 (s, 2h), 3.34-3.21 (m, 4h), 2.37 (s, 3h), 1.94-2.04 (m, 1h), 1.72-1.88 (m, 3h). ms m/z 481.54 (m + 1)+0.092f42[ftimg=68000197]ms m/z 475.2 (m + 1)+0.013f43[ftimg=68000198]1h nmr (400 mhz, d6-dmso) delta 10.18 (s, 1h), 9.52 (d, j = 6.8 hz, 1h), 8.70 (s, 1h), 8.10 (d, j = 2.5 hz, 1h), 7.88 (m, 1h), 7.67 (m, 1h), 7.53 (d, j = 8.4 hz, 1h), 7.30 (t, j = 7.2 hz, 1h), 7.26 (t, j = 5.2 hz, 1h), 4.59 (m, 2h), 4.47 (m, 3h), 2.38 (s, 3h). ms m/z 489.2 (m + 1)+0.024f44[ftimg=68000199]1h nmr (400 mhz, d6-dmso) delta 10.03 (s, 1h), 9.46 (d, j = 6.9 hz, 1h), 8.59 (s, 1h), 8.07 (d, j = 1.6 hz, 1h), 7.84-7.76 (m, 2h), 7.55-7.46 (m, 2h), 7.11-7.15 (m, 3h), 3.07-3.37 (m, 5h), 2.37 (s, 3h), 1.68-1.80 (m, 3h), 1.23-1.59 (m, 6h) ms m/z 418.46 (m + 1)+0.017f45[ftimg=68000200]1h nmr (400 mhz, cdcl3) delta 9.48 (d, j = 7.2 hz, 1h), 9.08 (dd, j = 2.0, 7.6 hz, 1h), 8.19 (s, 1h), 7.81 (m, 2h), 7.70 (d, j = 8.8 hz, 1h), 7.40 (m, 1h), 7.22 (m, 1h), 7.01 (m, 1h), 4.00 (s, 2h), 3.11 (t, j = 13.2 hz, 2h), 2.94 (t, j = 7.2 hz, 2h), 2.29 (m, 2h). ms m/z 443.1 (m + 1)+0.09f46[ftimg=68000201]1h nmr (400 mhz, cdcl3) delta 9.49 (m, 1h), 9.07 (dd, j = 2.0, 7.6 hz, 1h), 8.18 (s, 1h), 7.81 (m, 2h), 7.70 (m, 1h), 7.40 (m, 1h), 7.22 (m, 1h), 7.01 (m, 1h), 3.91 (s, 4h), 2.02 (m, 4h). ms m/z 457.1 (m + 1)+0.073f47 [ftimg=68000202]ms m/z 481.54 (m + 1)+0.047f48[ftimg=68000203]1h nmr (400 mhz, cdcl3) delta 8.54 (d, j = 6.5 hz, 1h), 8.53 (s, 1h), 8.36 (m, 2h), 7.81 (d, j = 7.9 hz, 1h), 7.76 (s, 1h), 7.41 (dd, j = 8.9, 6.9 hz, 1h), 7.35 (d, j = 7.9 hz, 1h), 6.99 (t, j = 6.1 hz, 1h), 4.41 (m, 4h), 4.12 (m, 1h), 3.71 (s, 3h), 2.41 (s, 3h). ms m/z 433.2 (m + 1)+0.08f49[ftimg=68000204]1h nmr (400 mhz, d6-dmso) delta 10.19 (s, 1h), 9.54-9.50 (m, 1h), 8.71 (s, 1h), 8.06 (d, j = 1.7 hz, 1h), 7.89 (d, j = 9.0 hz, 1h), 7.83 (dd, j = 1.8, 7.9 hz, 1h), 7.73-7.66 (m, 1h), 7.50 (d, j = 8.1 hz, 1h), 7.32 (td, j = 1.1, 6.9 hz, 1h), 3.83 (dd, j = 2.3, 11.1 hz, 1h), 3.73 (dt, j = 3.6, 10.9 hz, 1h), 3.34 (td, j = 3.0, 10.8 hz, 1h), 3.18 (dd, j = 9.3, 11.1 hz, 1h), 2.93 (qd, j = 7.2, 15.6 hz, 2h), 2.36 (s, 3h), 2.15-2.05 (m, 1h), 1.88-1.78 (m, 1h), 1.64-1.44 (m, 2h), 1.30-1.41 (m, 1h). ms m/z 418.46 (m + 1)+0.04f50[ftimg=68000205]ms m/z 439.0 (m + 1)+0.077f51[ftimg=68000206]ms m/z 453.2 (m + 1)+0.043f52[ftimg=68000207]1h nmr (400 mhz, d6-dmso) delta 10.27 (s, 1h), 9.88 (s, 1h), 8.72 (s, 1h), 8.08 (d, j = 1.6 hz, 1h), 8.01 (d, j = 9.5 hz, 1h), 7.86 (dd, j = 1.7, 7.9 hz, 1h), 7.79 (dd, j = 1.9, 9.5 hz, 1h), 7.52 (d, j = 8.1 hz, 1h), 4.39-4.10 (m, 6h), 3.59 (s, 3h), 2.37 (s, 3h). ms m/z 501.43 (m + 1)+0.218f53[ftimg=68000208]1h nmr (400 mhz, d6-dmso) delta 10.16 (s, 1h), 9.51 (d, j = 6.9 hz, 1h), 8.69 (s, 1h), 8.10 (d, j = 1.7 hz, 1h), 7.86 (dd, j = 5.4, 11.7 hz, 2h), 7.69-7.63 (m, 1h), 7.51 (d, j = 8.1 hz, 1h), 7.29 (t, j = 6.9 hz, 1h), 4.37 (s, 3h), 4.27 (dd, j = 5.4, 8.6 hz, 2h), 4.18 (s, 3h), 4.04 (q, j = 7.1 hz, 3h), 2.37 (s, 3h), 1.17 (t, j = 7.1 hz, 3h) ms m/z 447.46 (m + 1)+0.093f54[ftimg=68000209]1h nmr (400 mhz, d6-dmso) delta 10.15 (s, 1h), 9.49 (dd, j = 2.5, 5.0 hz, 1h), 8.66 (s, 1h), 8.09 (d, j = 1.6 hz, 1h), 7.88 (ddd, j = 3.4, 8.9, 9.6 hz, 2h), 7.72-7.63 (m, 1h), 7.52 (d, j = 8.1 hz, 1h), 4.38 (s, 2h), 4.34-4.24 (m, 1h), 4.23 (d, j = 19.4 hz, 2h), 3.60 (s, 3h), 2.35 (d, j = 15.0 hz, 3h) ms m/z 451.1 (m + 1)+0.037f55[ftimg=68000210]1h nmr (400 mhz, d6-dmso) delta 10.13 (s, 1h), 9.48-9.46 (m, 1h), 8.64 (s, 1h), 8.08 (d, j = 1.6 hz, 1h), 7.90-7.87 (m, 1h), 7.85 (dd, j = 2.0, 8.0 hz, 1h), 7.67-7.62 (m, 1h), 7.51 (d, j = 8.4 hz, 1h), 4.42-4.33 (m, 2h), 4.31-4.24 (m, 1h), 4.27-4.15 (m, 2h), 3.59 (s, 3h), 2.36 (s, 3h). ms m/z 451.42 (m + 1)+0.054f56[ftimg=68000211]ms m/z 513.2 (m + 1)+0.006f57[ftimg=68000212]1h nmr (400 mhz, d6-dmso) delta 10.25 (s, 1h), 9.64-9.61 (m, 1h), 9.75 (s, 1h), 8.33-8.30 (m, 1h), 8.10 (dd, j = 1.6 hz, 1h), 7.86 (dd, j = 1.6, 8.0 hz, 1h), 7.52 (d, j = 8.4 hz, 1h), 7.46 (dd, j = 2.0, 7.6 hz, 1h), 4.40-4.33 (m, 2h), 4.31-4.25 (m, 1h), 4.22-4.18 (m, 2h), 3.59 (s, 3h), 2.38 (s, 3h). ms m/z 501.43 (m + 1)+0.135f8[ftimg=68000213]ms m/z 467.1 (m + 1)+0.089f59[ftimg=68000214]1h nmr (400 mhz, d6-dmso) delta 10.13 (s, 1h), 9.38-9.36 (m, 1h), 8.66 (s, 1h), 8.11 (d, j = 1.6 hz, 1h), 7.86-7.82 (m, 2h), 7.63-7.60 (m, 1h), 7.51 (d, j = 8.0 hz, 1h), 4.39-4.34 (m, 2h), 4.31-4.24 (m, 1h), 4.21-4.18 (m, 2h), 3.59 (s, 3h), 2.81-2.77 (m, 2h), 2.60-2.52 (m, 2h), 2.38 (s, 3h), 1.97-1.90 (m, 2h). ms m/z 500.52 (m + 1)+0.033f60[ftimg=68000215]1h nmr (400 mhz, d6-dmso) delta 10.01 (s, 1h), 9.12 (d, j = 2.4 hz, 1h), 8.54 (s, 1h), 8.09 (d, j = 1.6 hz, 1h), 7.85 (dd, j = 1.6, 7.8 hz, 1h), 7.72 (d, j = 9.6 hz, 1h), 7.51 (d, j = 8.0 hz, 1h), 7.32 (dd, j = 2.4, 9.6 hz, 1h), 4.38 (bs, 2h), 4.32-4.25 (m, 1h), 4.20 (bs, 2h), 3.83 (s, 3h), 3.59 (s, 3h), 2.37 (s, 3h). ms m/z 463.1 (m + 1)+0.028f61[ftimg=68000216]1h nmr (400 mhz, d6-dmso) delta 9.97 (s, 1h), 9.33 (d, j = 7.2 hz, 1h), 8.52 (s, 1h), 8.09 (d, j = 1.6 hz, 1h), 7.83 (dd, j = 1.6, 7.6 hz, 1h), 7.58 (s, 1h), 7.50 (d, j = 8.0 hz, 1h), 7.03 (dd, j = 1.6, 7.2 hz, 1h), 4.39-4.33 (m, 2h), 4.31-4.24 (m, 1h), 4.22-4.16 (m, 2h), 3.59 (s, 3h), 2.43 (s, 3h), 2.36 (s, 3h). ms m/z 447.17 (m + 1)+0.026f62[ftimg=68000217]1h nmr (400 mhz, d6-dmso) delta 10.15 (s, 1h), 9.36 (s, 1h), 8.67 (s, 1h), 8.11 (d, j = 2.0 hz, 1h), 7.85 (dd, j = 2.0, 8.0 hz, 1h), 7.81 (d, j = 9.2 hz, 1h), 7.57 (dd, j = 1.2, 9.2 hz, 1h), 7.51 (d, j = 8.0 hz, 1h), 4.39-4.34 (m, 2h), 4.31-4.24 (m, 1h), 4.22-4.17 (m, 2h), 3.59 (s, 3h), 2.41 (s, 3h), 2.37 (s, 3h). ms m/z 447.17 (m + 1)+0.036f63[ftimg=68000218]ms m/z 612.2 (m + 1)+0.013f64 [ftimg=68000219]1h nmr (400 mhz, d6-dmso) delta 10.08 (s, 1h), 9.45 (s, 1h), 8.63 (s, 1h), 8.12 (d, j = 1.6 hz, 1h), 7.85 (dd, j = 2.0, 5.6 hz, 1h), 7.82 (d, j = 6.8 hz, 1h), 7.60 (dd, j = 1.6, 9.2 hz, 1h), 7.51 (d, j = 8.0 hz, 1h), 4.38-4.33 (m, 2h), 4.31-4.24 (m, 1h), 4.21-4.18 (m, 2h), 3.59 (s, 3h), 3.01 (t, j = 7.6 hz, 2h), 2.91 (t, j = 6.4 hz, 2h), 2.38 (s, 3h). ms m/z 486.18 (m + 1)+0.064f65[ftimg=68000220]1h nmr (400 mhz, d6-dmso) delta 10.02 (s, 1h), 9.31 (s, 1h), 8.55 (s, 1h), 8.10 (d, j = 1.6 hz, 1h), 7.83 (dd, j = 2.0, 8.0 hz, 1h), 7.73 (d, j = 9.2 hz, 1h), 7.50 (d, j = 8.0 hz, 1h), 7.46 (dd, j = 1.6, 9.2 hz, 1h), 4.39-4.34 (m, 2h), 4.31-4.25 (m, 1h), 4.22-4.18 (m, 2h), 3.59 (s, 3h), 2.85 (s, 4h), 2.37 (s, 3h), 2.10 (s, 3h). ms m/z 503.2 (m + 1)+0.033f66[ftimg=68000221]1h nmr (400 mhz, d6-dmso) delta 10.07 (s, 1h), 9.46 (s, 1h), 8.61 (s, 1h), 8.12 (d, j = 1.6 hz, 1h), 7.86-7.83 (m, 2h), 7.52-7.49 (m, 2h), 4.39-4.36 (m, 2h), 4.31-4.26 (m, 1h), 4.21-4.17 (m, 2h), 4.03-4.00 (m, 2h), 3.69-3.63 (m, 2h), 3.59 (s, 3h), 3.54-3.44 (m, 4h), 3.14-3.10 (m, 4h), 2.38 (s, 3h). ms m/z 546.24 (m + 1)+0.05f67[ftimg=68000222]1h nmr (400 mhz, d6-dmso) delta 10.10 (s, 1h), 9.34 (s, 1h), 8.63 (s, 1h), 8.10 (d, j = 1.6 hz, 1h), 7.84 (dd, j = 1.6, 8.0 hz, 1h), 7.78 (d, j = 9.2 hz, 1h), 7.56-7.54 (m, 1h), 7.51 (d, j = 8.4 hz, 1h), 4.39-4.34 (m, 2h), 4.31-4.25 (m, 1h), 4.22-4.17 (m, 2h), 3.59 (s, 3h), 2.76-2.72 (m, 2h), 2.37 (s, 3h), 1.71-1.67 (m, 2h), 1.15 (s, 6h). ms m/z 519.23 (m + 1)+0.029f68[ftimg=68000223]ms m/z 499.1 (m + 1)+0.013f69[ftimg=68000224]ms m/z 419.1 (m + 1)+0.039f70[ftimg=68000225]ms m/z 419.1 (m + 1)+0.006f71[ftimg=68000226]ms m/z 405.2 (m + 1)+0.011f72[ftimg=68000227]ms m/z 405.2 (m + 1)+0.006f73[ftimg=68000228]1h nmr (400 mhz, d-dmso) delta 10.24 (s, 1h), 9.44-9.41 (m, 1h), 8.73 (s, 1h), 8.09 (d, j = 1.6 hz, 1h), 7.85 (dd, j = 1.6, 8.0 hz, 1h), 7.73 (s, 1h), 7.51 (d, j = 8.4 hz, 1h), 7.32-7.29 (m, 1h), 4.39-4.35 (m, 2h), 4.31-4.24 (m, 1h), 4.21-4.17 (m, 2h), 3.59 (s, 3h), 2.98-2.91 (m, 4h), 2.37 (s, 3h), 2.13 (s, 3h). ms m/z 503.2 (m + 1)+0.037f4[ftimg=68000229]1h nmr (400 mhz, d6-dmso) delta 10.11 (s, 1h), 9.41-9.38 (m, 1h), 8.64 (s, 1h), 8.10 (s, 1h),

(dd, j = 2.0, 8.0 hz, 1h), 7.57 (s, 1h), 7.42 (d, j = 8.0 hz, 1h), 7.02 (dd, j = 1.6, 7.2 hz, 1h), 5.89 (s, 1h), 4.12-4.07 (m, 4h), 2.42 (s, 3h), 2.33 (s, 3h), 1.45 (s, 3h). ms m/z 418.18 (m + 1)+.0.062f89[ftimg=68000244]1h nmr (400 mhz, d6-dmso) delta 9.95 (s, 1h), 9.33-9.31 (m, 1h), 8.51 (s, 1h), 7.95 (d, j = 1.6 hz, 1h). 7.71 (dd, j = 1.6, 7.6 hz, 1h), 7.57 (s, 1h), 7.43 (d, j = 8.4 hz, 1h), 7.03 (dd, j = 1.6, 7.2 hz, 1h), 3.77-3.74 (m, 4h), 2.42 (s, 3h), 2.33 (s, 3h), 2.20-2.10 (m, 4h). ms m/z 452.18 (m + 1)+.0.031f90[ftimg=68000245]1h nmr (400 mhz, d6-dmso) delta 9.95 (s, 1h), 9.33-9.31 (m, 1h), 8.51 (s, 1h), 7.93 (d, j = 2.0 hz, 1h), 7.70 (dd, j = 1.6, 8.0 hz, 1h), 7.57 (s, 1h), 7.42 (d, j = 8.0 hz, 1h), 7.03 (dd, j = 2.0, 7.2 hz, 1h), 5.02-4.86 (m, 1h), 3.72-3.62 (m, 4h), 2.42 (s, 3h), 2.33 (s, 3h), 2.06-1.94 (m, 2h), 1.87-1.81 (m, 2h). ms m/z 434.19 (m + 1)+.0.033f91[ftimg=68000246]1h nmr (400 mhz, d6-dmso) delta 9.95 (s, 1h), 9.33-9.31 (m, 1h), 8.51 (s, 1h), 7.94 (d, j = 1.6 hz, 1h), 7.71 (dd, j = 2.0, 8.0 hz, 1h), 7.57 (s, 1h), 7.43 (d, j = 8.4 hz, 1h), 7.02 (dd, j = 2.0, 7.2 hz, 1h), 3.73-3.71 (m, 4h), 3.61-3.58 (m, 4h), 2.42 (s, 3h), 2.33 (s, 3h). ms m/z 418.18 (m + 1)+.0.064f92[ftimg=68000247]1h nmr (400 mhz, d6-dmso) delta 9.96 (s, 1h), 9.93-9.91 (m, 1h), 8.51 (s, 1h), 7.94 (d, j = 2.0 hz, 1h), 7.71 (dd, j = 1.6, 8.0 hz, 1h), 7.57 (s, 1h), 7.42 (d, j = 8.0 hz, 1h), 7.02 (dd, j = 1.6, 7.2 hz, 1h), 4.05-3.99 (m, 2h), 3.85-3.81 (m, 2h), 2.64-2.54 (m, 2h), 2.42 (s, 3h), 2.33 (s, 3h). ms m/z 438.16 (m + 1)+.0.021f93[ftimg=68000248]1h nmr (400 mhz, d6-dmso) delta 9.96 (s, 1h), 9.33-9.31 (m, 1h), 8.50 (s, 1h), 7.92 (d, j = 1.6 hz, 1h), 7.71 (dd, j = 1.6, 7.6 hz, 1h), 7.57 (s, 1h), 7.43 (d, j = 8.0 hz, 1h), 7.02 (dd, j = 1.6, 7.2 hz, 1h), 4.17-4.13 (m, 1h), 4.01-3.96 (m, 1h), 3.30-3.21 (m, 1h), 2.82-2.74 (m, 1h), 2.42 (s, 3h), 2.33 (s, 3h), 2.00-1.97 (m, 1h), 1.84-1.81 (m, 1h), 1.64-1.56 (m, 2h). ms m/z 484.18 (m + 1)+.0.048f94[ftimg=68000249]1h nmr (400 mhz, d6-dmso) delta 10.21 (s, 1h), 9.53-9.51 (m, 1h), 8.71 (s, 1h), 8.10 (d, j = 1.2 hz, 1h), 7.91-7.88 (m, 1h), 7.85 (dd, j = 1.2, 5.6 hz, 1h), 7.72-7.69 (m, 1h), 7.54 (d, j = 5.2 hz, 1h), 7.34-7.32 (m, 1h), 4.66 (s, 1h), 4.54 (s, 1h), 3.77-3.74 (m, 2h), 3.48-3.46 (m, 1h), 3.29-3.27 (m, 1h), 2.39 (s, 3h), 1.96-1.94 (m, 1h), 1.88-1.86 (m, 1h). ms m/z 416.16 (m + 1)+.0.092f95[ftimg=68000250]ms m/z 527.1 (m + 1)+.0.019f96[ftimg=68000251]ms m/z 509.1 (m + 1)+.0.026f97[ftimg=68000252]1h nmr (400 mhz, d4-meod) delta 9.53 (dd, j = 0.8, 7.2 hz, 1h), 8.49 (s, 1h), 8.16 (d, j = 1.6 hz, 1h), 7.94 (dd, j = 1.6, 8.0 hz, 1h), 7.75 (m, 1h), 7.49 (d, j = 8.0 hz, 1h), 7.18 (dd, j = 0.8, 7.2 hz, 1h), 4.47 (m, 2h), 4.33 (m, 2h), 4.24 (m, 1h), 3.70 (s, 3h), 2.43 (s, 3h) ms m/z 434.1 (m + 1)+.0.044f98[ftimg=68000253]1h nmr (400 mhz, d4-meod) delta 9.53 (s, 1h), 8.49 (s, 1h), 8.16 (d, j = 1.6 hz, 1h), 7.94 (dd, j = 2.0, 8.0 hz, 1h), 7.75 (dd, j = 0.8, 8.8 hz, 1h), 7.58 (dd, j = 1.2, 8.8 hz, 1h), 7.49 (d, j = 8.0 hz, 1h), 4.47 (m, 2h), 4.33 (m, 2h), 4.24 (m, 1h), 3.70 (s, 3h), 2.43 (s, 3h) ms m/z 434.1 (m + 1)+.0.043f99[ftimg=68000254]ms m/z 525.1 (m + 1)+.0.049*20 percent fbs, otherwise 1 percent fbsrepresentative compounds of formula (i) and formula (ii) with c-kit inhibition ic50 values greater than 100 nm and prepared following the procedures described above, are set forth in table 2c-kitcmpd(mo7e)no.structurephysical data micro mf100[ftimg=68000255]ms m/z 537.2 (m + 1)+.0.198f101[ftimg=68000256]ms m/z 433.2 (m + 1)+.0.332f102[ftimg=68000257]1h nmr (400 mhz, d4-meoh) delta 9.73 (d, j = 7.2 hz, 1h), 8.74 (s, 1h), 8.15-8.14 (m, 1h), 7.98-7.92 (m, 3h), 7.53-7.49 (m, 2h), 4.03 (ddd, j = 12, 4, 4 hz, 2 h), 3.61 (ddd, j = 12, 12, 4 hz, 2 h), 3.40-3.30 (m, 1h), 2.46 (s, 3h), 2.11-2.07 (m, 2h), 2.02-1.96 (m, 2h). ms m/z 404.1 (m + 1)+.0.286f103[ftimg=68000258]1h nmr (400 mhz, d4-meoh) delta 9.77 (d, j = 7.1 hz, 1h), 8.79 (d, j = 2.4 hz, 1h), 8.16-8.15 (m, 1 h), 8.07-8.03 (m, 2h), 7.95-7.93 (m, 1h), 7.59-7.55 (m, 1h), 7.50 (d, j = 8 hz, 1h), 4.85 (dd, j = 10.4, 2.8 hz, 1h), 4.08 (d, j = 11.6, 1h), 3.70 (ddd, j = 11.6, 3.2, 3.2 hz, 1h), 2.43 (s, 3 h), 2.11-2.07 (m, 1h), 2.01-1.87 (m, 1h), 1.82-1.63 (m, 2h), ms m/z 390.1 (m + 1)+.0.229*f104[ftimg=68000259]1h nmr (400 mhz, d4-meoh) delta 9.77 (d, j = 7.1 hz, 1h), 8.79 (d, j = 2.4 hz, 1h), 8.16-8.15 (m, 1 h), 8.07-8.03 (m, 2h), 7.95-7.93 (m, 1h), 7.59-7.55 (m, 1h), 7.50 (d, j = 8 hz, 1h), 4.85 (dd, j = 10.4, 2.8 hz, 1h), 4.08 (d, j = 11.6, 1h), 3.70 (ddd, j = 11.6, 3.2, 3.2 hz, 1h), 2.43 (s, 3 h), 2.11-2.07 (m, 1h), 2.01-1.87 (m, 1h), 1.82-1.63 (m, 2h), ms m/z 390.1 (m + 1)+.0.224*f105[ftimg=68000260]1h nmr (400 mhz, d4-meoh) delta 9.73-9.68 (m, 1h), 8.73-8.70 (m, 1h), 8.16-8.14 (m, 1h), 7.97-7.87 (m, 3h), 7.51-7.39 (m, 2h), 4.12-4.07 (m, 1h), 3.54-3.50 (m, 2h), 3.23-3.20 (m, 2h), 2.57 (s, 3h), 2.20-2.04 (m, 2h), 1.86-1.79 (m, 2h), 1.48 (s, 9h). ms m/z 503.1 (m + 1)+.0.505f106[ftimg=68000261]1h nmr (400 mhz, d4-meoh) delta 9.73-9.76 (d, j = 7.2 hz, 1h), 8.78 (s, 1h), 8.15-8.13 (m, 1 h), 8.06-8.00 (m, 2h), 7.95-7.91 (m, 2h), 7.58-7.48 (m, 2 h), 5.12 (dd, j = 8.0, 4.0 hz, 1 h), 3.63-3.60 (m, 1h), 3.48-3.45 (m, 1h), 2.49-2.35 (m, 1 h), 2.41 (s, 3h), 2.10-2.05 (m, 3h). ms m/z 489.2 (m + 1)+.0.648*f109[ftimg=68000264]1h nmr (400 mhz, d4-meoh) delta 9.78 (d, j = 7.2 hz, 1h), 8.79-8.70 (m, 1h), 8.15 (d, j = 2.0 hz, 1h), 8.03-7.94 (m, 3h), 7.60-7.50 (m, 2h), 5.58 (m, 1h), 3.98-3.90 (m, 2h), 2.43 (s, 3h), 2.01-1.95 (m, 2h), 1.75-1.68 (m, 2h), 1.50-1.30 (m, 2h). ms m/z 403.2 (m + 1)+.0.215f110[ftimg=68000265]1h nmr (400 mhz, d4-meoh) delta 9.77 (d, j = 7.2 hz, 1h), 8.78 (s, 1h), 8.14-8.13 (m, 1h), 8.04-8.03 (m, 2h), 7.95-7.93 (m, 1h), 7.57 (ddd, j = 6.8, 6.8, 1.2 hz, 1h), 7.50 (d, j = 8.0, 1h), 5.54 (d, j = 4.4 hz, 1h), 3.83-3.80 (m, 1h), 3.65-3.55 (m, 1 h), 3.07 (s, 3h), 2.43 (s, 3h), 2.04-1.94 (m, 2h), 1.80-1.71 (m, 2h), 1.61-1.40 (m, 4h). ms m/z 481.2 (m + 1)+.0.227*f111[ftimg=68000266]1h nmr (400 mhz, d4-meoh) delta 9.76 (d, j = 7.2 hz, 1h), 8.77 (s, 1h), 8.14-8.13 (m, 1h), 8.04-8.03 (m, 2h), 7.95-7.93 (m, 1 h), 7.57 (ddd, j = 6.8, 6.8, 1.2 hz, 1h), 7.52 (ddd, j = 6.8, 6.8, 1.2 hz, 1h), 7.52 (d, j = 8.0, 1h), 5.01-4.98 (m, 1h), 3.75-3.72 (m, 1h), 3.37-3.30 (m, 1h), 2.96 (s, 3h), 2.46 (s, 3h), 2.46-2.38 (m, 1h), 2.21-2.16 (m, 1 h), 2.07-1.90 (m, 2h), 1.82-1.74 (m, 1h). ms m/z 417.2 (m + 1)+.0.243f112[ftimg=68000267]1h nmr (400 mhz, d4-meoh) delta 9.76 (d, j = 7.2 hz, 1h), 8.78 (s, 1h), 8.14-8.13 (m, 1h), 8.04-8.03 (m, 2h), 7.95-7.93 (m, 1 h), 7.57 (ddd, j = 6.8, 6.8, 1.2 hz, 1h), 7.52 (d, j = 8.0, 1h), 4.79 (dd, j = 10.4, 2.4 hz, 1h), 4.10-4.05 (m, 1h), 3.75-3.70 (m, 1h), 3.38-3.31 (m, 1h), 2.43 (s, 3h), 2.28-2.19 (m, 2 h), 2.04-1.95 (m, 1h), 1.70-1.60 (m, 1h). ms m/z 420.1 (m + 1)+.0.227f113[ftimg=68000268]1h nmr (400 mhz, d6-dmso) delta 10.17 (s, 1h), 9.51 (d, j = 6.8 hz, 1h), 8.70 (s, 1h), 8.10 (d, j = 2.0 hz, 1h), 7.86 (dt, j = 12, 2.0 hz, 1h), 7.68 (t, j = 8.0 hz, 1h), 7.51 (d, j = 8 hz, 1h), 7.31 (t, d, j = 6.8, 0.8 hz, 1h), 4.06-4.38 (m, 5h) 2.37 (s, 3h), 1.40 (s, 9h) ms m/z 476.2 (m + 1)+.0.623f114[ftimg=68000269]0.183f115[ftimg=68000270]1h nmr (400 mhz, d6-dmso) delta 10.14 (s, 1h), 9.51-9.49 (m, 1 h), 8.67 (s, 1h), 8.10 (d, j = 1.6, hz, 1h), 7.86-7.84 (m, 2h), 7.66-7.61 (m, 1h), 7.51 (d, j = 8.0 hz, 1h), 7.29-7.25 (m, 1 h), 4.60-4.56 (m, 1h), 4.43-4.40 (m, 1h), 4.31-4.25 (m, 2 h), 4.12-4.10 (m, 1h), 2.37 (s, 3h), 1.80 (s, 3h). ms m/z 417.43 (m + 1)+.0.464f116[ftimg=68000271]1h nmr (400 mhz, d6-dmso) delta 10.19 (s, 1h), 9.52-9.49 (m, 1 h), 8.69 (s, 1h), 8.06 (s, 1h), 7.89-7.85 (m, 1h), 7.82 (dd, j = 1.2, 7.6 hz, 1h), 7.69-7.64 (m, 1h), 7.52 (d, j = 8.0 hz, 1h), 7.32-7.27 (m, 1h), 5.44-5.41 (m, 1h), 4.35-4.32 (m, 2h), 3.87-3.82 (m, 2h), 3.74-3.70 (m, 1h), 3.53-3.48 (m, 2h), 2.37 (s, 3h), 1.45 (s, 9h). ms m/z 505.54 (m + 1)+.0.792f117[ftimg=68000272]1h nmr (400 mhz, d6-dmso) delta 10.19 (s, 1h), 9.52-9.48 (m, 1 h), 8.69 (s, 1h), 8.06 (s, 1h), 7.89-7.85 (m, 1h), 7.82 (dd, j = 1.2, 7.6 hz, 1h), 7.68-7.64 (m, 1h), 7.52 (d, j = 8.4 hz, 1h), 7.32-7.28 (m, 1h), 5.44-5.41 (m, 1h), 4.35-4.31 (m, 2h), 3.87-3.83 (m, 2h), 3.74-3.70 (m, 1h), 3.53-3.47 (m, 1), 2.37 (s, 3h), 1.44 (s, 9h). ms m/z 505.54 (m + 1)+.0.629f118[ftimg=68000273]ms m/z 405.42 (m + 1)+.0.936f119[ftimg=68000274]ms m/z 417.43 (m + 1)+.0.434f120[ftimg=68000275]1h nmr (400 mhz, d6-dmso) delta 10.16 (s, 1h), 9.51-9.48 (m, 1 h), 8.67 (s, 1h), 8.06 (s, 1h), 7.87-7.82 (m, 2h), 7.67-7.63 (m, 1h), 7.51 (d, j = 8.0 hz, 1 h), 7.30-7.27 (m, 1h), 5.48-5.43 (m, 1h), 3.96-3.90 (m, 3 h), 3.18-3.06 (m, 1h), 2.37 (s, 3h), 1.30 (s, 9h). ms m/z 525.40 (m + 1)+.0.311f121[ftimg=68000276]1h nmr (400 mhz, d6-dmso) delta 10.11 (s, 1h), 9.49-9.47 (m, 1 h), 8.65 (s, 1h), 8.09 (d, j = 4.0 hz, 1h), 7.85-7.82 (m, 2h), 7.61-7.57 (m, 1h), 7.51 (d, j = 8.0 hz, 1h), 7.25-7.22 (m, 1 h), 4.97-4.93 (m, 1h), 3.40-3.34 (m, 2h), 2.94-2.68 (m, 2h), 2.37 (s, 3h). ms m/z 425.40 (m + 1)+.0.205f122[ftimg=68000277]1h nmr (400 mhz, d6-dmso) delta 10.16 (s, 1h), 9.52- (m, 1h), 8.69 (s, 1h), 8.10 (d, j = 2.0 hz, 1h), 7.88-7.83 (m, 2h), 7.68-7.63 (m, 1h), 7.52 (d, j = 8.4 hz, 1h), 7.31-7.27 (m, 1h), 5.08-5.05 (m, 1h), 3.94-3.89 (m, 2h), 3.71-3.60 (m, 3h), 3.26-3.19 (m, 1h), 2.38 (s, 3h), 1.40 (s, 9h). ms m/z 505.54 (m + 1)+.0.296f123[ftimg=68000278]ms m/z 405.42 (m + 1)+.0.527f124[ftimg=68000279]1h nmr (400 mhz, d6-dmso) delta 10.14 (s, 1h), 9.46 (d, j = 7.2 hz, 1h), 8.66 (s, 1h), 7.99 (s, 1h), 7.83 (d, j = 9.2 hz, 1h), 7.75 (dd, j = 7.6, 1.6 hz, 1h), 7.75 (dt, j = 7.6, 1.6 hz, 1h), 7.43 (d, j = 8 hz, 1h), 7.28 (t, j = 7.2 hz, 1h), 3.53 (t, j = 4.4, hz, 1h), 3.46 (t, j = 4.4, hz, 2h), 3.43 (t, j = 4.4, hz, 2h), 3.35 (t, j = 4.4, hz, 2h), 2.30 (s, 3h). ms m/z 461.49 (m + 1)+.0.426f125[ftimg=68000280]1h nmr (400 mhz, d6-dmso) delta 10.15 (s, 1h), 9.50 (d, j = 7.2 hz, 1h), 8.68 (s, 1h), 8.05 (s, 1h), 7.68 (d, j = 8.8 hz, 1h), 7.80 (dd, j = 8.0, 1.6 hz, 1h), 7.65 (t, j = 8.8 hz, 1h), 7.50 (d, j = 8 hz, 1h), 7.29 (t, j = 6.8 hz, 1h), 3.95-4.05 (m, 3h), 3.25-3.63 (m, 4h), 3.50 (t, j = 7.6 hz, 2h), 3.15 (t, j = 7.2 hz, 2h), 2.68 (t, j = 7.2 hz, 2h), 2.36 (s, 3h). ms m/z 481.47 (m + 1)+.0.426f126[ftimg=68000281]1h nmr (400 mhz, d6-dmso) delta 1h nmr (400 mhz, d6-dmso) delta 10.16 (s, 1h), 9.52 (dt, j = 7.2, 1.2 hz, 1h), 8.69 (s, 1h), 8.09 (d, j = 1.2 hz, 1h), 7.84-7.89 (m, 2h), 7.67 (t, j = 8.0, 1h), 7.51 (d, j = 8.0 hz, 1h), 7.30 (t, d, j = 7.2, 0.8 hz, 1h), 4.11-4.34 (m, 5h), 2.37 (s, 3h), 1.46 (s, 3h), 0.76-0.81 (m, 2h), 0.57-0.62 (m, 2h). ms m/z 473.50 (m + 1).0.891f127[ftimg=68000282]1h nmr (400 mhz, d6-dmso) delta 10.19 (s, 1h), 9.52 (d, j = 6.9, 1h), 8.71 (s, 1h), 8.09 (s, 1h), 7.76-7.91 (m, 2h), 7.72-7.62 (m, 1h), 7.51 (d, j = 8.1, 1h), 7.30 (d, j = 6.9, 1h), 4.32-4.23 (m, 10h), 4.14-4.08 (m, 3h), 3.53-3.46 (m, 2h), 3.24 (s, 3h), 2.37 (s, 4h). ms m/z 477.48 (m + 1)+.0.517f128[ftimg=68000283]1h nmr (400 mhz, dmso) delta 10.24 (s, 1h), 9.52 (dd, j = 7.5, 1.1 hz, 1h), 8.73 (s, 1h), 8.05 (s, 1h), 7.86 (m, 2h), 7.69 (m, 1h), 7.51 (dd, j = 6.3, 1.6 hz, 1h), 7.31 (m, 1h), 4.12 (d, j = 10.8 hz, 1h), 3.98 (d, j = 10.7 hz, 1h), 3.76 (m, 2h), 2.37 (s, 3h), 1.5 (s, 3h). ms m/z 390.2 (m + 1)+.0.141f129[ftimg=68000284]ms m/z 414.1 (m + 1)+.0.313f130[ftimg=68000285]ms m/z 407.1 (m + 1)+.0.127f131[ftimg=68000286]ms m/z 405.2 (m + 1)+.0.738f132[ftimg=68000287]ms m/z 419.1 (m + 1)+.0.283f133[ftimg=68000288]1h nmr (400 mhz, d6-dmso) delta 11.27 (s, 1h), 10.25 (s, 1h), 9.55-9.51 (m, 1h), 8.76 (s, 1h), 8.07 (d, j = 1.6 hz, 1h), 7.93-7.89 (m, 1h), 7.85 (dd, j = 1.6, 8.0 hz, 1h), 7.75-7.71 (m, 1h), 7.52 (d, j = 8.4 hz, 1h), 7.37-7.34 (m, 1h), 4.37-4.32 (m, 5h), 2.38 (s, 3h), 1.38 (s, 9h). ms m/z 554.59 (m + 1)+.0.138f134[ftimg=68000289]1h nmr (400 mhz, d6-dmso) delta 10.08 (s, 1h), 9.48 (d, j = 6.9, 1h), 8.64 (s, 1h), 8.11 (s, 1h), 7.87-7.79 (m, 2h), 7.59 (s, 1h), 7.52 (d, j = 8.2, 1h), 7.23 (s, 1h), 4.24-4.18 (m, 1h), 4.16-4.12 (m, 2h), 4.05-4.01 (m, 2 h), 3.31-3.38 (m, 2h), 2.37 (s, 3h). ms m/z 532.56 (m + 1)+.0.892f135[ftimg=68000290]1h nmr (400 mhz, d6-dmso) delta 10.12 (s, 1h), 9.46 (d, j = 7.0, 1h), 8.66 (s, 1h), 8.07 (d, j = 1.6, 1h), 7.93-7.83 (m, 2h), 7.67-7.57 (m, 1h), 7.48 (d, j = 8.1, 1h), 7.24 (t, j = 6.9, 1h), 4.24-4.18 (m, 1h), 4.16-4.12 (m, 2h), 4.05-4.01 (m, 2h), 3.31-3.38 (m, 14h), 2.37 (s, 3h) 1.98-1.88 (m, 2h). ms m/z 546.59 (m + 1)+.0.751f136[ftimg=68000291]1h nmr (400 mhz, d6-dmso) delta 10.48 (s, 1h), 9.57 (d, j = 7.0, 1h), 8.96 (s, 1h), 8.13 (s, 1h), 7.97 (d, j = 9.0, 1h), 7.94-7.87 (m, 1h), 7.81 (s, 1h), 7.56 (d, j = 8.1, 1h), 7.42 (s, 1h), 5.96-5.80 (m, 1h), 4.19-4.02 (m, 3h), 3.00 (s, 1h), 2.88 (s, 1h), 2.40 (s, 3h). ms m/z 375.40 (m + 1)+.0.543f137[ftimg=68000292]ms m/z 462.2 (m + 1)+.0.792f138[ftimg=68000293]ms m/z 463.1 (m + 1)+.0.271f139[ftimg=68000294]ms m/z 491.2 (m + 1)+.0.139f140[ftimg=68000295]1h nmr (400 mhz, cdcl3) delta 9.46 (m, 1h), 8.48 (s, 1h), 8.14 (s, 1h), 7.81 (dd, j = 1.6, 8.0 hz, 1h), 7.69 (d, j = 7.2 hz, 1h), 7.56 (s, 1h), 7.38 (m, 1h), 7.31 (d, j = 8.0 hz, 1h), 6.98 (dt, j = 0.8, 6.8 hz, 1h), 5.12 (m, 2h), 4.91 (m, 2h), 3.66 (s, 3h), 2.36 (s, 3h). ms m/z 449.0 (m + 1)+.0.103f141[ftimg=68000296]ms m/z 463.1 (m + 1)+.0.714f142[ftimg=68000297]ms m/z 419.41 (m + 1)+.0.578f143[ftimg=68000298]ms m/z 417.43 (m + 1)+.0.314f144[ftimg=68000299]1h nmr (400 mhz, d6-dmso) delta 10.05 (s, 1h), 9.46 (d, j = 6.9, 2h), 8.63 (s, 1h), 8.07 (s, 1h), 7.88-7.73 (m, 2h), 7.51 (d, j = 8.2, 2h), 7.22 (s, 1h), 4.77 (d, j = 5.7, 2h), 4.17-4.08 (m, 2h), 3.4-3.98 (m, 10h), 2.37 (s, 3h) ms m/z 476.50 (m + 1)+.0.963f145[ftimg=68000300]ms m/z 461.49 (m + 1)+.0.447f146[ftimg=68000301]1h nmr (400 mhz, d6-dmso) delta 10.15 (s, 1h), 9.51 (d, j = 6.9 1h), 8.68 (s, 2h), 8.07 (s, 1h), 7.88-7.73 (m, 2h), 7.69-7.60 (m, 1h), 7.51 (d, j = 8.1, 1h), 7.29 (t, j = 6.9, 1h), 4.62 (d, j = 5.9, 2h), 4.32 (m, 2h), 3.94 (m, 2h), 3.80 (m, 2h), 2.37 (s, 3h), 2.10-2.15 (m, 1h), 1.96-1.76 (m, 3h). ms m/z 447.46 (m + 1)+.0.187f147[ftimg=68000302]1h nmr (400 mhz, d6-dmso) delta 10.15 (s, 1h), 9.51 (d, j = 6.9, 1h), 8.68 (s, 2h), 8.07 (s, 1h), 7.88-7.73 (m, 2h), 7.69-7.60 (m, 1h), 7.51 (d, j = 8.1, 1h), 7.29 (t, j = 6.9, 1h), 4.62 (d, j = 5.9, 2h), 4.32 (m, 2h), 3.94 (m, 2h), 3.80 (m, 2h), 2.37 (s, 3h), 2.10-2.15 (m, 1h), 1.96-1.76 (m, 3h). ms m/z 447.46 (m + 1)+.0.232f148[ftimg=68000303]1h nmr (400 mhz, d6-dmso) delta 10.14 (s, 1h), 9.50 (d, j = 7.0, 1h), 8.81 (t, j = 5.7, 1h), 8.67 (s, 1h), 8.08 (d, j = 1.7, 1h), 7.87-7.77 (m, 2h), 7.68-7.60 (m, 1h), 7.51 (d, j = 8.1, 1h), 7.28 (t, j = 6.9, 1h), 4.75 (d, j = 5.9, 2h), 4.66 (d, j = 5.9, 2h), 4.27-4.34 (m, 3h), 2.37 (s, 3h), 1.54 (s, 3h). ms m/z 447.46 (m + 1)+.0.151f149[ftimg=68000304]1h nmr (400 mhz, d6-dmso) delta 10.13 (s, 1h), 8.73 (s, 1h), 8.67 (s, 1h), 8.07 (s, 1h), 7.87-7.77 (m, 2h), 7.65 (s, 1h), 7.51 (d, j = 8.1, 1h), 7.28 (s, 1h), 4.61 (d, j = 5.7, 2h), 3.85 (t, j = 5.7, 2h), 3.32 (t, j = 5.7, 2h), 2.37 (s, 3h), 2.07 (s, 1h), 1.60-1.71 (m, 4h). ms m/z 461.49 (m + 1)+.0.684f150[ftimg=68000305]1h nmr (400 mhz, d6-dmso) delta 10.10 (s, 1h), 9.49 (d, j = 6.9, 1h), 8.71 (s, 1h), 8.65 (s, 1h), 8.07 (s, 1h), 7.87-7.77 (m, 2h), 7.68-7.58 (m, 1h), 7.51 (d, j = 8.1, 1h), 7.25 (s, 1h), 4.63 (d, j = 5.7, 2h), 2.37 (s, 3h), 2.31 (s, 2h), 1.19 (s, 6h). ms m/z 463.46 (m + 1)+.0.718f151[ftimg=68000306]1h nmr

3.93- 3.76 (m, 3h), 3.60-3.39 (m, 2h), 2.36 (s, 3h), 2.14 (s, 3h). ms m/z 447.46 (m + 1)+0.358f169[ftimg=68000324]1h nmr (400 mhz, d6-dmso) delta 10.18 (s, 1h), 9.51 (d, j = 6.9, 1h), 8.69 (s, 1h), 8.06 (d, j = 1.7, 1h), 7.90-7.79 (m, 2h), 7.70-7.64 (m, 1h), 7.51 (d, j = 8.1, 1h), 7.30 (t, j = 6.5, 1h), 3.88-3.94 (m, 1h), 3.74-3.85 (m, 1h), 3.64- 3.71 (m, 1h), 3.54-3.63 (m, 3h), 3.52-3.42 (m, 3h), 2.36 (s, 3h). ms m/z 447.46 (m + 1)+0.132f170[ftimg=68000325]1h nmr (400 mhz, d6-dmso) delta 10.14 (s, 1h), 9.50 (d, j = 6.9, 1h), 8.67 (s, 1h), 8.08 (d, j = 1.7, 1h), 7.89-7.84 (m, 2h), 7.67-7.61 (m, 1h), 7.51 (d, j = 8.1, 1h), 7.28 (t, j = 6.9, 1h), 4.02- 3.93 (m, 2h), 3.74-3.85 (m, 1h), 3.51-3.55 (m, 1h), 3.41-3.45 (m, 2h), 2.98 (s, 3h), 2.37 (s, 3h), 2.33-2.22 (m, 1h), 1.96 (m, 1h). ms m/z 467.51 (m + 1)+0.137f171[ftimg=68000326]1h nmr (400 mhz, d6-dmso) delta 10.21 (s, 1h), 9.52 (d, j = 6.9, 1h), 8.71 (s, 1h), 8.06 (d, j = 1.6, 1h), 7.87 (dd, j = 8.4, 24.5, 2h), 7.71 (t, j = 8.0, 1h), 7.51 (d, j = 7.9, 1h), 7.33 (t, j = 6.9, 1h), 3.34-4.02 (m, 6h), 2.37 (s, 4h), 1.97 (s, 3h). ms m/z 431.46 (m + 1)+0.24f172 [ftimg=68000327]1h nmr (400 mhz, d6-dmso) delta 10.18 (s, 1h), 9.51 (d, j = 6.9, 1h), 8.68 (s, 1h), 8.05 (d, j = 1.6, 1h), 7.89-7.84 (m, 2h), 7.70-7.63 (m, 1h), 7.52 (d, j = 8.1, 1h), 7.29 (t, j = 6.9, 1h), 5.54 (s, 1h), 3.90- 4.10 (m, 2h), 3.61-3.71 (m, 2h), 3.22-3.01 (m, 1h), 2.88-2.76 (m, 1h), 2.37 (s, 3h). ms m/z 483.44 (m + 1)+0.122f173[ftimg=68000328]1h nmr (400 mhz, d6-dmso) delta 10.19 (d, j = 11.4, 1h), 9.50 (d, j = 6.9, 1h), 8.68 (s, 1h), 8.04 (s, 1h), 7.91- 7.77 (m, 2h), 7.71- 7.61 (m, 1h), 7.51 (d, j = 8.1, 1h), 7.29 (t, j = 6.6, 1h), 5.51-5.60 (m, 1h), 4.20-4.29 (m, 2h), 3.01-3.08 (m, 1h), 2.71-2.91 (m, 1h), 2.37 (s, 3h), 2.01-2.09 (m, 3h). ms m/z 467.44 (m + 1)+0.212f174[ftimg=68000329]1h nmr (400 mhz, d6-dmso) delta 10.13 (s, 1h), 9.50 (d, j = 6.9, 1h), 8.66 (s, 1h), 8.09 (s, 1h), 7.85 (d, j = 9.3, 2h), 7.62 (s, 1h), 7.51 (d, j = 8.1, 1h), 7.26 (s, 1h), 4.32 (t, j = 7.9, 2h), 4.16 (d, j = 5.6, 2h), 2.78 (s, 6h), 2.38 (s, 3h). ms m/z 446.47 (m + 1)+0.831f175[ftimg=68000330]1h nmr (400 mhz, d6-dmso) delta 10.15 (s, 1h), 9.51 (d, j = 6.9, 1h), 8.68 (s, 1h), 8.10 (s, 1h), 7.85 (t, j = 8.1, 2h), 7.65 (s, 1h), 7.52 (d, j = 8.1, 1h), 7.28 (s, 1h), 5.03- 5.10 (m, 1h), 3.28-3.84 (m, 6h), 2.37 (s, 3h), 1.40 (s, 9h). ms m/z 505.54 (m + 1)+0.728f176 [ftimg=68000331]ms m/z 489.54 (m + 1)+0.452f177[ftimg=68000332]ms m/z 447.1 (m + 1)+0.398f178[ftimg=68000333]ms m/z 467.1 (m + 1)+0.476f179 [ftimg=68000334]ms m/z 439.2 (m + 1)+0.119f180[ftimg=68000335]ms m/z 433.1 (m + 1)+0.169f181[ftimg=68000336]ms m/z 419.1 (m + 1)+0.337f182 [ftimg=68000337]ms m/z 433.1 (m + 1)+0.259f183[ftimg=68000338]1h nmr (400 mhz, d6-dmso) delta 10.15 (s, 1h), 9.51-9.348 (m, 1 h), 8.66 (s, 1h), 8.03 (d, j = 1.6 hz, 1h), 7.91-7.88 (m, 1h), 7.87-7.84 (m, 1h), 7.81-7.79 (m, 1h), 7.66-7.62 (m, 1h), 7.50 (d, j = 8.4 hz, 1h), 5.32- 5.27 (m, 1h), 4.71-4.65 (m, 2 h), 4.51-4.44 (m, 2h), 3.58- 3.52 (m, 1h), 2.36 (s, 3h), 1.41 (s, 9h). ms m/z 505.54 (m + 1)+0.454f184[ftimg=68000339]1h nmr (400 mhz, d6-dmso) delta 10.19 (s, 1h), 9.53-9.51 (m, 1 h), 8.72 (s, 1h), 8.07-8.06 (m, 1h), 7.89 (d, j = 8.8 hz, 1h), 7.84-7.82 (m, 1h), 7.73-7.68 (m, 1h), 7.51 (d, j = 8.0 hz, 1 h), 7.35-7.31 (m, 1h), 3.56- 3.52 (m, 1h), 3.40-3.34 (m, 1 h), 3.26-3.17 (m, 1h), 3.14- 3.12 (m, 2h), 3.04-2.98 (m, 2 h), 2.37 (s, 3h), 2.09-2.01 (m, 1h), 1.70-1.61 (m, 1h), 1.38 (s, 9h). ms m/z 503.56 (m + 1)+0.496f185[ftimg=68000340]1h nmr (400 mhz, d6-dmso) delta 10.19 (s, 1h), 9.53-9.51 (m, 1 h), 8.71 (s, 1h), 8.07-8.06 (m, 1h), 7.89 (d, j = 8.8 hz, 1h), 7.84-7.82 (m, 1h), 7.72-7.67 (m, 1h), 7.51 (d, j = 8.0 hz, 1 h), 7.34-7.30 (m, 1h), 3.56- 3.52 (m, 1h), 3.40-3.34 (m, 1 h), 3.26-3.17 (m, 1h), 3.14- 3.12 (m, 2h), 3.04-2.98 (m, 1 h), 2.71-2.62 (m, 1h), 2.37 (s, 3h), 2.08-2.02 (m, 1h), 1.70- 1.61 (m, 1h), 1.38 (s, 9h). ms m/z 503.56 (m + 1)+0.452f186[ftimg=68000341]1h nmr (400 mhz, d6-dmso) delta 10.19 (s, 1h), 9.53-9.51 (m, 1 h), 8.70 (s, 1h), 8.06 (d, j = 1.2 hz, 1h), 7.90-7.87 (m, 1h), 7.83 (dd, j = 1.6, 8.0 hz, 1h), 7.71-7.67 (m, 1h), 7.50 (d, j = 8.0 hz, 1h), 7.33-7.30 (m, 1 h), 3.72-3.62 (m, 1h), 3.29- 3.21 (m, 2h), 2.36 (s, 3h), 2.15- 2.07 (m, 1h), 1.98-1.87 (m, 1 h), 1.79-1.75 (m, 1h), 1.55- 1.48 (m, 1h), 1.35 (s, 9h). ms m/z 503.56 (m + 1)+0.291f187[ftimg=68000342]1h nmr (400 mhz, d6-dmso) delta 10.20 (s, 1h), 9.53-9.50 (m, 1 h), 8.70 (s, 1h), 8.06 (d, j = 1.6 hz, 1h), 7.90-7.87 (m, 1h), 7.83 (dd, j = 2.0, 8.0 hz, 1h), 7.71-7.67 (m, 1h), 7.50 (d, j = 8.0 hz, 1h), 7.34-7.30 (m, 1 h), 3.67-3.46 (m, 1h), 3.30- 3.27 (m, 2h), 2.36 (s, 3h), 2.18- 2.09 (m, 1h), 1.98-1.87 (m, 1 h), 1.79-1.75 (m, 1h), 1.55- 1.49 (m, 1h), 1.35 (s, 9h). ms m/z 503.56 (m + 1)+0.32f188[ftimg=68000343]1h nmr (400 mhz, d6-dmso) delta 10.10 (s, 1h), 9.48 (d, j = 7.0, 1h), 9.25 (s, 2h), 8.65 (s, 1h), 8.11 (s, 1h), 7.84 (d, j = 7.9, 2h), 7.73- 7.56 (m, 1h), 7.53 (d, j = 8.1, 1h), 7.25 (d, j = 6.9, 1h), 5.33 (t, j = 7.0, 1h), 4.10-4.15 (m, 2h), 3.91-4.01 (m, 2h), 3.79-3.69 (m, 2h), 3.30 (br s, 2h), 2.38 (s, 3h). ms m/z 405.42 (m + 1)+0.399f189[ftimg=68000344]1h nmr (400 mhz, d6-dmso) delta 10.13 (s, 1h), 9.49 (d, j = 6.9, 1h), 9.29 (s, 1h), 8.68 (s, 1h), 8.11 (d, j = 1.7, 1h), 7.93-7.81 (m, 2h), 7.69-7.57 (m, 1h), 7.53 (d, j = 8.2, 1h), 7.27 (t, j = 6.9, 1h), 5.37-5.26 (m, 1h), 4.15 (d, j = 12.9, 1h), 3.96 (s, 1h), 3.73 (s, 1h), 3.60-3.38 (m, 1h), 3.30 (br s, 2h), 2.38 (s, 3h). ms m/z 405.42 (m + 1)+0.824f190 [ftimg=68000345]1h nmr (400 mhz, d6-dmso) delta 10.10 (s, 1h), 9.46 (d, j = 6.9, 1h), 8.65 (s, 1h), 8.12 (s, 1h), 7.85 (t, j = 9.1, 2h), 7.65-7.49 (m, 2h), 7.25 (d, j = 7.0, 1h), 5.17 (s, 1h), 3.41 (m, 2h), 2.39 (s, 3h), 2.35- 2.26 (m, 2h), 2.01-2.15 (m, 2h). ms m/z 389.42 (m + 1)+0.476f191[ftimg=68000346]1h nmr (400 mhz, d6-dmso) delta 10.15 (s, 1h), 9.50 (d, j = 7.0, 1h), 8.40 (s, 1h), 8.09 (s, 1h), 7.85 (t, j = 9.1, 2h), 7.65 (s, 1h), 7.51 (d, j = 8.1, 1h), 7.28 (s, 1h), 5.23- 5.03 (m, 1h), 2.64-2.52 (m, 1h), 2.37 (s, 3h), 2.21-2.38 (m, 3h). ms m/z 403.41 (m + 1)+0.465f192[ftimg=68000347]1h nmr (400 mhz, d6-dmso) delta 10.17 (s, 1h), 9.51 (d, j = 7.0, 1h), 8.69 (s, 1h), 8.40 (s, 1h), 8.09 (s, 1h), 7.89-7.84 (m, 2h), 7.67 (s, 1h), 7.52 (d, j = 8.1, 1h), 7.30 (s, 1h), 5.12 (s, 1h), 2.72- 2.52 (m, 1h), 2.37 (s, 3h), 2.33-2.20 (m, 2h). ms m/z 403.41 (m + 1)+0.672f193[ftimg=68000348]1h nmr (400 mhz, d6-dmso) delta 10.18 (s, 1h), 9.51 (d, j = 7.0, 1h), 8.69 (s, 1h), 8.06 (s, 1h), 7.89- 7.84 (m, 2h), 7.68 (s, 1h), 7.50 (d, j = 8.1, 1h), 7.30 (s, 1h), 4.35- 4.25 (m, 1h), 3.36-3.41 (m, 1h), 3.24 (s, 1h), 2.96-2.78 (m, 1h), 2.36 (s, 3h), 2.01-2.15 (m, 2h), 2.02 (s, 3h), 1.86-1.71 (m, 1h), 1.68-1.55 (m, 1h). ms m/z 445.49 (m + 1)+0.354f194[ftimg=68000349]1h nmr (400 mhz, d6-dmso) delta 10.13 (s, 1h), 9.50 (d, j = 6.9, 1h), 8.66 (s, 1h), 8.10 (s, 1h), 7.89- 7.84 (m, 2h), 7.64 (d, j = 7.2, 1h), 7.52 (d, j = 8.1, 1h), 7.26 (t, j = 7.2, 1h), 5.01-5.11 (m, 1h), 3.94-4.19 (m, 6h), 3.65 (s, 3h), 2.37 (s, 3h). ms m/z 463.46 (m + 1)+0.105f195[ftimg=68000350]1h nmr (400 mhz, d6-dmso) delta 10.12 (s, 1h), 9.57-9.44 (m, 1h), 8.66 (s, 1h), 8.11 (s, 1h), 7.85 (d, j = 9.0, 2h), 7.69-7.56 (m, 1h), 7.54-7.46 (m, 1h), 7.26 (s, 1h), 5.19-4.96 (m, 1h), 3.94-4.19 (m, 6h), 3.34-3.10 (m, 3h), 2.38 (s, 3h). ms m/z 447.46 (m + 1)+0.566f196[ftimg=68000351]1h nmr (400 mhz, d6-dmso) delta 10.13 (s, 1h), 9.49 (d, j = 6.9, 1h), 8.64 (s, 1h), 8.04 (s, 1h), 7.83 (t, j = 7.6, 2h), 5.31-5.15 (m, 1h), 3.61 (s, 3h), 2.67 (s, 1h), 2.36 (s, 3h), 2.33 (s, 1h), 1.99 (br s, 3h). ms m/z 447.46 (m + 1)+0.475f197[ftimg=68000352]1h nmr (400 mhz, d6-dmso) delta 10.14 (s, 1h), 9.49 (d, j = 6.9, 1h), 8.65 (s, 1h), 8.03 (s, 1h), 7.89- 7.84 (m, 2h), 7.69-7.57 (m, 1h), 7.50 (d, j = 8.1, 1h), 7.26 (s, 1h), 5.24-5.16 (m, 1h), 2.36 (s, 3h), 2.21-1.87 (m, 6h). ms m/z 431.46 (m + 1)+0.46f198 [ftimg=68000353]1h nmr (400 mhz, d6-dmso) delta 10.13 (s, 1h), 9.50 (d, j = 6.9, 1h), 8.66 (s, 1h), 8.10 (s, 1h), 7.89- 7.84 (m, 2h), 7.64 (d, j = 7.2, 1h), 7.52 (d, j = 8.1, 1h), 7.26 (t, j = 7.2, 1h), 5.01-5.11 (m, 1h), 3.94-4.19 (m, 6h), 3.65 (s, 3h), 2.37 (s, 3h). ms m/z 463.46 (m + 1)+0.142f199[ftimg=68000354]1h nmr (400 mhz, d6-dmso) delta 10.12 (s, 1h), 9.57-9.44 (m, 1h), 8.66 (s, 1h), 8.11 (s, 1h), 7.85 (d, j = 9.0, 2h), 7.69-7.56 (m, 1h), 7.54-7.46 (m, 1h), 7.26 (s, 1h), 5.19-4.96 (m, 1h), 3.94-4.19 (m, 6h), 3.34-3.10 (m, 3h), 2.38 (s, 3h). ms m/z 447.46 (m + 1)+0.509f200[ftimg=68000355]1h nmr (400 mhz, d6-dmso) delta 10.09 (s, 1h), 9.46 (d, j = 6.9, 2h), 8.65 (s, 1h), 8.13 (s, 1h), 7.85 (t, j = 9.1, 2h), 7.63-7.53 (m, 2h), 7.53 (s, 1h), 7.24 (s, 1h), 5.25- 5.10 (m, 1h), 3.49- 3.30 (m, 3h), 2.39 (s, 3h), 2.35-2.28 (m, 2h), 2.01-2.14 (m, 2h). ms m/z 389.42 (m + 1)+0.395f201[ftimg=68000356]ms m/z 437.2 (m + 1)+0.443f202 [ftimg=68000357]1h nmr (400 mhz, d6-dmso) delta 10.17 (s, 1h), 9.51 (d, j = 6.9, 1h), 8.69 (s, 1h), 8.10 (s, 1h), 7.64- 7.77 (m, 2h), 7.20-7.61 (m, 1h), 7.53 (d, j = 8.1, 1h), 7.29 (t, j = 6.9, 1h), 5.51-5.63 (m, 1h), 4.03 (s, 3h), 2.80-2.67 (m, 1h), 2.38 (s, 3h), 1.38 (s, 3h), 0.91- 0.70 (m, 1h), 0.56 (s, 3h). ms m/z 473.50 (m + 1)+0.208f203[ftimg=68000358]1h nmr (400 mhz, d6-dmso) delta 10.11 (s, 1h), 9.48 (d, j = 7.0, 1h), 8.66 (s, 1h), 8.09 (d, j = 1.6, 1h), 7.86-7.80 (m, 2h), 7.64-7.58 (m, 1h), 7.52 (d, j = 8.1, 1h), 7.25 (t, j = 6.4, 1h), 3.61-3.74 (m, 1h), 3.51-3.58 (m, 1h), 3.29-3.38 (m, 2h), 2.37 (s, 3h), 1.81-1.92 (m, 4h). ms m/z 403.45 (m + 1)+0.826f204[ftimg=68000359]1h nmr (400 mhz, d6-dmso) delta 10.22 (s, 1h), 9.53 (d, j = 6.9, 1h), 8.72 (s, 1h), 8.06 (s, 1h), 7.90 (d, j = 9.0, 1h), 7.83 (d, j = 7.9, 1h), 7.75-7.67 (m, 1h), 7.51 (d, j = 8.1, 1h), 7.34 (t, j = 6.9, 1h), 3.61-3.53 (m, 4h), 3.40- 3.45 (m, 1h), 3.33-3.21 (m, 1h), 3.10- 3.21 (m, 2h), 3.08 (t, j = 7.2, 1h), 2.76-2.59 (m, 1h), 2.37 (s, 3h), 2.07 (s, 1h), 1.69 (s, 1h). ms m/z 461.49 (m + 1)+0.2f205[ftimg=68000360]1h nmr (400 mhz, d6-dmso) delta 10.22 (s, 1h), 9.53 (d, j = 6.9, 1h), 8.72 (s, 1h), 8.06 (s, 1h), 7.90 (d, j = 9.0, 1h), 7.83 (d, j = 7.9, 1h), 7.75-7.67 (m, 1h), 7.51 (d, j = 8.1, 1h), 7.34 (t, j = 6.9, 1h), 3.61-3.53 (m, 4h), 3.40- 3.45 (m, 1h), 3.33-3.21 (m, 2h), 3.08 (t, j = 7.2, 1h), 2.76-2.59 (m, 1h), 2.37 (s, 3h), 2.07 (s, 1h), 1.69 (s, 1h). ms m/z 461.49 (m + 1)+0.284f206[ftimg=68000361]1h nmr (400 mhz, d6-dmso) delta 10.21 (s, 1h), 9.52 (d, j = 7.0, 1h), 8.72 (s, 1h), 8.07 (d, j = 1.7, 1h), 7.90 (d, j = 9.0, 1h), 7.84 (dd, j = 1.7, 7.9, 1h), 7.74-7.66 (m, 1h), 7.51 (d, j = 8.1, 1h), 7.33 (t, j = 6.9, 1h), 3.51-3.54 (m, 1h), 3.41- 3.33 (m, 1h), 3.30-3.21 (m, 1h), 3.11-3.19 (m, 2h), 3.00- 3.08 (m, 1h) = 8.0, 10.0, 1h), 2.91 (s, 3h), 2.70-2.81 (m, 1h), 2.37 (s, 3h), 2.11-2.21 (m, 1h), 1.62- 1.74 (m, 1h). ms m/z 481.54 (m + 1)+0.169f207[ftimg=68000362]1h nmr (400 mhz, d6-dmso) delta 10.17 (s, 1h), 9.51 (d, j = 6.9, 1h), 8.69 (s, 1h), 8.06 (s, 1h), 7.86- 7.80 (m, 2h), 7.66 (s, 1h), 7.51 (d, j = 8.1, 1h), 7.29 (s, 1h), 5.12 (s, 1h), 2.72- 2.52 (m, 1h), 2.37 (s, 3h), 2.33-2.20 (m, 2h), 2.02 (s, 3h), 1.86-1.71 (m, 1h), 1.68-1.55 (m, 1h). ms m/z 445.49 (m + 1)+0.354f194[ftimg=68000349]1h nmr (400 mhz, d6-dmso) delta 10.13 (s, 1h), 9.50 (d, j = 6.9, 1h), 8.66 (s, 1h), 8.10 (s, 1h), 7.89- 7.84 (m, 2h), 7.64 (d, j = 7.2, 1h), 7.52 (d, j = 8.1, 1h), 7.26 (t, j = 7.2, 1h), 5.01-5.11 (m, 1h), 3.94-4.19 (m, 6h), 3.65 (s, 3h), 2.37 (s, 3h). ms m/z 463.46 (m + 1)+0.105f195[ftimg=68000350]1h nmr (400 mhz, d6-dmso) delta 10.12 (s, 1h), 9.57-9.44 (m, 1h), 8.66 (s, 1h), 8.11 (s, 1h), 7.85 (d, j = 9.0, 2h), 7.69-7.56 (m, 1h), 7.54-7.46 (m, 1h), 7.26 (s, 1h), 5.19-4.96 (m, 1h), 3.94-4.19 (m, 6h), 3.34-3.10 (m, 3h), 2.38 (s, 3h). ms m/z 447.46 (m + 1)+0.566f196[ftimg=68000351]1h nmr (400 mhz, d6-dmso) delta 10.13 (s, 1h), 9.49 (d, j = 6.9, 1h), 8.64 (s, 1h), 8.04 (s, 1h), 7.83 (t, j = 7.6, 2h), 5.31-5.15 (m, 1h), 3.61 (s, 3h), 2.67 (s, 1h), 2.36 (s, 3h), 2.33 (s, 1h), 1.99 (br s, 3h). ms m/z 447.46 (m + 1)+0.475f197[ftimg=68000352]1h nmr (400 mhz, d6-dmso) delta 10.14 (s, 1h), 9.49 (d, j = 6.9, 1h), 8.65 (s, 1h), 8.03 (s, 1h), 7.89- 7.84 (m, 2h), 7.69-7.57 (m, 1h), 7.50 (d, j = 8.1, 1h), 7.26 (s, 1h), 5.24-5.16 (m, 1h), 2.36 (s, 3h), 2.21-1.87 (m, 6h). ms m/z 431.46 (m + 1)+0.46f198 [ftimg=68000353]1h nmr (400 mhz, d6-dmso) delta 10.13 (s, 1h), 9.50 (d, j = 6.9, 1h), 8.66 (s, 1h), 8.10 (s, 1h), 7.89- 7.84 (m, 2h), 7.64 (d, j = 7.2, 1h), 7.52 (d, j = 8.1, 1h), 7.26 (t, j = 7.2, 1h), 5.01-5.11 (m, 1h), 3.94-4.19 (m, 6h), 3.65 (s, 3h), 2.37 (s, 3h). ms m/z 463.46 (m + 1)+0.142f199[ftimg=68000354]1h nmr (400 mhz, d6-dmso) delta 10.12 (s, 1h), 9.57-9.44 (m, 1h), 8.66 (s, 1h), 8.11 (s, 1h), 7.85 (d, j = 9.0, 2h), 7.69-7.56 (m, 1h), 7.54-7.46 (m, 1h), 7.26 (s, 1h), 5.19-4.96 (m, 1h), 3.94-4.19 (m, 6h), 3.34-3.10 (m, 3h), 2.38 (s, 3h). ms m/z 447.46 (m + 1)+0.509f200[ftimg=68000355]1h nmr (400 mhz, d6-dmso) delta 10.09 (s, 1h), 9.46 (d, j = 6.9, 2h), 8.65 (s, 1h), 8.13 (s, 1h), 7.85 (t, j = 9.1, 2h), 7.63-7.53 (m, 2h), 7.53 (s, 1h), 7.24 (s, 1h), 5.25- 5.10 (m, 1h), 3.49- 3.30 (m, 3h), 2.39 (s, 3h), 2.35-2.28 (m, 2h), 2.01-2.14 (m, 2h). ms m/z 389.42 (m + 1)+0.395f201[ftimg=68000356]ms m/z 437.2 (m + 1)+0.443f202 [ftimg=68000357]1h nmr (400 mhz, d6-dmso) delta 10.17 (s, 1h), 9.51 (d, j = 6.9, 1h), 8.69 (s, 1h), 8.10 (s, 1h), 7.64- 7.77 (m, 2h), 7.20-7.61 (m, 1h), 7.53 (d, j = 8.1, 1h), 7.29 (t, j = 6.9, 1h), 5.51-5.63 (m, 1h), 4.03 (s, 3h), 2.80-2.67 (m, 1h), 2.38 (s, 3h), 1.38 (s, 3h), 0.91- 0.70 (m, 1h), 0.56 (s, 3h). ms m/z 473.50 (m + 1)+0.208f203[ftimg=68000358]1h nmr (400 mhz, d6-dmso) delta 10.11 (s, 1h), 9.48 (d, j = 7.0, 1h), 8.66 (s, 1h), 8.09 (d, j = 1.6, 1h), 7.86-7.80 (m, 2h), 7.64-7.58 (m, 1h), 7.52 (d, j = 8.1, 1h), 7.25 (t, j = 6.4, 1h), 3.61-3.74 (m, 1h), 3.51-3.58 (m, 1h), 3.29-3.38 (m, 2h), 2.37 (s, 3h), 1.81-1.92 (m, 4h). ms m/z 403.45 (m + 1)+0.826f204[ftimg=68000359]1h nmr (400 mhz, d6-dmso) delta 10.22 (s, 1h), 9.53 (d, j = 6.9, 1h), 8.72 (s, 1h), 8.06 (s, 1h), 7.90 (d, j = 9.0, 1h), 7.83 (d, j = 7.9, 1h), 7.75-7.67 (m, 1h), 7.51 (d, j = 8.1, 1h), 7.34 (t, j = 6.9, 1h), 3.61-3.53 (m, 4h), 3.40- 3.45 (m, 1h), 3.33-3.21 (m, 1h), 3.10- 3.21 (m, 2h), 3.08 (t, j = 7.2, 1h), 2.76-2.59 (m, 1h), 2.37 (s, 3h), 2.07 (s, 1h), 1.69 (s, 1h). ms m/z 461.49 (m + 1)+0.2f205[ftimg=68000360]1h nmr (400 mhz, d6-dmso) delta 10.22 (s, 1h), 9.53 (d, j = 6.9, 1h), 8.72 (s, 1h), 8.06 (s, 1h), 7.90 (d, j = 9.0, 1h), 7.83 (d, j = 7.9, 1h), 7.75-7.67 (m, 1h), 7.51 (d, j = 8.1, 1h), 7.34 (t, j = 6.9, 1h), 3.61-3.53 (m, 4h), 3.40- 3.45 (m, 1h), 3.33-3.21 (m, 2h), 3.08 (t, j = 7.2, 1h), 2.76-2.59 (m, 1h), 2.37 (s, 3h), 2.07 (s, 1h), 1.69 (s, 1h). ms m/z 461.49 (m + 1)+0.284f206[ftimg=68000361]1h nmr (400 mhz, d6-dmso) delta 10.21 (s, 1h), 9.52 (d, j = 7.0, 1h), 8.72 (s, 1h), 8.07 (d, j = 1.7, 1h), 7.90 (d, j = 9.0, 1h), 7.84 (dd, j = 1.7, 7.9, 1h), 7.74-7.66 (m, 1h), 7.51 (d, j = 8.1, 1h), 7.33 (t, j = 6.9, 1h), 3.51-3.54 (m, 1h), 3.41- 3.33 (m, 1h), 3.30-3.21 (m, 1h), 3.11-3.19 (m, 2h), 3.00-

490.20 (m + 1)+.0.317f247[ftimg=68000402]ms m/z 505.1 (m + 1)+.0.328f248[ftimg=68000403]1h nmr (400 mhz, d6-dmso) delta 10.10 (s, 1h), 9.51-9.48 (m, 1h), 8.65 (s, 1h), 7.94 (d, j = 1.6 hz, 1h), 7.86-7.83 (m, 1h), 7.71 (dd, j = 1.6, 7.6 hz, 1h), 7.64-7.60 (m, 1h), 7.43 (d, j = 8.0 hz, 1h), 7.27-7.24 (m, 1h), 4.26-4.22 (m, 4h), 2.48-2.40 (m, 2h), 2.34 (s, 3h). ms m/z 374.15 (m + 1)+.0.132f249[ftimg=68000404]ms m/z 447.1 (m + 1)+.0.426f250[ftimg=68000405]ms m/z 518.1 (m + 1)+.0.114f251[ftimg=68000406]1h nmr (400 mhz, d6-dmso) delta 10.15 (s, 1h), 9.51-9.48 (m, 1h), 8.67 (s, 1h), 8.09 (d, j = 1.6 hz, 1h), 7.87-7.82 (m, 2h), 7.66- 7.62 (m, 1h), 7.53 (d, j = 8.4 hz, 1h), 7.30-7.26 (m, 1h), 3.90 (s, 4h), 2.39 (s, 3h), 1.44 (s, 3h). ms m/z 404.16 (m + 1)+.0.157f252[ftimg=68000407]ms m/z 498.7 (m + 1)+.0.421f253[ftimg=68000408]ms m/z 543.7 (m + 1)+.0.215f254[ftimg=68000409]1h nmr (400 mhz, d6-dmso) delta 9.93 (s, 1h), 9.33-9.31 (m, 1h), 8.50 (s, 1h), 7.93 (d, j = 1.6 hz, 1h), 7.69 (dd, j = 1.6, 7.6 hz, 1h), 7.57 (s, 1h), 7.42 (d, j = 8.0 hz, 1h), 7.02 (dd, j = 1.6, 7.2 hz, 1h), 4.45-4.38 (m, 3h), 4.10- 4.06 (m, 2h), 3.25 (s, 3h), 2.42 (s, 3h), 2.33 (s, 3h). ms m/z 418.18 (m + 1)+.0.111f255[ftimg=68000410]1h nmr (400 mhz, d6-dmso) delta 9.94 (s, 1h), 9.32-9.31 (m, 1h), 8.51 (s, 1h), 7.95 (d, j = 1.6 hz, 1h), 7.71 (dd, j = 1.6, 8.0 hz, 1h), 7.57 (s, 1h), 7.43 (d, j = 8.0 hz, 1h), 7.03 (dd, j = 1.6, 7.2 hz, 1h), 4.43-4.38 (m, 1h), 4.25- 4.21 (m, 1h), 4.06-4.00 (m, 3h), 3.70-3.67 (m, 1h), 3.23-3.16 (m, 3h), 2.42 (s, 3h), 2.34 (s, 3h). ms m/z 473.18 (m + 1)+.0.129f256[ftimg=68000411]ms m/z 494.2 (m + 1)+.0.106f257[ftimg=68000412]ms m/z 501.14 (m + 1)+.0.13f258[ftimg=68000413]ms m/z 552.24 (m + 1)+.0.146f259[ftimg=68000414]ms m/z 483.15 (m + 1)+.0.177f260[ftimg=68000415]ms m/z 420.17 (m + 1)+.0.205f261[ftimg=68000416]ms m/z 489.22 (m + 1)+.0.291f262[ftimg=68000417]ms m/z 447.17 (m + 1)+.0.309f263[ftimg=68000418]ms m/z 376.13 (m + 1)+.0.35f264[ftimg=68000419]ms m/z 501.14 (m + 1)+.0.438f265[ftimg=68000420]ms m/z 503.24 (m + 1)+.0.505f266[ftimg=68000421]ms m/z 463.16 (m + 1)+.0.523f267[ftimg=68000422]ms m/z 519.23 (m + 1)+.0.65f268[ftimg=68000423]ms m/z 489.22 (m + 1)+.0.912f269[ftimg=68000424]ms m/z 431.17 (m + 1)+.1.012f270[ftimg=68000425]ms m/z 475.2 (m + 1)+.1.038f271[ftimg=68000426]ms m/z 403.18 (m + 1)+.1.12f272[ftimg=68000427]ms m/z 501.13 (m + 1)+.1.139f273[ftimg=68000428]ms m/z 501.13 (m + 1)+.1.168f274[ftimg=68000429]ms m/z 403.18 (m + 1)+.1.204f275[ftimg=68000430]ms m/z 447.18 (m + 1)+.1.233f276[ftimg=68000431]ms m/z 405.17 (m + 1)+.1.243f277[ftimg=68000432]ms m/z 505.21 (m + 1)+.1.247f278[ftimg=68000433]ms m/z 489.22 (m + 1)+.1.278f279[ftimg=68000434]ms m/z 493.19 (m + 1)+.1.284f280[ftimg=68000435]ms m/z 389.15 (m + 1)+.1.309f281[ftimg=68000436]ms m/z 467.15 (m + 1)+.1.373f282[ftimg=68000437]ms m/z 503.24 (m + 1)+.1.6*f283[ftimg=68000438]ms m/z 489.22 (m + 1)+.1.633f284[ftimg=68000439]ms m/z 403.18 (m + 1)+.1.649f285[ftimg=68000440]ms m/z 403.18 (m + 1)+.1.673f286[ftimg=68000441]ms m/z 391.14 (m + 1)+.1.681f287[ftimg=68000442]ms m/z 501.13 (m + 1)+.1.681f288[ftimg=68000443]ms m/z 503.24 (m + 1)+.1.78*f289[ftimg=68000444]ms m/z 417.19 (m + 1)+.1.884f290[ftimg=68000445]ms m/z 403.19 (m + 1)+.1.887f291[ftimg=68000446]ms m/z 467.15 (m + 1)+.1.921f292[ftimg=68000447]ms m/z 462.18 (m + 1)+.1.934f293[ftimg=68000448]ms m/z 419.17 (m + 1)+.2.153f294[ftimg=68000449]ms m/z 417.17 (m + 1)+.2.201f295[ftimg=68000450]ms m/z 389.17 (m + 1)+.2.203f296[ftimg=68000451]ms m/z 389.17 (m + 1)+.2.443f297[ftimg=68000452]ms m/z 390.15 (m + 1)+.2.79f298[ftimg=68000453]ms m/z 375.16 (m + 1)+.2.857f299[ftimg=68000454]ms m/z 505.14 (m + 1)+.3.52f300[ftimg=68000455]ms m/z 475.2 (m + 1)+.3.56f301[ftimg=68000456]ms m/z 519.16 (m + 1)+.3.97f302[ftimg=68000457]ms m/z 423.15 (m + 1)+.4.33f303[ftimg=68000458]ms m/z 474.21 (m + 1)+.4.64f304[ftimg=68000459]ms m/z 403.18 (m + 1)+.5.23f305[ftimg=68000460]ms m/z 423.15 (m + 1)+.8.08f306[ftimg=68000461]ms m/z 423.15 (m + 1)+.8.37f307[ftimg=68000462]ms m/z 505.17 (m + 1)+.10f308[ftimg=68000463]ms m/z 529.21 (m + 1)+.10f309[ftimg=68000464]ms m/z 511.14 (m + 1)+.10f310[ftimg=68000465]ms m/z 543.21 (m + 1)+.10*20 percent fbs instead of 1 percent fbs assays compounds of formula (i) and formula (ii) provided herein were assayed to measure their capacity to inhibit c-kit and pdgfr kinases using the appropriate assay described below: c-kit inhibition was evaluated using the mo7e cell proliferation assay, and pdgfr inhibition was evaluated using the rat a10 cell proliferation assay and the human tg/ha-vsmc cell proliferation assay.mo7e cell proliferation assaythe compounds of table 1 and table 2 were tested for inhibition of scf dependent proliferation using human mo7e cells which endogenously express c-kit in a 384 well format. three-fold serially diluted test compounds (cmax=10 nm) were evaluated for their antiproliferative activity of mo7e cells stimulated with human recombinant scf. after 48 hours of incubation at 37 degrees centigrade, cell viability was measured by adding 25 ul of celltiter glo (promega) to the cells and the luminescence was measured by a clipr ccd camera (molecular devices).rat a10 cell proliferation assayrat a10 cells (atcc) were resuspended in dmem supplemented with 1 percent fbs or 20 percent fbs and 10 ng/ml recombinant rat pdgfr-bb at 20,000 cells/ml. the cells were aliquoted into 384 well plates at 50 micro l/well and incubated for 4 hours at 37 degrees centigrade 0.5 micro l of test compound 3-fold serially diluted in dmsol was added to each well. the plates were returned to the incubator for a further 68 hours. 25 micro l of celltiter-glo (promega) was added to each well and the plates were incubated on the bench for 15 minutes. luminescence was then read using a clipr ccd camera (molecular devices).human tg/ha-vsmc cell proliferation assayhuman tg/ha-vsmc cells (atcc) were resuspended in dmem supplemented with 1 percent fbs and 30 ng/ml recombinant human pdgfr-bb at 60,000 cells/ml. the cells were aliquoted into 384 well plates at 50 micro l/well and incubated for 4 hours at 37 degrees centigrade 0.5 micro l of test compound 3-fold serially diluted in dmsol was added to each well. the plates were returned to the incubator for a further 68 hours. 25 micro l of celltiter-glo (promega) was added to each well and the plates were incubated on the bench for 15 minutes. luminescence was then read using a clipr ccd camera (molecular devices).certain assay resultsvarious compounds of formula (i) and formula (ii) in free form or in pharmaceutically acceptable salt form, exhibit pharmacological properties, for example, as indicated by the tests described herein and presented in table 1 and table 2. the ic50 value is given as that concentration of the test compound in question that provoke a response halfway between the baseline and maximum responses. certain compounds of formula (i) or formula (ii) having specific ic50 for c-kit inhibition values of less than or equal to 100 nm are listed in table 1, while certain compounds of formula (i) or formula (ii) having specific ic50 for c-kit inhibition values greater than 100 nm are listed in table 2.in other embodiments, compounds of formula (i) or formula (ii) have ic50 values for c-kit inhibition in the range from 1 nm to 1 micro m. in other embodiments, compounds of formula (i) or formula (ii) have ic50 values for c-kit inhibition in the range from 1 nm to 500 nm. in other embodiments, compounds of formula (i) or formula (ii) have ic50 values for c-kit inhibition in the range from 1 nm to 200 nm. in other embodiments, compounds of formula (i) or formula (ii) have ic50 values for c-kit inhibition in the range from 1 nm to 100 nm. in other embodiments, compounds of formula (i) or formula (ii) have ic50 values for c-kit inhibition in the range from 1 nm to 50 nm. in other embodiments, compounds of formula (i) or formula (ii) have ic50 values for c-kit inhibition in the range from 1 nm to 25 nm. in other embodiments, compounds of formula (i) or formula (ii) have ic50 values for c-kit inhibition in the range from 1 nm to 10 nm. in other embodiments, compounds of formula (i) or formula (ii) have ic50 values for c-kit inhibition in the range from 1 nm to 5 nm. in other embodiments, compounds of formula (i) or formula (ii) have ic50 values for c-kit inhibition in the range from 1 nm to 2.5 nm.it is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. (Results 0)

Search 23: PN=(WO2013033228) (Results 1)

Search 24: TAC=(hexahydrocyclopenta[c]pyrrol) and PN=(WO2013033228) and IC=(A61K31/473) (Results 1)

Search 25: TAC=(hexahydrocyclopenta[c]pyrrol) and IC=(A61K31/473) (Results 2)

Search 26: TAC=(antibacterial) and IC=(A61K31/473) (Results 71)

Search 27: TAC=(antibacterial) and CPC=(C07D495/04) (Results 84)

Search 28: TAC=(antibacterial) and IC=(A61K31/473) and CPC=(C07D495/04 or C07D491/14) (Results 2)

Search 29: (26) AND PD=(2005 OR 2004 OR 2009 OR 2001 OR 2002 OR 2003 OR 2006 OR 2008 OR 2010 OR 2000 OR 2007 OR 2011) (Results 53)

Title: PYRIDONE CARBOXYLIC ACID COMPOUNDS AND THEIR USES FOR TREATING INFECTIOUS DISEASES CAUSED BY BACTERIA

Abstract: Source: US5527910A Pyridone carboxylic acid compounds or physiologically hydrolyzable esters thereof are provided which are represented by the formula: (I) wherein R1 is a lower alkyl, a halogen-substituted lower alkyl, a lower alkenyl, a cycloalkyl, or a substituted- or unsubstituted-phenyl group; R2 is a hydrogen atom, or a lower alkyl or an amino group; A is a nitrogen atom or the group C-X wherein X is a hydrogen or a halogen atom, or an alkoxy group; and Z is a group having the formula: (IV) wherein n is 1 or 2; R3 and R4 each represent a hydrogen atom or a lower alkyl group, with proviso that, if n is 2, one of R3 and R4 is a hydrogen atom; R5 and R6 each represent a hydrogen atom, or a hydroxy, a lower alkoxy or an amino group which is unsubstituted or substituted by a lower alkyl group, with proviso that one of R5 and R6 is a hydrogen atom; and R7 is a hydrogen atom or a lower alkyl group. The compounds of the present invention show potent and broad spectrum of **antibacterial** activities.

Classifications:

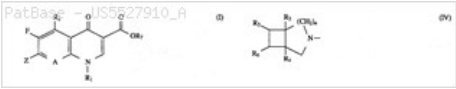
International (IPC 8-9): A61K31/4375 A61K31/44 A61K31/4427 A61K31/4439 A61K31/47 A61K31/4709 A61K31/472 A61K31/4725 A61K31/473 A61P31/04 C07D209/52 C07D221/04 C07D401/04 C07D401/06 C07D401/14 C07D471/04 (Advanced/Invention); A61K31/44 A61K31/4427 A61K31/47 A61K31/472 A61K31/473 (Advanced/Non-invention); A61K31/4353 A61K31/44 A61K31/4427 A61K31/47 A61K31/4709 A61K31/472 A61K31/473 A61P31/00 C07D209/00 C07D221/00 C07D401/00 C07D471/00 (Core/Invention)

International (IPC 1-7): A61K31/40 A61K31/435 A61K31/4375 A61K31/44 A61K31/455 A61K31/47 A61K31/4709 A61P31/04 C07D209/02 C07D209/04 C07D209/08 C07D209/52 C07D209/94 C07D211/10 C07D215/233 C07D221/04 C07D401/04 C07D401/06 C07D401/10 C07D401/14 C07D471/04 C07D498/06

CPC: A61K31/4375 C07D401/04 C07D471/04

European: A61K31/4375 C07D401/04 C07D471/04

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Family:

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AU19940057181 19931229	US19960592171 19960126	AU19970039220 19970924
CA19932152817 19931229	US19940332780 19941101	KR19940017460 19940718

Probable Assignee: CHEIL FOODS AND CHEM

Assignee(s): (std): CHEIL FOODS AND CHEMICALS INC ; CHEIL JEDANG CORP ; NO 1 SUGAR REFINING CO LTD ; CHEJL FUDZ EHND KEMIKAL INK ; INK KR ; CHEJL FUDZ EHND KEMIKALZ ; CHEIL FOODS AND CHEM

Assignee(s): CHEJL FUDZ EHND KEMIKALZ INK ; NO1 SUGAR REFINING CO LTD ; KAIRU FUUZU ANDO CHEM INC ; NO 1 SUGAR REFINING CO ; CHEIL JEDANG CORP SEOUL SOUL

Inventor(s): (std): AN SEOUNG HO ; AN SEUNG H ; AN SEUNG HO ; ANSEUNG KHO ; BAIK YEONG O ; BANG WON Y ; CHO IL H ; CHO IL HWAN ; CHO IL KHVAN ; KIM CHE KHAK ; KIM CHIN VUNG ; KIM CHOONG ; KIM CHOONG SUP ; KIM CHUNG SUP ; KIM JE H ; KIM JE HAK ; KIM JIM WOONG ; KIM JIN ; KIM JIN W ; KIM JIN WOONG ; KIM JIN WOONG HYUNDAI APARTMEN ; JUNG ENG KHVAN ; JUNG YONG H ; JUNG YONG HWAN ; KIM YOUNG H ; LEE JAE ; LEE JAE MOK ; LEE KI H ; LEE KI HO ; LI CHE MOK ; LI KI KHI ; JUN ENG SIK ; PARK KWAN H ; SHIN JUNG CHUN ; SHIN YOUNG J ; SHIN YOUNG JUN ; YEON KYU J ; YOUN YONG S ; YOUN YONG SIK ; YUN YONG SIK ; YOUN Y S ; YOUN SIK ; YOUN IL HWAN CHO YONG SIK ; SHIN YOUNG JOON ; SHIN Y J ; LEE MOK ; LEE K H ; LEE JAE M ; LEE J M ; LEE HO ; KIM WOONG ; KIM SUP ; KIM J W ; KIM J K ; KIM HAK ; KIM C S ; JUNG YOUNG HWAN ; JUNG Y H ; JUNG HWAN ; SEONGNAMI SHI ; SHIN JUN ; KIM CHOONG S ; CHO J H ; CHO ILL HWAN ; AN SEUNG KHO ; AN S H ; AN HO ; AHN SEUNG HO ; CHO HWAN ; AN YONG HWAN JUNG Y SEOUNG HO

Inventor(s): AN SEUNG KHO[KR] ; AN SEON HO ; CHO IL KHVAN[KR] ; KIM CHIN VUNG[KR] ; KIM CHE KHAK[KR] ; LI KI KHI[KR] ; LI CHE MOK[KR] ; SEOUNG HO AN ; JUNG ENG KHVAN[KR] ; JUN ENG SIK[KR] ; JIN WOONG KIM ; JAE MOK LEE ; CHOONG SUP KIM ; KIM CHUNG SUP[KR] ; SHIN JUNG CHUN[KR] ; YOUNG JUN SHIN ; YUN YON SHIKU ; YONG HWAN JUNG ; YONG HWAN JUNG Y SEOUNG HO AN ; YONG SIK YOUN ; SHIN YUN JUN ; RII KI HO ; RII YAE MOKU ; JUN YON HOWAN ; NAME NOT GIVEN ; KIMU CHON SUPU ; KIMU JE HAKU ; KIMU JIN UON ; KI HO LEE ; KIM JIN WOONG HYUNDAI APARTMENT 412 ; KIM JIN WOONG HYUNDAI APARTMENT 412 703 ; CHOO IRU HOWAN ; IL HWAN CHO ; IL HWAN CHO YONG SIK YOUN ; JE HAK KIM

Designated states: AT AU BE CA CH DE DK ES FR GB GR HU IE IT JP LI LU MC NL NO PT RU SE

Title: Phenanthridine derivatives, methods of producing them and medicaments containing phenanthridine derivatives

Abstract: Source: US6030981A PCT No. PCT/DE96/01958 Sec. 371 Date Apr. 13, 1998 Sec. 102(e) Date Apr. 13, 1998 PCT Filed Oct. 11, 1996 PCT Pub. No. WO97/14683 PCT Pub. Date Apr. 24, 1997The invention relates to phenanthridine derivatives of the general formula I and II and also its salts, in which R1 means a hydrogen atom, an aromatic, carbocyclic or heterocyclic or heterocyclic residue and in which R2 and R3, which can be the same or different, mean a hydrogen atom, an alkyloxy residue, an alkylenoxy residue, a halogen atom or a nitro group.

Classifications:

International (IPC 8-9): A01N43/42 A61K31/00 A61K31/44 A61K31/47 A61K31/473 A61P29/00 A61P31/00 A61P35/00 C07D221/12 C07D221/18 C07D401/04 C07D405/04 C07D409/04 C07D413/04 C07D417/04 C07D491/056 C07J73/00 (Advanced/Invention); A61K31/00 A61K31/47 A61K31/473 A61P29/00 A61P31/00 A61P35/00 (Advanced/Non-invention);

A01N43/34 A61K31/00 A61K31/44 A61K31/47 A61K31/473 A61P29/00 A61P31/00 A61P35/00 C07D221/00 C07D491/00 C07J73/00 (Core/Invention)

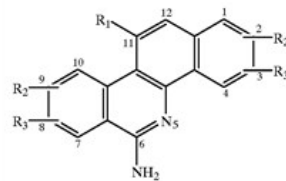
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CPC: C07J73/005

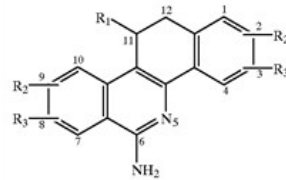
European: C07J73/00B2

US: 514/284 546/61

PatBase - US6030981_A



I



II

Family:

Publication number	Publication date	Application number	Application date
AT238284 E	20030515	AT19960945501T	19961011
AU199715895 A1	19970507	AU19970015895	19961011
AU707092 B2	19990701	AU19970015895	19961011
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PL326155 A1	19980831	PL19960326155	19961011
RU2180333 C2	20020310	RU19980108615	19961011
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US6030981 A	20000229	US19980051606	19980413
WO9714683 A2	19970424	WO1996DE01958	19961011
WO9714683 A3	20010913	WO1996DE01958	19961011

Priority:

DE19951038088 19951013 CN19961097596 19961011 DE19965010387 19961011
WO1996DE01958 19961011

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Inventor(s): CLEMENT BERND PROF DR 24106 KIEL DE ; IVAN HU VER

Designated states: AM AT AU AZ BE BG BR BY CA CH CN CZ DE DK ES FI FR GB GR HU IE IL IT JP KG KP KZ LI LU MC MD MX NL NO NZ PL PT RO RU SE SK TJ TM TR UA US

Title: Cis-substituted aminocycloalkylpyrrolidine derivatives

Abstract: Source: US2002077345A Antimicrobial agents being excellent in antimicrobial activity and safety. Compounds represented by formula (I), its. salts and hydrates thereof: wherein R1 represents a hydrogen atom or an alkyl group; R2 represents a hydrogen atom or an alkyl group; R3 and R5, each represents a hydrogen atom; R4 represents a hydroxyl group, a halogen atom, a carbamoyl group, an alkyl group, an alkoxy group or an alkylthio group; R6 and R7, each independently represents a hydrogen atom or an alkyl group; n is an integer of from 1 to 3; R4 and the substituent on the pyrrolidine ring of the following formula: are located in the cis-configuration; and Q represents a partial structure represented by the following formula:

Classifications:

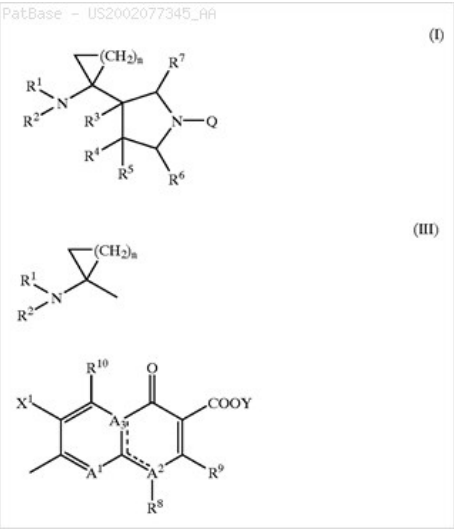
International (IPC 8-9): A01N43/42 A01N43/84 A23K1/17 A61K31/40 A61K31/435 A61K31/47 A61K31/4709 A61K31/495 A61K31/535 A61K31/5383 A61K31/54 A61P31/04 C07D207/00 C07D207/08 C07D207/09 C07D207/10 C07D207/20 C07D207/24 C07D207/26 C07D207/273 C07D207/38 C07D207/46 C07D215/16 C07D401/04 C07D405/14 C07D471/02 C07D471/04 C07D471/06 C07D498/06 C07D498/08 C07D513/06 (Advanced/Invention); C07D401/04 C07D498/06 (Advanced/Non-invention); C07D401/00 C07D498/00 (Core/Invention); C07D (Subclass/Invention)

International (IPC 1-7): A01N43/42 A01N43/84 A23K1/17 A61K31/40 A61K31/435 A61K31/47 A61K31/4709 A61K31/473 A61K31/495 A61K31/535 A61K31/54 A61P31/04 C07D207/00 C07D207/08 C07D207/09 C07D207/10 C07D207/46 C07D215/16 C07D401/04 C07D405/14 C07D471/02 C07D471/04 C07D471/06 C07D498/06 C07D513/06

CPC: C07D401/04 C07D207/09 C07D207/10 C07D207/20 C07D207/24 C07D207/26 C07D207/273 C07D207/38 C07D498/04

European: C07D207/09 C07D207/10 C07D207/20 C07D207/24 C07D207/26 C07D207/273 C07D207/38 C07D401/04 C07D498/06 C07D498/06 C07D498/08

US: 514/299 514/303 514/305 514/312 514/408 546/119 546/121 546/123 546/153 546/156 548/400 548/400S 548/530 548/541 548/566



Family:

Publication number	Publication date	Application number	Application date
AT292632 E	20050415	AT19980921738T	19980520
AT317393 E	20060215	AT19960938533T	19961122
AU199675898 A1	19970611	AU19960075898	19961122
AU199874493 A1	19981211	AU19980074493	19980520
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CA2238765 AA	19980521	CA19962238765	19961122
CA2289605 AA	19991112	CA19982289605	19980520
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CN1207738 A	19990210	CN19961099713	19961122
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EP0911328 A4	19990428	EP19960938533	19961122
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EP1020459 A1	20000719	EP19980921738	19980520
EP1020459 A4	20010307	EP19980921738	19980520
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IL132982 A0	20010319	IL19980132982	19980520
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NO995653 A	20000121	NO19990005653	19991118
NO995653 A0	19991118	NO19990005653	19991118
NZ322202 A	20000526	NZ19960322202	19961122
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TW402601 B	20000821	TW19960114493	19961122
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US6184388 BA	20010206	US19990397515	19990917
WO9719072 A1	19970529	WO1996JP03440	19961122
WO9852939 A1	19981126	WO1998JP02219	19980520
ZA9804273 A	19981125	ZA19980004273	19980520

Priority:

JP19950304129 19951122	JP19960192637 19960723	WO1996JP03440 19961122
US19990397515 19990917	US19980082155 19980521	JP19970131413 19970521
JP19970140643 19970529	WO1998JP02219 19980520	US19990424112 19991119
US20010985256 20011102		

Probable Assignee: DAIICHI SEIYAKU CO

Assignee(s): (std): DAIICHI SEIYAKU CO ; TAKEMURA MAKOTO ; KIMURA YOUICHI ; TAKAHASHI HISASHI ; KIMURA KENICHI ; MIYAUCHI SATORU ; OHKI HITOSHI ; SUGITA KAZUYUKI ; MIYAUCHI RIE ; DAIICHI PHARMACEUTICAL CO LTD ; DAIICHI PHARMACEUTICAL COMPANY

Assignee(s): DAIICHI PHARMACEUTICAL COMPANY LTD ; DAIICHI SANKYO CO LTD ; DAIICHI PHARMACEUTICAL CO

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Designated states: AL AM AT AU AZ BA BB BE BF BG BJ BR BY CA CF CG CH CI CM CN CU CY CZ DE DK EE ES FI FR GA GB GE GH GM GN GR
GW HU ID IE IL IS IT JP KE KG KR KZ LC LI LK LR LS LT LU LV MC MD MG MK ML MN MR MW MX NE NL NO NZ PL PT RO RU
SD SE SG SI SK SL SN SZ TD TG TJ TM TR TT UA UG US UZ VN YU ZW

Title: Process for the preparation of N-[2-(dimethylamino)ethyl]acridine-4-carboxamide

Abstract: Source: US6111109A PCT No. PCT/GB97/02884 Sec. 371 Date Jun. 18, 1999 Sec. 102(e) Date Jun. 18, 1999 PCT Filed Oct. 17, 1997 PCT Pub. No. WO98/17649 PCT Pub. Date Apr. 30, 1998A process for producing an acridine carboxamide of formula (I): wherein each of R1, R2, R5 and R6, which may be the same or different, is H or an organic substituent, x is from 1 to 6 and Y is N(R)2 wherein R is C1-C6 alkyl, or a pharmaceutically acceptable salt thereof.

Classifications:

International (IPC 8-9): A61K31/435 A61K31/473 A61K31/495 A61K31/498 A61P35/00 C07C227/16 C07C227/18 C07C229/58 C07D215/02 C07D219/04 C07D241/38 C07D241/46 C07D403/12 (Advanced/Invention); A61K31/435 A61K31/473 A61K31/495 A61K31/498 A61P35/00 C07C229/58 C07D219/04 (Advanced/Non-invention); A61K31/00 A61K31/435 A61K31/473 A61K31/495 A61K31/498 A61P35/00 C07C227/00 C07C229/00 C07D219/00 C07D241/00 (Core/Invention); C07C229/00 (Core/Non-invention)

International (IPC 1-7): A01N43/42 A01N43/58 A61K31/435 A61K31/473 A61K31/495 A61K31/498 A61P35/00 C07C227/16 C07C229/58 C07D215/02 C07D219/00 C07D219/02 C07D219/04 C07D219/08 C07D219/10 C07D241/36 C07D241/38 C07D241/46 C07D401/00 C07D403/12

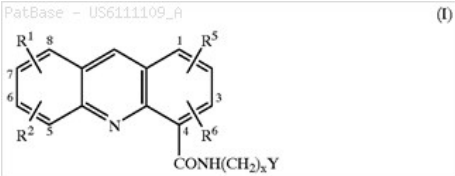
CPC: C07C227/18 C07D219/04

European: C07C227/18 C07D219/04

US: 514/250 514/287 514/297 544/338 544/343 544/347 544/348 544/361 546/102 546/103 546/104 546/105 546/65

Family:

Publication number	Publication date	Application number	Application date	
AT223381 E	20020915	AT19970909456T	19971017	
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AU199747136 A1	19980515	AU19970047136	19971017	
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Priority:

GB19960021795 19961018 GB19960026457 19961220 WO1997GB02886 19971017
WO1997GB02884 19971017

Probable Assignee: XENOVA LTD

Assignee(s): (std): BAGULEY BRUCE CHARLES ; DENNY WILLIAM ALEXANDER ; FINLAY GRAEME JOHN ; GAMAGE SWARNALATHA AKURATIYA ; GAMAGE SWARNALATHA AKURITAYA ; WRIGHT MICHAEL ; SPICER JULIE ANN ; HAYMAN DAVID FRANK ; XENOVA LTD ; XENOVA LTD ; XENOVA LTD SLOUGH ; XENOVA LTD A BRITISH BODY CORP ; KSENOVA LTD ; ZINOVA LTD

Assignee(s): XENOVA LIMITED A BRITISH BODY CORPORATE ; ZINOVA LIMITED ; XENOVA LIMITED ; GAMAGE SWARNATHALA AKURATIYA ; XENOVA LIMITED SLOUGH ; XENOVA LIMITED SLOUGH BERKSHIRE ; KSENOVA LIMITED

Inventor(s): (std): DENNY ALEXANDER ; DENNY W A ; DENNY WILLIAM ; DENNY WILLIAM A ; DENNY WILLIAM ALEXANDER ; FINLAY GRAEME JOHN ; FINLAY GREAME ; FINLAY GREAME J ; FINLAY GREEME JOHN ; FINLAY JOHN ; FINLEHJ GREHME DZHON ; GAMADZHE SWARNALATA AKURITAYA ; GAMAGE A ; GAMAGE S A ; GAMAGE SWAMALATHA AKURITAYA ; GAMAGE SWARNALATHA ; GAMAGE SWARNALATHA A ; GAMAGE SWARNALATHA AKURATIYA ; GAMAGE SWARNALATHA AKURITAYA ; GAMAGE SWARNATHALA AKURATIYA ; GEHMEHDZH SVARNALATA AKURATIJA ; BAGUILEY BRUCE CHARLES ; BAGULEY BRUCE ; BAGULEY BRUCE C ; BAGULEY BRUCE CHARLES ; BAGULEY CHARLES ; BEHGULI BRJUS CHARL Z ; HAYMAN DAVID F ; HAYMAN DAVID FRANK ; HYMAN DAVID FRANK ; DENNI VILL JAM ALEKSANDR ; KHEHJMAN DEHVID FREHNNK ; SPAJSER DZHULI EHNN ; SPICER ANN ; SPICER J A ; SPICER JULIE ; SPICER JULIE A ; SPICER JULIE ANN ; SPIGER JULIE ANN ; RAJT MAJKL ; WRIGHT MICHAEL

Inventor(s): S A GAMAGE ; SWAMALATHA AKURITAYA GAMAGE ; SWARNALATHA A GAMAGE ; SWARNALATHA AKURATIYA GAMAGE ; SWARNALATHA AKURITAYA GAMAGE ; W A DENNY ; WILLIAM ALEXANDER DENNY ; MICHAEL WRIGHT ; DENNI VILL'JAM ALEKSANDR ; J A SPICER ; JULIE ANN SPICER ; JULIE ANN SPIGER ; BEHGULI BRJUS CHARL'Z ; BRUCE CHARLES BAGUILEY ; BRUCE CHARLES BAGULEY ; DAVID FRANK HAYMAN ; GRAEME JOHN FINLAY ; GREEME JOHN FINLAY

Designated states: AL AM AT AU AZ BA BB BE BF BG BJ BR BY CA CF CG CH CI CM CN CU CZ DE DK EE ES FI FR GA GB GE GH GR HU ID IE IL IS IT JP KE KG KP KR KZ LC LI LK LR LS LT LU LV MC MD MG MK MN MR MW MX NE NL NO NZ PL PT RO RU SD SE SG SI SK SL SN SZ TG TJ TM TR TT UA UG US UZ VN YU ZW

Title: Isoquinolones

Abstract: Source: US6177423B Benzo[de]isoquinoline-1,3-dione of Formulaor a pharmaceutically acceptable salt thereof wherein R is hydrogen or a protecting group typically used in the art for protecting alcohols and R1-R5 are each independently chosen from H, Cl, Br, F, straight or branched alkyl C1-C8 alkyl, C3-C8 cycloalkyl, heterocycle or bridged heterocycle of 4-9 atoms containing 1-3 heteroatoms, -(CR'2)nOR6, -(CR'2)nN(R6)2, -(CR'2)nNR6COR7, -(CR'2)nNR6SO2OR7, -(CR'2)nNR6SO2 N(R6)2, -(CR'2)nOSO2 N(R6)2, -(CR'2)nCN, -(CR'2)n(NOR6)R7, NO2, CF3, -(CR'2)nSOMR7, -(CR'2)nSOMR7, -(CR'2)nCO2R6, -(CR'2)nCON(R6)2, Ph, and any two of R1-R5 may form a substituted or unsubstituted ring of 5-7 total atoms having 0-2 heteroatoms are claimed which are selective inhibitors of bacterial DNA gyrase and DNA topoisomerase useful in **antibacterial** agents. Methods for their preparation and formulation as well as novel intermediates useful in the preparation of the final products are also claimed.

Classifications:

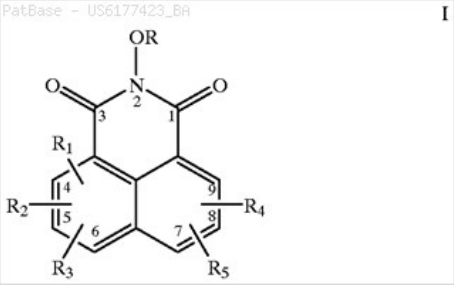
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International (IPC 1-7): A61K31/00 A61K31/395 A61K31/435 A61K31/44 A61K31/47 A61K31/473 A61K31/495 A61K31/50 A61K31/535 A61K31/54 A61K31/695 C07D217/00 C07D217/12 C07D217/16 C07D221/00 C07D221/04 C07D221/14 C07D401/00 C07D403/00 C07D405/00 C07D409/00 C07D413/00 C07D417/00 C07D471/02 C07D471/04 C07D487/08 C07D491/06 C07D497/06 C07D498/06 C07D519/00 C07F7/10

CPC: C07D221/14 C07D401/04 C07D491/06

European: C07D221/14 C07D401/04 C07D491/06

US: 514/232.8 514/235.5 514/253.03 514/290 544/126 544/361 544/96 546/98 546/99



Family:

Publication number	Publication date	Application number	Application date
AU199851604 A1	19980529	AU19980051604	19971031
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CA2263301 AA	19990210	CA19972263301	19971031
EP0939754 A2	19990908	EP19970946438	19971031
IL128516 A0	20000131	IL19970128516	19971031
JP2001505554 T2	20010424	JP19980521618T	19971031
KR20000052949 A	20000825	KR19997003822	19990430
NO314304 B1	20030303	NO19990002104	19990430
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NZ334896 A	20010126	NZ19970334896	19971031
PL333238 A1	19991122	PL1997033238	19971031
US6177423 BA	20010123	US19990254645	19990312
US6362181 BA	20020326	US20000637949	20000811
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Priority:

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US20000637949 20000811

Probable Assignee: WARNER LAMBERT CO

Assignee(s): (std): AMEGADZIE ALBERT KUDZOI ; CAREY MAUREEN ELIZABETH ; DOMAGALA JOHN MICHAEL ; HUANG LIREN ; MICETICH RONALD GEORGE ; SANCHEZ JOSEPH PETER ; SINGH RAJESHWAR ; STIER MICHAEL ANDREW ; WARNER LAMBERT CO ; VAISBURG ARKADII

Assignee(s): WARNER LAMBERT COMPANY ; WARNER LAMBERT CO LLC

Inventor(s): (std): CAREY MAUREEN ELIZABETH ; DOMAGALA JOHN MICHAEL ; HUANG LIREN ; MICETICH RONALD G ; MICETICH RONALD GEORGE ; SANCHEZ JOSEPH PETER ; SINGH RAJESHWAR ; STIER MICHAEL ANDREW ; VAISBURG ARKADII ; AMEGADZIE ALBERT KUDZOI

Inventor(s): ARKADII VAISBURG ; ALBERT KUDZOI AMEGADZIE ; MICHAEL ANDREW STIER ; RAJESHWAR SINGH ; RONALD GEORGE MICETICH ; JOHN MICHAEL DOMAGALA ; JOSEPH PETER SANCHEZ ; LIREN HUANG ; MAUREEN ELIZABETH CAREY

Designated states: AL AM AT AU AZ BA BB BE BF BG BJ BR BY CA CF CG CH CI CM CN CZ DE DK EE ES FI FR GA GB GE GH GN GR HU ID IE IL IS IT JP KE KG KR KZ LC LI LK LR LS LT LU LV MC MD MG MK ML MN MR MW MX NE NL NO NZ PL PT RO RU SD SE SG SI SK SL SN SZ TD TG TJ TM TR TT UA UG US UZ VN YU ZW

Title: DELIVERY OF DRUGS TO MUCOSAL SURFACES

Abstract: Source: US2002197324A Liquid pharmaceutical compositions for administration to a mucosal surface, comprising a therapeutic agent and a pectin with a low degree of esterification are described. Such compositions gel, or can be adapted to gel, at the site of application in the absence of an extraneous source of divalent metal ions.

FDA Data:

Application numberActive ingredient**Proprietary name****Applicant****Date of approval**022569 FENTANYL CITRATE LAZANDA
ARCHIMEDES Jun 30, 2011022569 FENTANYL CITRATE LAZANDA DEPOMED INC Jun 30, 2011

Classifications:

International (IPC 8-9): A61K31/138 A61K31/167 A61K31/353 A61K31/4164 A61K31/44 A61K31/445 A61K31/4468 A61K31/454 A61K31/46 A61K31/465 A61K31/473 A61K31/485 A61K31/58 A61K31/7048 A61K31/7072 A61K38/21 A61K39/00 A61K39/05 A61K39/10 A61K39/12 A61K39/145 A61K39/165 A61K39/39 A61K39/395 A61K47/02 A61K47/36 A61K48/00 A61K9/00 A61K9/06 A61K9/08 A61K9/10 A61K9/12 A61K9/14 A61P11/00 A61P11/02 A61P23/02 A61P25/00 A61P25/04 A61P25/16 A61P25/18 A61P29/00 A61P31/04 A61P31/14 A61P31/16 A61P37/08 A61P43/00 A61P9/06 A61P9/08 A61P9/12 (Advanced/Invention); A61K31/44 A61K39/39 (Core/Invention)

International (IPC 1-7): A61F6/06 A61K47/36 A61K9/00 A61K9/06 A61K9/12 A61K9/14 A61P11/02 A61P11/06 A61P15/02 A61P15/18 A61P37/08

CPC: A61K9/0043 A61K9/06 A61K9/12 A61K47/36

European: A61K47/36 A61K9/00M14 A61K9/06 A61K9/12

US: 424/130.1 424/130.100S 424/159.1 424/159.100S 424/184.1 424/184.100S 424/204.1 424/204.100P 424/209.1 424/209.100S 424/212.1 424/212.100S 424/245.1 424/245.100S 424/254.1 424/254.100S 424/427 424/430 424/434 424/435 424/436 424/437 424/45 424/45P 424/46 424/488 424/488P 424/488S 424/85.5 424/85.500P 424/85.6 424/85.600S 424/85.7 424/85.700S 514/174 514/174S 514/284 514/284S 514/31 514/317 514/317S 514/31S 514/329 514/329S 514/401 514/401S 514/44.00RS 514/44R 514/456 514/456S 514/50 514/50S 514/648 514/648S

Family:

Publication number	Publication date	Application number	Application date
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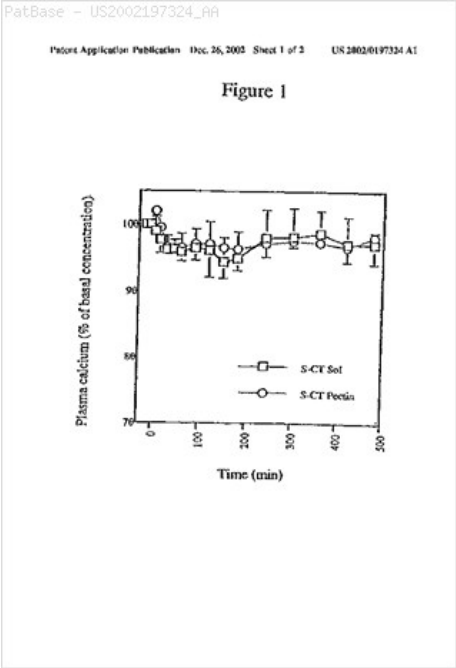
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Probable Assignee: DEPOMED INC

Assignee(s): (std): ARCHIMEDES DEV LTD ; DANBIOSYST UK ; ILLUM LISBETH ; WATTS PETER JAMES ; WEST PHARM SERV DRUG RES LTD ; WEST PHARMACEUTICAL DRUG DELIV ; WEST PHARMACEUTICAL SERVICE DR ; WEST PHARMACEUTICAL SERVICE DRUG DELIVERY AND CLIN ; DANBIOSYST UK LTD

Assignee(s): DEERFIELD PRIVATE DESIGN FUND III LP ; DEPOMED INC ; WEST PHARMACEUTICAL SERV DRUG D AND C RES CTR LTD ; WEST PHARMACEUTICAL SERVICES DRUG DELIVERY AND CLI ; WEST PHARMACEUTICAL SERVICES DRUG DELIVERY AND CLINICAL RESEARCH CENTRE LIMITED ; WEST PHARMACEUTICAL SERVICES DRUG DELIVERY AND CLINICAL RESEARCH ; WEST PHARMACEUTICAL SERVICES DRUG DELIVERY AND CLINICAL RESEARCH CENTRE LI MITED ; WEST PHARMACEUTICAL SERVICES DRUG DELIVERY AND CLINICAL RESEARCH CENTRE LI ; WEST PHARMACEUTICAL SERVICES DRUG DELIVERY AND CLINICAL RESEARCH CENTRE LTD NOTTINGHAM ; WEST PHARMACEUTICAL SERVICES DRUG DELIVERY AND CLINICAL RESEARCH CENTRE LTD ; WEST PHARMACEUTICAL SERVICE DRUG DELIVERY AND CLINICAL RESEARCH CENTRE LIMITED ; WEST PHARMACEUTICAL DRUG DELIVERY AND RESEARCH CENTRE LIMITED ; WEST



PHARMACEUTICAL DRUG DELIVERY AND RESEARCH CENTRE LTD ; WEST PHARMACEUTICAL DRUG DELIVERY AND RESEARCH CEN ; DANBIOSYST UK LIMITED ; ARCHIMEDES DEVELOPMENT LIMITED ; ARCHIMEDES DEVELOPMENT LTD

Inventor(s): (std): ILLUM LISBETH ; LISBETH ILLUM ; PETER JAMES WATTS ; WATTS JAMES ; WATTS PETER J ; WATTS PETER JAMES

Agent(s): AKIN GUMP STRAUSS HAUER AND FELD LLP

Designated states: AT AU BE CA CH CY DE DK ES FI FR GB GR IE IT JP LI LU MC NL NO NZ PT SE US

Title: Benzoquinoline derivatives useful as **antibacterial** agents

Abstract: Source: US6274596B Disclosed are pharmaceutical compositions and formulations comprising benzoquinoline derivatives having the formula (I) to (V), wherein formula (I) is: X is selected from the group consisting of O, S, CH₂, CH₂-CH₂, C=O or NRB; Y is C or N; R₁, R₂, R₃ and R₄ are independently selected from the group consisting of hydrogen, halogen, linear or branched chain lower alkyl, alkenyl, alkynyl, alkoxy or acyl; X-RA and R₃, or R₃ and R₄, are optionally linked together to form a C3-C4 alkylene bridge, where X is CH₂ or C=O; provided that: when X is NRB, then (a) RB is hydrogen, and RA is a linear or branched chain lower alkyl, aryl, heteroaryl, cycloalkyl or cycloalkenyl optionally interrupted by at least one heteroatom, said alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl or cycloalkenyl being optionally substituted singly or plurally by at least one of a linear or branched chain lower alkyl, alkenyl, alkynyl, acyl, alkoxy, or cycloalkyl optionally interrupted by at least one heteroatom and optionally substituted by at least one linear or branched chain lower alkyl, alkenyl, alkynyl, acyl, or alkoxy, or a linear or branched chain lower alkyl mono- or dialkylamino, (linear or branched chain lower alkyl N-mono- or N,N-dialkylamino)(lower alkyl), (linear or branched chain lower alkyl N-mono- or N,N-dialkyl)carbonyl, aryl or heteroaryl; or (b) X, RA and RB together form a ring system comprising from about five to about twelve linked carbon atoms, said system being optionally interrupted by at least one heteroatom, optionally mono- or polyunsaturated and optionally substituted singly or plurally by at least one of a linear or branched chain lower alkyl, alkenyl, alkynyl, acyl, or alkoxy, a linear or branched chain lower alkyl N-mono- or N,N-dialkylamino, (linear or branched chain lower alkyl N-mono- or N,N-dialkylamino)(lower alkyl), (linear or branched chain lower alkyl N-mono- or N,N-dialkylamino)(lower alkyl), halogen, cyano, trifluoromethyl, nitro, aryl or heteroaryl; and when X is O, S, CH₂, CH₂-CH₂ or C=O, then (a) RA is hydrogen or a linear or branched chain lower alkyl, alkenyl, alkynyl, aryl or heteroaryl, said alkyl, alkenyl, alkynyl, aryl or heteroaryl being optionally substituted singly or plurally by at least one of a linear or branched chain lower alkyl, alkenyl, alkynyl, acyl, or alkoxy, a linear or branched chain lower alkyl N-mono- or N,N-dialkylamino, (linear or branched chain lower alkyl N-mono- or N,N-dialkylamino)(lower alkyl), halogen, cyano, trifluoromethyl, nitro, aryl or heteroaryl; and (b) R₃ is a linear or branched chain lower alkyl substituted by hydroxyphenyl or linear or branched chain lower alkoxyphenyl singly or plurally substituted by CH₂NRCD wherein N, RC and RD together form a ring system comprising from about five to about twelve linked carbon atoms, said system being optionally interrupted by at least one heteroatom, optionally mono- or polyunsaturated and optionally substituted singly or plurally by at least one of a linear or branched chain lower alkyl, acyl, or alkoxy, a linear or branched chain lower alkyl N-mono- or N,N-dialkylamino, (linear or branched chain lower alkyl N-mono- or N,N-dialkylamino)(lower alkyl), halogen, cyano, trifluoromethyl, nitro, aryl or heteroaryl; or a salt thereof, and a pharmaceutically acceptable carrier or diluent. Also disclosed are methods of inhibiting bacterial growth, comprising the administration of formulations comprising the compounds of formulas (I) to (V).

Classifications:

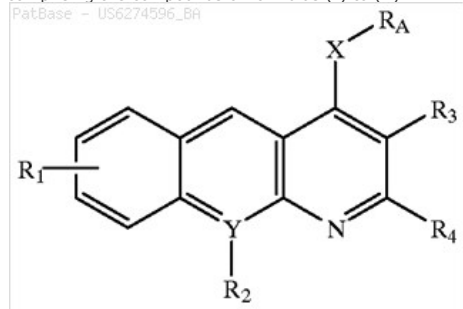
International (IPC 8-9): A61K31/00 A61K31/473 A61K31/496 (Advanced/Invention)

International (IPC 1-7): A61K31/00 A61K31/445 A61K31/47 A61K31/495 A61K31/55

CPC: A61K31/00 A61K31/473 A61K31/496

European: A61K31/00 A61K31/473 A61K31/496

US: 514/314 514/317 514/324



Family:

Publication number	Publication date	Application number	Application date
AU200015163 A1	20000515	AU20000015163	19991006
AU200015163 A5	20000515	AU20000015163	19991006
US6274596 BA	20010814	US19990413405	19991006
WO0024389 A2	20000504	WO1999US23582	19991006
WO0024389 A3	20000928	WO1999US23582	19991006

Priority:

US19980103822P 19981009 US19990413405 19991006 WO1999US23582 19991006

Probable Assignee: ANADYS PHARMACEUTICALS INC

Assignee(s): (std): ANADYS PHARMACEUTICALS INC ; BOYD VINCENT ; LAM KELVIN ; SCRIPTGEN PHARM INC ; XIANG YI BIN

Assignee(s): SCRIPTGEN PHARMACEUTICALS INC

Inventor(s): (std): BOYD VINCENT ; LAM KELVIN ; XIANG YI BIN

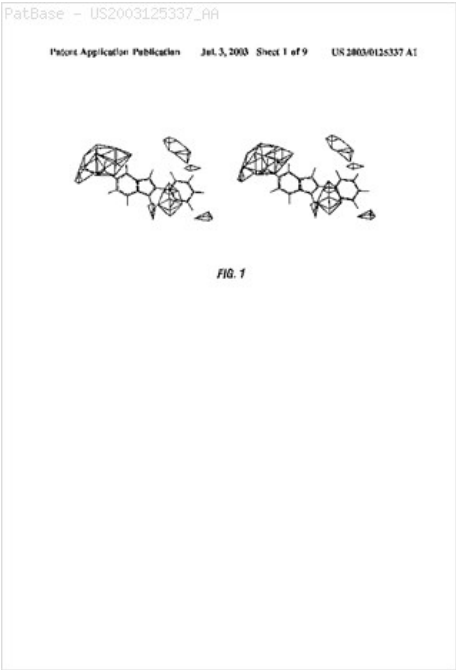
Inventor(s): YI BIN XIANG ; VINCENT BOYD ; KELVIN LAM

Designated states: AE AL AM AT AU AZ BA BB BE BF BG BJ BR BY CA CF CG CH CI CM CN CR CU CY CZ DE DK DM EE ES FI FR GA GB GD GE GH GM GN GR GW HR HU ID IE IL IN IS IT JP KE KG KP KR KZ LC LK LR LS LT LU LV MC MD MG MK ML MN MR MW MX NE NL NO NZ PL PT RO RU SD SE SG SI SK SL SN SZ TD TG TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

Title: INHIBITORS OF MULTIDRUG TRANSPORTERS

Abstract: Source: US2003125337A The present invention relates generally to the fields of bacteriology and mycology. More particularly, the present invention provides novel inhibitors of multidrug transport proteins that may be used in combination with existing **antibacterial** agent and/or antifungal agents to increase the toxic effects of the antimicrobial agents. More specifically, the present invention provides methods and compositions for enhancing the **antibacterial** action of fluoroquinolones by administering fluoroquinolones in combination with an inhibitor of multidrug transporters and of enhancing the antifungal action of azole antifungal agents by administering an azole antifungal agent in combination with an inhibitor of multidrug transporters. Compositions comprising indole, urea, quinoline or aromatic amide based inhibitors also are disclosed.

Classifications:
International (IPC 8-9): A61K31/166 A61K31/167 A61K31/17 A61K31/403 A61K31/404 A61K31/47 A61K31/473 A61K31/495 A61K31/519 A61P31/04 A61P31/10 C07C233/02 C07C275/28 C07D209/04 C07D209/08 C07D209/12 C07D215/00 C07D215/02 C07D221/18 C07D239/68 C12Q1/02 G01N33/15 G01N33/50 G01N37/00 (Advanced/Invention); A61K31/166 A61K31/17 A61K31/403 A61K31/47 A61K31/473 A61K31/519 C12Q1/02 G01N33/15 G01N33/50 G01N37/00 (Advanced/Non-invention)
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US: 514/253.08 514/253.080P 514/311 514/312 514/312S 514/41 514/410 514/410S 514/412 514/415 514/415S 514/596 546/112 546/134 546/139 546/152 548/420 548/452 548/469 564/48 564/53



Family:

Publication number	Publication date	Application number	Application date
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IL143535 A0	20020421	IL19990143535	19991202
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US2003125337 AA	20030703	US20020106839	20020326
US6326391 BA	20011204	US19990454258	19991202
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Priority:
US19980110841P 19981204 US19990454258 19991202 WO1999US28732 19991202
US20020106839 20020326 US20000640890 20000817

Probable Assignee: BOARD OF TRUSTEES OF UNIV OF ILLINOIS
Assignee(s): (std): CRICH DAVID ; INFLUX INC ; JABER MOHAMAD RAMI ; JOHNSON MICHAEL E ; MARKHAM PENELOPE N ; MULHEARN DEBBIE C ; NEYFAKH ALEXANDER A
Assignee(s): PROTEZ PHARMACEUTICALS INC ; NATIONAL INST ; NATIONAL INSTITUTES OF HEALTH ; BOARD OF TRUSTEES OF UNIV ; BOARD OF TRUSTEES OF UNIV OF ILLINOIS
Inventor(s): (std): JABER MOHAMAD RAMI ; JOHNSON E ; JOHNSON MICHAEL E ; MARKHAM N ; MARKHAM PENELOPE N ; MULHEARN C ; MULHEARN DEBBIE C ; NEYFAKH A ; NEYFAKH ALEXANDER A ; CRICH DAVID
Inventor(s): DAVID CRICH ; DEBBIE C MULHEARN ; ALEXANDER A NEYFAKH ; PENELOPE N MARKHAM ; MICHAEL E JOHNSON ; MOHAMAD RAMI JABER
Designated states: AE AL AM AT AU AZ BA BB BE BF BG BJ BR BY CA CF CG CH CI CM CN CR CU CY CZ DE DK DM EE ES FI FR GA GB GD GE GH GM GN GR GW HR HU ID IE IL IN IS IT JP KE KG KP KR KZ LC LI LK LR LS LT LU LV MA MC MD MG MK ML MN MR MW MX NE NL NO NZ PL PT RO RU SD SE SG SI SK SL SN SZ TD TG TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

Title: Chiral fluoroquinolone arginine salt forms

Abstract: Source: US2002061908A The invention relates to the new arginine salt forms of S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid, a process for their preparation and pharmaceutical formulations which comprise those arginine salt forms as the active ingredient for its use in treating antimicrobial infections.

Classifications:

International (IPC 8-9): A61K31/095 A61K31/191 A61K31/397 A61K31/43 A61K31/4375 A61K31/44 A61K31/4468 A61K31/47 A61K31/4709 A61K31/473 A61K31/4745 A61K31/65 A61K31/7048 A61K38/12 A61K45/06 A61K9/64 A61P11/00 A61P13/10 A61P13/12 A61P19/02 A61P27/16 A61P29/00 A61P3/04 A61P31/00 A61P31/04 A61P31/06 A61P31/10 C07C279/14 C07D211/56 C07D215/58 C07D215/22 C07D215/233 C07D215/38 C07D401/04 C07D401/14 C07D413/04 C07D413/12 C07D451/04 C07D455/00 C07D455/04 C07D455/06 C07D471/02 C07D471/04 C07D471/08 C07D487/12 C07D519/00 C12N1/10 C12N1/14 C12N1/16 C12N1/20 (Advanced/Invention); A61P31/00 C07D215/22 (Advanced/Non-invention); A61K31/47 A61K31/4709 A61K45/00 A61P31/00 C07D215/00 C07D401/00 C07D413/00 C07D455/00 C07D471/00 C07D519/00 (Core/Invention)

International (IPC 1-7): A61K31/095 A61K31/191 A61K31/4375 A61K31/44 A61K31/47 A61K31/4709 A61K31/4738 A61K31/4745 A61K31/496 A61K31/497 A61K31/519 A61K31/5377 A61K31/541 A61K38/05 A61K38/06 A61K45/06 A61P11/00 A61P13/10 A61P13/12 A61P19/02 A61P27/16 A61P29/00 A61P3/04 A61P31/00 A61P31/04 A61P31/06 C0743/02 C0743/14 C07C279/14 C07D215/16 C07D215/36 C07D279/12 C07D401/00 C07D401/04 C07D413/02 C07D413/04 C07D413/14 C07D417/02 C07D417/14 C07D453/02 C07D455/00 C07D455/02 C07D455/04 C07D455/06 C07D471/02 C07D471/14 C07F5/02 C07F9/6561

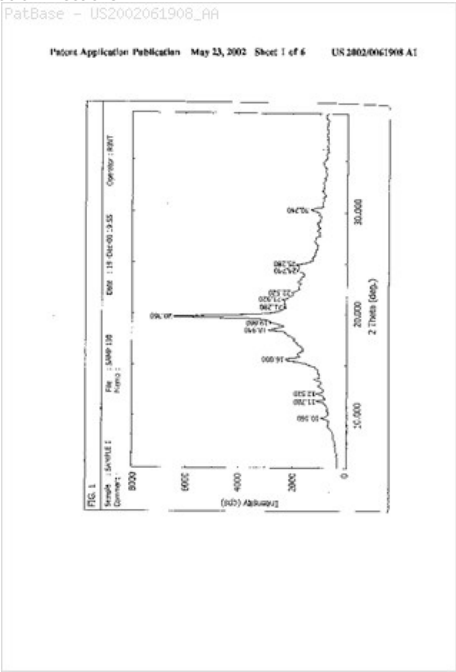
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European: A61K31/47 A61K31/4745 A61K45/06 C07C279/14 C07D215/233 C07D401/04 C07D401/14 C07D413/12 C07D451/04 C07D455/04 C07D471/04 C07D471/08 C07D519/00 M07B200/07

US: 424/451 424/456 424/456P 424/461 424/474 424/489 435/252.1 435/254.1 435/255.1 435/258.1 514/154 514/18 514/19 514/2.3 514/2.300S 514/2.6 514/2.600S 514/2.7 514/2.700S 514/2.8 514/2.800S 514/2.9 514/203 514/228.2 514/228.200P 514/228.5 514/230.5 514/233.2 514/233.200S 514/233.8 514/233.800S 514/253 514/253.03 514/253.030S 514/253.08 514/253.080P 514/253.080S 514/254 514/267 514/267S 514/29 514/292 514/294 514/294S 514/295 514/296 514/296S 514/3.1 514/3.100S 514/3.6 514/300 514/300S 514/306 514/311 514/312 514/312S 514/314 514/315 514/859 540/577 540/577P 544/126 544/126S 544/128 544/128S 544/229 544/346 544/346S 544/360 544/361 544/361S 544/363 544/363S 544/383 544/383S 544/58.6 544/6 544/60 544/60S 544/69 546/122 546/123 546/123S 546/13 546/154 546/156 546/156S 546/159 546/22 546/223 546/224 546/22S 546/23 546/23S 546/244 546/244S 546/81 546/87 546/87S 546/94 546/94P 546/94S 546/95 546/95S 546/96 546/99 546/99S

Family:

Publication number	Publication date	Application number	Application date	
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Priority:

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WO2002IN00111	20020424	WO2002IN00232	20021212	US20100578428	20100401
WO2010IB51434	20100401				

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Agent(s): MAY MARK ANDREW ET AL; MAY MARK ANDREW; LADAS AND PARRY; LADAS AND PARRY LLP

Designated states: AE AG AL AM AT AU AZ BA BB BE BF BG BJ BR BY BZ CA CF CG CH CI CM CN CO CR CU CY CZ DE DK DM DZ EC EE ES FI FR GA GB GD GE GH GM GN GQ GR GW HR HU ID IE IL IN IS IT JP KE KG KP KR KZ LC LI LK LR LS LT LU LV MA MC MD MG MK ML MN MR MW MX MZ NE NL NO NZ OM PH PL PT RO RU SC SD SE SG SI SK SL SN SZ TD TG TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

Title: 9-BENZYLIDENEHYDRAZINO-1,2,3,4-TETRAHYDROACRIDINE SHOWING ANALGETIC AND **ANTIBACTERIAL** ACTIVITY AGAINST STAPHYLOCOCCUS AUREUS

Abstract: Source: RU2161606C

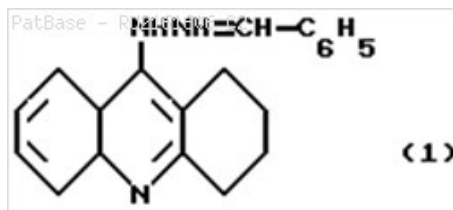
FIELD: organic chemistry, microbiology. SUBSTANCE: invention describes 9-benzylidenehydrazino-1,2,3,4-tetrahydro-acridine of the formula (I) that shows analgetic and **antibacterial** activity against Staphylococcus aureus. This ensures to use this compound as analgetic and **antibacterial** drug. EFFECT: valuable medicinal properties of compound. 1 tbl, 2 ex

Classifications:

International (IPC 8-9): A61K31/473 A61P29/00 A61P31/00 C07D219/10 (Advanced/Invention);

A61K31/473 A61P29/00 A61P31/00 C07D219/00 (Core/Invention)

International (IPC 1-7): A61K31/473 A61P29/00 A61P31/00 C07D219/10



Family:

Publication number	Publication date	Application number	Application date
RU2161606 C2	20010110	RU19990107614	19990407
RU99107614 A	20010220	RU19990107614	19990407

Priority:

RU19990107614 19990407

Probable Assignee: PERM G FARMATSEVTICHESKAJA AKA

Assignee(s): (std): DEMIJA ; PERM G FARMATSEVTICHESKAJA AKA ; PERMSKAJA GOSUDARSTVENNAJA FARMATSEVTICHESKAJA AKA

Assignee(s): PERMSKAJA GOSUDARSTVENNAJA FARMATSEVTICHESKAJA AKADEMIJA

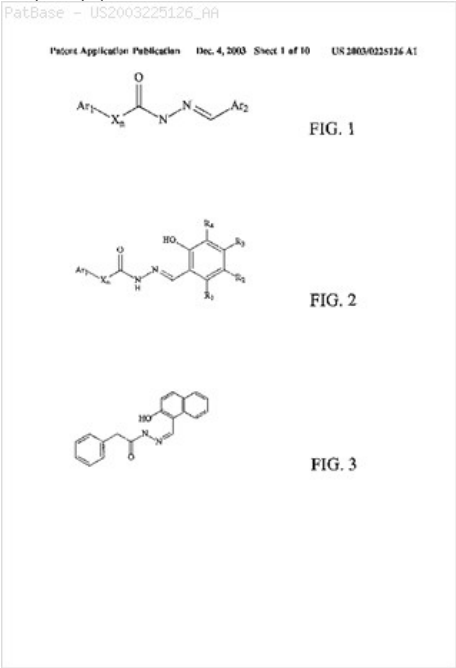
Inventor(s): (std): DONTSOVA L P ; DONTSOVA LP ; KOLLA V EH ; KOLLA VEH ; KONSHIN M E ; KONSHIN ME ; MARDANOVA L G ; MARDANOVA LG ; NOVOSELOVA G N ; NOVOSELOVA GN

Title: BACTERICIDAL ANTIMICROBIAL METHODS AND COMPOSITIONS FOR USE IN TREATING GRAM POSITIVE INFECTIONS

Abstract: Source: US2003225126A The present invention relates generally to the field of bacteriology. More particularly, the present invention provides methods and compositions for increasing the effectiveness of existing **antibacterial** agents and methods of overcoming bacterial resistance. Specifically, the invention provides methods of enhancing the action of an **antibacterial** agent by use of an antibiotic potentiator. Compositions of antibiotic potentiators including an acyl hydrazide, an oxy amide, and an 8-hydroxy quinoline also are disclosed.

Classifications:

International (IPC 8-9): A61K31/155 A61K31/16 A61K31/165 A61K31/167 A61K31/175 A61K31/395 A61K31/47 A61K31/4709 A61K31/473 A61K31/496 A61K31/505 A61K31/65 A61K31/655 A61K31/7048 A61K31/7056 A61P31/04 A61P43/00 (Advanced/Invention)
International (IPC 1-7): A61K31/00 A61K31/155 A61K31/16 A61K31/165 A61K31/167 A61K31/175 A61K31/27 A61K31/325 A61K31/395 A61K31/44 A61K31/47 A61K31/4709 A61K31/473 A61K31/496 A61K31/505 A61K31/65 A61K31/655 A61K31/7048 A61K31/7056 A61P31/04 A61P43/00
CPC: A61K31/16 A61K31/175 A61K31/47 A61K31/655
European: A61K31/16 A61K31/175 A61K31/47 A61K31/655
US: 514/312 514/357 514/482 514/482S 514/590 514/590S 514/614 514/614S 514/615 514/615S



Family:

Publication number	Publication date	Application number	Application date
AU2001256965 AA	20011003	AU20010256965	20010323
AU200156965 A5	20011003	AU20010056965	20010323
EP1296688 A2	20030402	EP20010930428	20010323
JP2003527417 T2	20030916	JP20010568411T	20010323
US2003225126 AA	20031204	US20010816761	20010323
US2005043369 AA	20050224	US20040897873	20040723
WO0170213 A2	20010927	WO2001US09578	20010323
WO0170213 A3	20030109	WO2001US09578	20010323

Priority:
US20000191879P 20000323 US20010816761 20010323 WO2001US09578 20010323
US20040897873 20040723

Probable Assignee: BOARD OF TRUSTEES OF UNIV OF ILLINOIS

Assignee(s): (std): CRICH DAVID ; INFLUX INC ; JABER MOHAMAD RAMI ; JOHNSON MICHAEL E ; KLYACHKO EKATERINA A ; MARKHAM PENELOPE N ; MULHEARN DEBBIE C ; NEYFAKH ALEXANDER A ; PROTEZ PHARMACEUTICALS INC ; TRUSTEES OF UNIV OF ; UNIV ILLINOIS

Assignee(s): THE BOARD OF TRUSTEES OF THE UNIVERSITY OF ILLINOIS ; BOARD OF TRUSTEES OF UNIV ; BOARD OF TRUSTEES OF UNIV ILLINOIS ; BOARD OF TRUSTEES OF UNIV OF ILLINOIS ; THE BOARD OF TRUSTEES OF THE UNIVERSITY OF ILLINOI

Inventor(s): (std): JABER MOHAMED RAMI ; NEYFAKH ALEXANDER A ; MULHEARN DEBBIE C ; MARKHAM PENELOPE N ; KLYACHKO EKATERINA A ; JOHNSON MICHAEL E ; JABER MOHAMAD RAMI ; CRICH DAVID

Inventor(s): KLYACHKO EKATERINA ; JOHNSON MICHAEL ; MARKHAM PENELOPE ; MULHEARN DEBBIE ; NEYFAKH ALEXANDER ; MICHAEL E JOHNSON ; MOHAMAD RAMI JABER ; PENELOPE N MARKHAM ; ALEXANDER A NEYFAKH ; DAVID CRICH ; DEBBIE C MULHEARN ; EKATERINA A KLYACHKO

Agent(s): POTTER ANDERSON AND CORROON LLP ATTN KATHLEEN W GEIGER ESQ

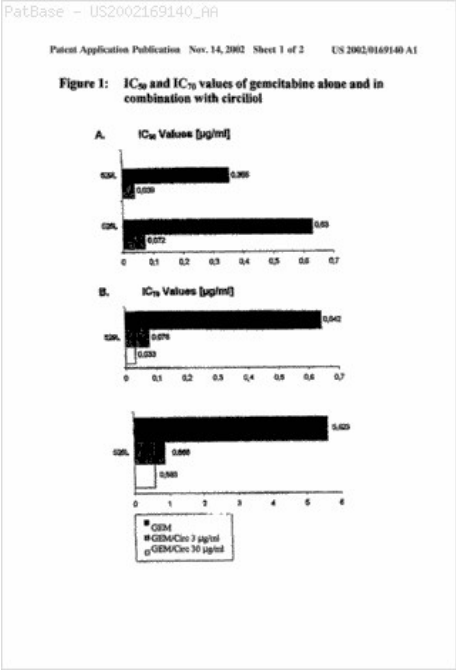
Designated states: AE AG AL AM AT AU AZ BA BB BE BF BG BJ BR BY BZ CA CF CG CH CI CM CN CO CR CU CY CZ DE DK DM DZ EE ES FI FR GA GB GD GE GH GM GN GR GW HR HU ID IE IL IN IS IT JP KE KG KP KR KZ LC LI LK LR LS LT LU LV MA MC MD MG MK ML MN MR MW MX MZ NE NL NO NZ PL PT RO RU SD SE SG SI SK SL SN SZ TD TG TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

Title: COMBINATION THERAPY FOR REDUCTION OF TOXICITY OF CHEMOTHERAPEUTIC AGENTS

Abstract: Source: US2002169140A There are provided compositions, pharmaceutical formulations and kits for treating neoplasms and tumours, viral infections, bacterial infections, or parasite infections. There are also provided compositions, pharmaceutical formulations and kits for suppression of immune response rejection in tissue transplantation. Also provided are methods of treating such conditions.

Classifications:

International (IPC 8-9): A61K31/12 A61K31/235 A61K31/352 A61K31/353 A61K31/522 A61K31/7076 A61K45/06 A61K9/32 A61K9/36 A61P31/00 A61P31/04 A61P31/12 A61P31/18 A61P33/00 A61P35/00 A61P37/06 (Advanced/Invention); A61K31/12 A61K31/21 A61K31/352 A61K45/00 A61K9/30 A61P31/00 A61P33/00 A61P35/00 A61P37/00 (Core/Invention)
International (IPC 1-7): A61K31/00 A61K31/00 A61K31/12 A61K31/137 A61K31/155 A61K31/185 A61K31/191 A61K31/235 A61K31/341 A61K31/352 A61K31/353 A61K31/365 A61K31/407 A61K31/4164 A61K31/4375 A61K31/4706 A61K31/4709 A61K31/473 A61K31/505 A61K31/513 A61K31/52 A61K31/522 A61K31/541 A61K31/555 A61K31/65 A61K31/7048 A61K31/7056 A61K31/7064 A61K31/7068 A61K31/7072 A61K31/7076 A61K39/395 A61K39/42 A61K39/44 A61K9/127 A61K9/16 A61K9/32 A61K9/36 A61P31/00 A61P31/00 A61P31/04 A61P31/12 A61P31/18 A61P33/00 A61P33/00 A61P35/00 A61P35/00 A61P37/06
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European: A61K31/12 A61K31/235 A61K31/352 A61K45/06
US: 514/263.31 514/263.310S 514/45 514/456 514/456S 514/45P 514/679 514/679S



Family:

Publication number	Publication date	Application number	Application date
AU2002238799 AA	20020919	AU20020238799	20020305
US2002169140 AA	20021114	US20020091855	20020306
US2008139496 AA	20080612	US20080034289	20080220
WO02069949 A2	20020912	WO2002IB00632	20020305
WO02069949 A3	20030605	WO2002IB00632	20020305

Priority:
IE20010000209 20010306 WO2002IB00632 20020305 US20020091855 20020306
US20080034289 20080220

Probable Assignee: PRENDERGAST PATRICK T
Assignee(s): (std): PRENDERGAST PATRICK T
Assignee(s): CASCADE ESTATE LTD ; HOLLIS EDEN PHARMACEUTICALS INC
Inventor(s): (std): PRENDERGAST PATRICK T
Agent(s): BURR AND BROWN
Designated states: AE AG AL AM AT AU AZ BA BB BE BF BG BJ BR BY BZ CA CF CG CH CI CM CN CO CR CU CY CZ DE DK DM DZ EC EE ES FI FR GA GB GD GE GH GM GN GQ GR GW HR HU ID IE IL IN IS IT JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MC MD MG MK ML MN MR MW MX MZ NE NL NO NZ OM PH PL PT RO RU SD SE SG SI SK SL SN SZ TD TG TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW

European: A61K31/473 A61K31/7028 A61K31/706

Family:

Publication number	Publication date	Application number	Application date
EA005929 B1	20050825	EA20030001035	20020318
RU2197248 C2	20030127	RU200110107818	20010320
WO02074311 A1	20020926	WO2002RU00117	20020318

Priority:

RU20010107818 20010320 WO2002RU00117 20020318

Probable Assignee: JAKOVLEVA ELENA VLADIMIROVNA

Assignee(s): (std): JAKOVLEVA ELENA VLADIMIROVNA ; TRAVKIN OLEG VIKTOROVICH ; YAKOVLEVA ELENA VLADIMIROVNA

Inventor(s): (std): TRAVKIN OLEG VIKTOROVICH ; TRAVKIN OV ; YAKOVLEVA ELENA VLADIMIROVNA ; TRAVKIN O V ; JAKOVLEVA E V ; JAKOVLEVA EV

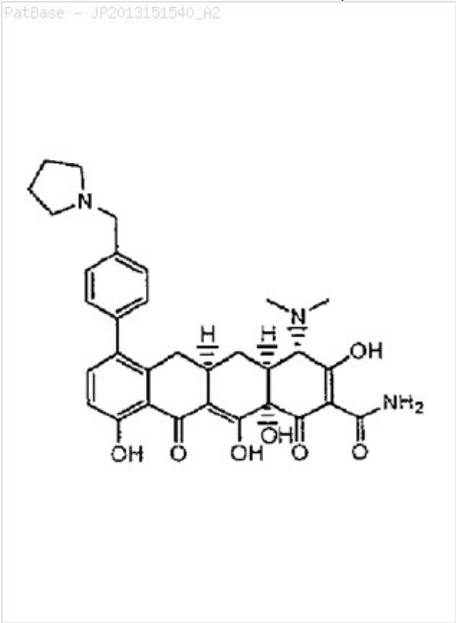
Designated states: AE AG AL AM AT AU AZ BA BB BE BF BG BJ BR BV BZ CA CF CG CH CI CM CN CO CR CU CY CZ DE DK DM DZ EE ES FI FR GA GB GD GE GH GM GN GQ GR GW HR HU ID IE IL IN IS IT JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MC MD MG MK ML MN MR MW MX MZ NE NL NO NZ OM PH PL PT RO RU SD SE SG SI SK SL SN SZ TD TG TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW

Title: Substituted tetracycline compounds for the treatment of malaria

Abstract: Source: US2004092490A This invention provides a method for treating or preventing malaria in a subject. The method includes administering to the subject an effective amount of a substituted tetracycline compound, such that malaria is treated or prevented. In one aspect, the invention relates to pharmaceutical compositions which include an effective amount of a tetracycline compound to treat malaria in a subject and a pharmaceutically acceptable carrier. The substituted tetracycline compounds of the invention can be used to in combination with one or more anti-malarial compounds or can be used to treat or prevent malaria which is resistant to one or more other anti-malarial compounds.

Classifications:

International (IPC 8-9): A61K31/353 A61K31/36 A61K31/385 A61K31/4706 A61K31/4709 A61K31/473 A61K31/49 A61K31/505 A61K31/65 A61K45/00 A61K9/02 A61K9/48 A61P25/26 A61P29/02 A61P31/04 A61P33/06 A61P43/00 A61P7/06 C07C237/26 C07C311/13 C07D295/14 C07D317/50 C07D317/54 C07D317/58 (Advanced/Invention); C07C237/26 C07C275/38 C07D213/30 C07D213/56 C07D213/64 C07D213/81 C07D295/08 C07D295/14 C07D307/42 C07D307/54 C07D317/54 C07D317/60 (Advanced/Non-invention); A61K31/4706 A61K31/4709 A61K31/505 (Core/Invention); A61K (Subclass/Invention)
International (IPC 1-7): A61K31/353 A61K31/385 A61K31/473 A61K31/65 A61K9/02 A61K9/48 A61P33/06 C07C237/26 C07C311/13 C07D295/14 C12N
CPC: A61K31/65 A61K31/353 A61K31/385 A61K31/473
European: A61K31/353 A61K31/385 A61K31/473 A61K31/65
US: 514/152 514/152S 514/154 514/284 514/284S 514/434 514/434S 514/441 514/452 514/453 514/453S 514/464 514/466 549/443 549/444 549/446



Family:

Publication number	Publication date	Application number	Application date
AT455092 E	20100115	AT20020723955T	20020424
AU2002254714 AA	20021105	AU20020254714	20020424
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AU2002254714 BH	20081002	AU20020254714	20020424
AU2002254714 CA	20100107	AU20020254714	20020424
AU2003287218 AA	20040513	AU20030287218	20031024
AU2003287218 BB	20091217	AU20030287218	20031024
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AU2008255241 AA	20090108	AU20080255241	20081211
AU2008255241 BB	20120628	AU20080255241	20081211
AU2010200971 AA	20100401	AU20100200971	20100316
AU2010200973 AA	20100401	AU20100200973	20100316
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CA2444899 C	20110621	CA20022444899	20020424
CA2502464 AA	20050414	CA20032502464	20031024
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EP1399414 A4	20060322	EP20020723955	20020424
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EP1556007 A2	20050727	EP20030781398	20031024
EP1556007 A4	20081217	EP20030781398	20031024
EP2186793 A1	20100519	EP20100150482	20020424
EP2277504 A1	20110126	EP20100171327	20031024
ES2338994 T3	20100514	ES20020723955T	20020424
IL168022 A0	20060205	IL20050168022	20050413
IL209319 A0	20110131	IL20100209319	20101115
JP2004529927 T2	20040930	JP20020582879T	20020424
JP2006503898 T2	20060202	JP20040547165T	20031024
JP2009221219 A2	20091001	JP20090128388	20090528
JP2011037890 A2	20110224	JP20100232352	20101015
JP2013010806 A2	20130117	JP20120232354	20121001
JP2013151540 A2	20130808	JP20130069469	20130328
US2004092490 AA	20040513	US20020128990	20020424
US2004242548 AA	20041202	US20030692563	20031024
US2012101071 AA	20120426	US20110338401	20111228
US8088820 BB	20120103	US20030692563	20031024
WO02085303 A2	20021031	WO2002US12935	20020424
WO02085303 A3	20030515	WO2002US12935	20020424
WO04038001 A2	20040506	WO2003US33927	20031024
WO04038001 A3	20041111	WO2003US33927	20031024

Priority:

US20010286193P	20010424	AU20020254714	20020424	JP20020582879	20020424
EP20020723955	20020424	WO2002US12935	20020424	US20020421259P	20021024
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JP20040547165	20031024	US20030692563	20031024	US20110338401	20111228

Probable Assignee: PARATEK PHARMACEUTICALS INC

Assignee(s): (std): DRAPER MICHAEL ; NELSON MARK L ; PARATEK PHARM INNOC ; PARATEK PHARMACEUTICALS INC

Assignee(s): BHM HEALTHCARE INVESTMENTS CAYMAN LTD COLLATERAL AGENT AS ; MIDCAP FINANCIAL LLC ; MINTZ LEVIN COHN FERRIS GLOVSKY AND POPEO PC

Inventor(s): (std): DRAPER MICHAEL ; FRECHETTE ROGER ; MARK L NELSON ; MICHAEL DRAPER ; NELSON MARK ; NELSON MARK L
Inventor(s): ROGER FRECHETTE
Agent(s): NASH DAVID ALLAN; JOHNSTON MAGNUS GEORGE; MINTZ LEVIN COHN FERRIS GLOVSKY AND POPEO PC; IVOR R; HEIDI A
Designated states: AE AG AL AM AT AU AZ BA BB BE BF BG BJ BR BY BZ CA CF CG CH CI CM CN CO CR CU CY CZ DE DK DM DZ EC EE EG ES FI FR GA GB GD GE GH GM GN GQ GR GW HR HU ID IE IL IN IS IT JP KE KG KP KR KZ LC LI LK LR LS LT LU LV MA MC MD MG MK ML MN MR MW MX MZ NE NI NL NO NZ OM PG PH PL PT RO RU SC SD SE SG SI SK SL SN SY SZ TD TG TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZM ZW

Title: REMEDIES FOR SEPSIS

Abstract: Source: US2004147536A Remedies for sepsis and symptoms associating sepsis (septic shock, disseminated intravascular coagulation syndrome, adult respiratory distress syndrome, multiorgan function failure, etc.). These remedies contain as the active ingredient opioid kappa receptor agonistic compounds such as (-)-17-(cyclopropylmethyl)-3,14ss-dihydroxy-4,5a-epoxy-6ss [N-methyl-trans-3-(3-furyl)acrylamido] morphinan hydrochloride. These opioid kappa receptor agonistic compounds may be orally or parenterally administered either as such or as in the form of medicinal compositions prepared by mixing with publicly known pharmacologically acceptable acids, carriers, excipients, etc.

Classifications:

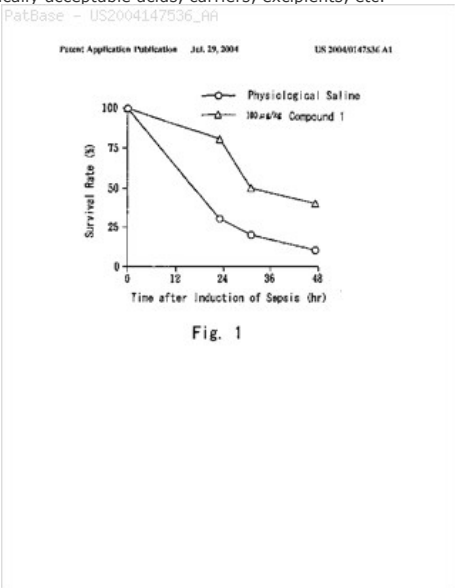
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International (IPC 1-7): A61K31/40 A61K31/473 A61K31/485 A61K38/00 A61K45/00 A61P31/04 A61P7/08 C07D295/12 C07D489/08 C07D489/08 C07K5/10

CPC: A61K31/40 A61K31/485 A61K38/00 C07D489/08 C07K5/1016

European: A61K31/40 A61K31/485 C07D489/08 C07K5/10A2 K61K38/00

US: 514/280 514/281



Family:

Publication number	Publication date	Application number	Application date
CA2451133 AA	20031218	CA20022451133	20020508
CA2451133 C	20120918	CA20022451133	20020508
CN1283317 C	20061108	CN20028009532	20020508
CN1507356 A	20040623	CN20028009532	20020508
EP1402899 A1	20040331	EP20020724723	20020508
EP1402899 A4	20090311	EP20020724723	20020508
JP4239592 B2	20090318	JP20020586977T	20020508
US2004147536 AA	20040729	US20030477062	20031218
US7652025 BB	20100126	US20030477062	20031218
WO02089845 A1	20021114	WO2002JP04469	20020508

Priority: JP20010137737 20010508 WO2002JP04469 20020508

Probable Assignee: TORAY IND INC

Assignee(s): (std): INADA HIDEAKI ; KAWAMURA KUNIAKI ; SUZUKI TOMOHIKO ; TANAKA TOSHIAKI ; TORAY IND ; YOSHIZAWA YOSHITAKA ; TORAY INDUSTRIES

Assignee(s): TORAY INDUSTRIES INC ; TORAY IND INC

Inventor(s): (std): HIDEAKI INADA ; INADA HIDEAKI ; KAWAMURA KUNIAKI ; SUZUKI TOMOHIKO ; TANAKA TOSHIAKI ; TOMOHIKO SUZUKI ; YOSHITAKA SUZUKI TOMOHIKO INAD ; YOSHITAKA YOSHIZAWA ; YOSHIZAWA YOSHITAKA

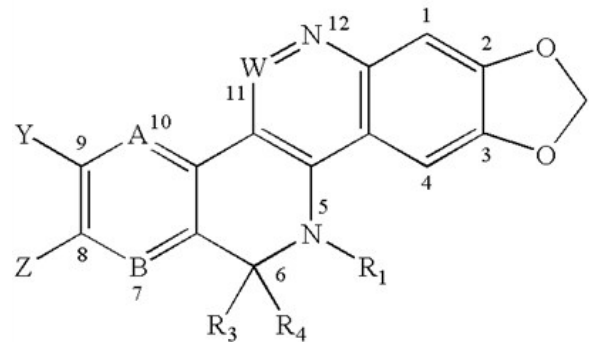
Inventor(s): SUZUKI TOMOHIKO INADA HIDEAKI YOSHIZAWA YOSHITAKA

Agent(s): DLA PIPER LLP (US) ; DLA PIPER LLP

Designated states: AE AG AL AM AT AU AZ BA BB BE BF BG BJ BR BY BZ CA CF CG CH CI CM CN CO CR CU CY CZ DE DK DM DZ EC EE ES FI FR GA GB GD GE GH GM GN GQ GR GW HR HU ID IE IL IN IS IT JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MC MD MG MK ML MN MR MW MX MZ NE NL NO NZ OM PH PL PT RO RU SD SE SG SI SK SL SN SZ TD TG TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW

Title: SOLUBILIZED TOPOISOMERASE POISONS

Abstract: Source: US2005009824A The invention provides compounds of formula I:



• A, B, W, Y, Z, and R₁ have any of the meanings defined in the specification and their pharmaceutically acceptable salts. The invention also provides pharmaceutical compositions comprising a compound of formula I, processes for preparing compounds of formula I, intermediates useful for preparing compounds of formula I, and therapeutic methods for treating cancer using compounds of formula I.

Classifications:
International (IPC 8-9): A61K31/4375 A61K31/473 A61K31/4738 A61K31/4745 A61K31/496 A61K31/4985 A61K31/5025 A61K31/503 A61P17/06 A61P31/04 A61P31/10 A61P31/12 A61P33/02 A61P35/00 A61P43/00 C07D221/18 C07D471/04 C07D471/22 C07D487/14 C07D491/04 C07D491/14 C07D491/147 C07D491/22 (Advanced/Invention); C07D491/147 C07D491/22 (Advanced/Non-invention); A61K31/00 A61P35/00 C07D491/00 (Core/Invention)
International (IPC 1-7): A61K0/00 A61K31/4375 A61K31/5025 A61K31/503 A61P17/06 A61P31/04 A61P31/10 A61P31/12 A61P33/02 A61P35/00 A61P43/00 C07D487/14 C07D491/147 C07D491/22
CPC: C07D491/14
European: C07D491/14 C07D491/14+317A+221B+221B+221B C07D491/14+317A+237B+221B+221B C07D491/22
US: 514/248 514/250 514/252.13 514/280 514/280S 514/283 514/283S 544/233 544/233S 544/234 544/242 544/342 546/48 546/48S 546/49 546/49S 546/58 546/58S

Family:

Publication number	Publication date	Application number	Application date
AT456952 E	20100215	AT20020801198T	20021114
AU2002363658 AA	20030526	AU20020363658	20021114
AU2002363658 BB	20080911	AU20020363658	20021114
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EP1465625 A4	20050608	EP20020801198	20021114
EP1465625 B1	20100203	EP20020801198	20021114
EP2196205 A1	20100616	EP20090015160	20021114
EP2286812 A1	20110223	EP20100011073	20021114
ES2340473 T3	20100604	ES20020801198T	20021114
JP2005511617 T2	20050428	JP20030543547T	20021114
JP2010184942 A2	20100826	JP20100126977	20100602
JP2013166801 A2	20130829	JP20130120501	20130607
JP4628675 B2	20110209	JP20030543547T	20021114
JP5337104 B2	20131106	JP20100126977	20100602
KR20050044491 A	20050512	KR20047007448	20040514
MXPA04004606 A1	20040910	MX2004PA04606	20040514
PT1465625 T	20100309	PT20020801198T	20021114
SI1465625 T1	20100630	SI20020030896T	20021114
US2005009824 AA	20050113	US20040846834	20040514
US2006052381 AA	20060309	US20050210456	20050824
US2009239871 AA	20090924	US20090413235	20090327
US2011136812 AA	20110609	US20100851370	20100805
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US7517883 BB	20090414	US20050210456	20050824
US7781587 BB	20100824	US20090413235	20090327
US8389721 BB	20130305	US20100851370	20100805
WO03041660 A2	20030522	WO2002US36901	20021114
WO03041660 A3	20031016	WO2002US36901	20021114

Priority:
US20010332734P 20011114 WO2002US36901 20021114 EP20020801198 20021114
JP20030543547 20021114 US20040846834 20040514 US20050210456 20050824
US20090413235 20090327 EP20090015160 20021114 US20100851370 20100805
JP20100126977 20021114

Probable Assignee: RUTGERS STATE UNIV OF NEW JERSEY
Assignee(s): (std): LAVOIE EDMOND J ; LIU LEROY F ; LIU LEROY FONG ; RUCHELMAN ALEXANDER L ; RUTGERS STATE UNIV ; RUTGERS THE STATE UNIV ; UNIV RUTGERS
Assignee(s): RUTGERS THE STATE UNIVERSITY OF NEW JERSEY ; RUTGERS THE STATE UNIVERSITY ; RUTGERS STATE UNIV NEW JERSEY ; RUTGERS STATE UNIV OF NEW JERSEY
Inventor(s): (std): LAVOIE EDMOND ; LAVOIE EDMOND J ; LEROY F LIU ; LIU LEROY ; LIU LEROY F ; RUCHELMAN ALEXANDER ; RUCHELMAN ALEXANDER L
Inventor(s): EDMOND J LAVOIE ; ALEXANDER L RUCHELMAN
Agent(s): CALAMITA ROBERTO; SCHWEGMAN LUNDBERG WOESSNER AND KLUTH PA; VIKSNINS HARRIS AND PADYS PLLP
Designated states: AE AG AL AM AT AU AZ BA BB BE BF BG BJ BR BY BZ CA CF CG CH CI CM CN CO CR CU CY CZ DE DK DM DZ EC EE ES FI FR GA GB GD GE GH GM GN GQ GR GW HR HU ID IE IL IN IS IT JP KE KG KP KR KZ LC LI LK LR LS LT LU LV MA MC MD

Title: METHODS FOR THERAPY OF CONNECTIVE TISSUE DISEASE

Abstract: Source: US2003206946A Compounds of a histone deacetylase inhibitor. The compounds are capable of simultaneously modulating cell cycle-related gene expression and inflammatory cytokine production, and are useful as anti-inflammatory agents in connective tissue disease resulting from altered patterns of immunoregulation. The present invention provides methods of treating, preventing or ameliorating connective tissue diseases, which share common features including inflammation of skin, joints and soft tissues as well as altered patterns of immunoregulation, by administering a therapeutically effective amount of a histone deacetylase inhibitor.

Classifications:

International (IPC 8-9): A61K31/075 A61K31/135 A61K31/15 A61K31/16 A61K31/165 A61K31/166 A61K31/167 A61K31/19 A61K31/192 A61K31/196 A61K31/198 A61K31/20 A61K31/22 A61K31/225 A61K31/336 A61K31/351 A61K31/40 A61K31/405 A61K31/4353 A61K31/4355 A61K31/4406 A61K31/445 A61K31/473 A61K31/505 A61K31/545 A61K31/56 A61K31/606 A61K31/609 A61K31/70 A61K35/74 A61K38/12 A61K38/15 A61K38/18 A61K38/20 A61K38/48 A61K39/395 A61K47/00 A61K47/06 A61K47/10 A61K47/38 A61K8/37 A61K8/40 A61K8/41 A61K8/42 A61K8/49 A61K8/60 A61K8/63 A61K8/64 A61K8/99 A61K9/00 A61K9/127 A61K9/14 A61P17/00 A61P17/02 A61P17/04 A61P17/10 A61Q19/00 (Advanced/Invention); A61K9/06 A61K9/127 A61P17/00 A61P17/02 (Advanced/Non-invention); A61K31/075 A61K31/165 A61K31/185 A61K31/4353 A61K31/445 A61K31/545 A61K31/56 A61K38/12 A61K38/15 A61K39/395 A61K47/00 A61K47/06 A61K47/10 A61K47/38 A61K9/00 A61K9/127 A61K9/14 A61P17/00 (Core/Invention); A61K31/15 A61K31/16 A61K8/40 A61K9/06 A61K9/127 A61P17/00 A61P17/02 (Core/Non-invention)

International (IPC 1-7): A61K31/075 A61K31/165 A61K31/19 A61K31/198 A61K31/445 A61K31/60 A61K38/12 A61K38/16 A61K9/127

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Family:

Publication number	Publication date	Application number	Application date
AU2011213694 AA	20110811	AU20110213694	20110207
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EP2531186 A4	20130717	EP20110740478	20110207
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US2003206946 AA	20031106	US20020132999	20020426
US2004018958 AA	20040129	US20020205738	20020725
US2005245439 AA	20051103	US20050079370	20050314
US2005272644 AA	20051208	US20040798119	20040311
US2006275370 AA	20061207	US20060499936	20060807
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WO11097549 A9	20111229	WO2011US23859	20110207

Priority:

US20020132999	20020426	US20020205738	20020725	US20040798119	20040311
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US20110021063	20110204	WO2011US23859	20110207		

Probable Assignee: SUNNY PHARMTECH INC

Assignee(s): (std): CHUNG YIH LIN ; PUI NAM MEW ; CHANG WEI WEI ; ASAN LAB CO CAYMAN LTD ; ASAN LAB CO CAYMEN LTD ; ASAN LAB COMPANY CAYMAN LTD ; ASAN LAB COMPANY CAYMEN LTD ; SUNNY PHARMTECH INC

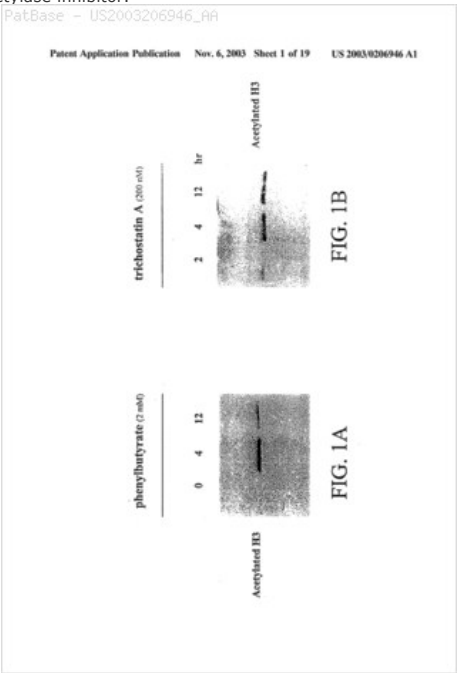
Assignee(s): ASAN LABORATORIES CO (CAYMAN) LTD ; ASAN LABORATORIES CO CAYMAN LTD ; ASAN LABORATORIES CO LTD ; ASAN LABORATORIES COMPANY CAYMAN LIMITED ; ASAN LABORATORIES CO CAYMEN LTD ; ASAN LABORATORIES COMPANY CAYMEN LIMITED ; SUNNY PHARMTECH INC

Inventor(s): (std): CHUNG YIH LIN ; PUI NAM MEW ; CHANG WEI WEI

Inventor(s): PUI, NAM-MEW ; CHANG, WEI-WEI

Agent(s): PURDY HUGH BARRY; FISH AND RICHARDSON PC; OCCHIUTI ROHLICEK AND TSAO LLP; CESARI AND MCKENNA LLP; TSAO Y ROCKY

Designated states: AE AG AL AM AO AT AU AZ BA BB BE BF BG BH BJ BR BW BY BZ CA CF CG CH CI CL CM CN CO CR CU CY CZ DE DK DM DO DZ EC EE EG ES FI FR GA GB GD GE GH GM GN GQ GR GT GW HN HR HU ID IE IL IN IS IT JP KE KG KM KN KP KR KZ LA LC LI LK LR LS LT LU LV LY MA MC MD ME MG MK ML MN MR MT MW MX MY MZ NA NE NG NI NL NO NZ OM PE PG PH PL PT RO RS RU SC SD SE SG SI SK SL SM SN ST SV SY SZ TD TG TH TJ TM TN TR TT TZ UA UG US UZ VC VN ZA ZM ZW



Title: NITRO AND AMINO SUBSTITUTED HETEROCYCLES AS TOPOISOMERASE I TARGETING AGENTS

Abstract: Source: US2004110782A The invention provides compounds of formula I: wherein: R1-R5, "a" and X have any of the meanings defined in the specification and their pharmaceutically acceptable salts. The invention also provides pharmaceutical compositions comprising a compound of formula I, processes for preparing compounds of formula I, intermediates useful for preparing compounds of formula I, and therapeutic methods for treating cancer using compounds of formula I.

Classifications:

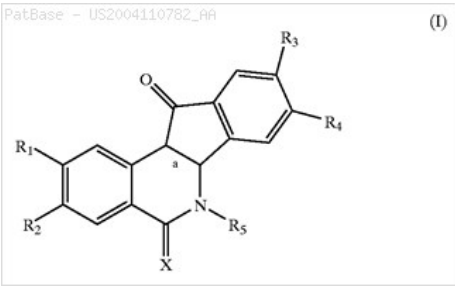
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International (IPC 1-7): A61K31/473 A61K31/4741 A61P35/00 C07D221/18 C07D221/22 C07D491/02 C07D491/04

CPC: C07D221/18 C07D471/04

European: C07D221/18 C07D471/04

US: 435/184 514/233.2 514/233.200P 514/280 514/283 514/283S 514/284 514/284S 544/125 544/125S 546/48 546/48S 546/61 546/61S



Family:

Publication number	Publication date	Application number	Application date
AU2003265405 AA	20040225	AU20030265405	20030811
US2004110782 AA	20040610	US20030638943	20030811
US2007015751 AA	20070118	US20060339296	20060125
US6992088 BB	20060131	US20030638943	20030811
WO04014862 A1	20040219	WO2003US25109	20030811

Priority:

US20020402166P 20020809 WO2003US25109 20030811 US20030638943 20030811
US20060339296 20060125

Probable Assignee: RUTGERS STATE UNIV OF NEW JERSEY

Assignee(s): (std): LAVOIE EDMOND J ; LIU LEROY F ; UNIV RUTGERS ; SINGH SUDHIR K

Assignee(s): RUTGERS STATE UNIV ; RUTGERS STATE UNIV OF NEW JERSEY ; RUTGERS THE STATE UNIVERSITY ; RUTGERS THE STATE UNIVERSITY OF NEW JERSEY

Inventor(s): (std): LAVOIE EDMOND J ; LIU LEROY F ; SINGH SUDHIR K

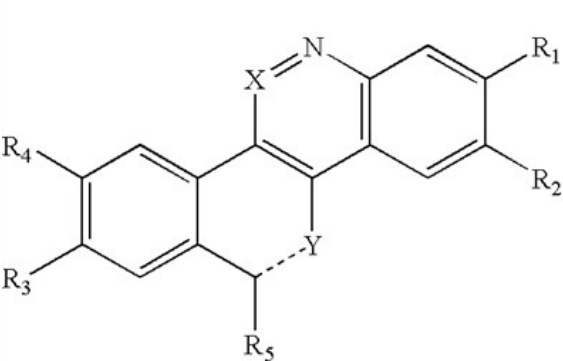
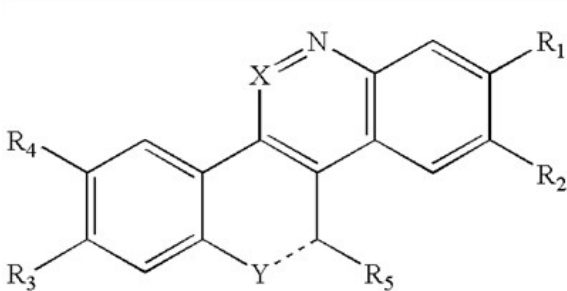
Inventor(s): SUDHIR K SINGH ; SINGH SUDHIR ; LEROY F LIU ; LIU LEROY ; EDMOND J LAVOIE ; LAVOIE EDMOND

Agent(s): VIKSNINS HARRIS AND PADYS PLLP

Designated states: AE AG AL AM AT AU AZ BA BB BE BF BG BJ BR BY BZ CA CF CG CH CI CM CN CO CR CU CY CZ DE DK DM DZ EC EE ES FI FR GA GB GD GE GH GM GN GQ GR GW HR HU ID IE IL IN IS IT JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MC MD MG MK ML MN MR MW MX MZ NE NI NL NO NZ OM PG PH PL PT RO RU SC SD SE SG SI SK SL SN SY SZ TD TG TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

Title: TOPOISOMERASE-TARGETING AGENTS

Abstract: Source: US2006004008A The invention provides compounds of formula I or formula II:



• the bond represented by - is a single bond or a double bond, and R₁ -R₅, X, and Y have any of the meanings defined in the specification and their pharmaceutically acceptable salts. The invention also provides pharmaceutical compositions comprising a compound of formula I or II, processes for preparing compounds of formula I or II, intermediates useful for preparing compounds of formula I or II, and therapeutic methods for treating cancer and other topoisomerase related conditions using compounds of formula I or II.

Classifications:

International (IPC 8-9): A61K31/415 A61K31/4162 A61K31/4353 A61K31/4355 A61K31/473 A61K31/4741 A61K31/4745 A61K31/5025 A61K31/503 A61P17/06 A61P31/00 A61P31/04 A61P31/10 A61P31/12 A61P33/00 A61P33/02 A61P33/10 A61P35/00 A61P43/00 C07D221/18 C07D237/26 C07D471/02 C07D471/04 C07D487/02 C07D487/04 C07D487/14 C07D491/04 C07D491/056 C07D491/147 (Advanced/Invention)

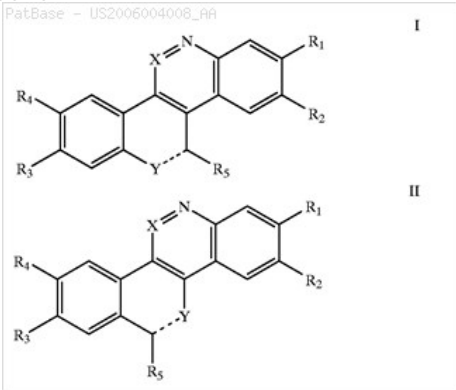
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CPC: C07D491/04

European: C07D491/04

US: 514/248 514/280 514/284 514/285 514/285S 514/80 544/233 544/233S 546/48 546/48S 546/61 546/62 546/62S 546/70

wherein:



Family:

Publication number	Publication date	Application number	Application date
AU2003290818 AA	20040603	AU20030290818	20031112
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CA2510337 AA	20050512	CA20032510337	20031112
CA2510337 C	20130108	CA20032510337	20031112
EP1562593 A2	20050817	EP20030783402	20031112
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EP1562593 B1	20140716	EP20030783402	20031112
JP2006512319 T2	20060413	JP20040552172T	20031112
JP4774212 B2	20110914	JP20040552172T	20031112
US2006004008 AA	20060105	US20050121292	20050503
US2007225289 AA	20070927	US20070714680	20070306
US2009258890 AA	20091015	US20090422394	20090413
US7208492 BB	20070424	US20050121292	20050503
US7517867 BB	20090414	US20070714680	20070306
US7858627 BB	20101228	US20090422394	20090413
WO04044174 A2	20040527	WO2003US36226	20031112
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Priority:

US20020425503P 20021112	US20020425535P 20021112	WO2003US36226 20031112
US20050121292 20050503	US20070714680 20070306	US20090422394 20090413

Probable Assignee: RUTGERS STATE UNIV OF NEW JERSEY

Assignee(s): (std): LAVOIE EDMOND J ; LIU LEROY F ; UNIV RUTGERS ; RUCHELMAN ALEXANDER L

Assignee(s): RUTGERS STATE UNIV ; RUTGERS STATE UNIV OF NEW JERSEY ; RUTGERS THE STATE UNIVERSITY OF NEW JERSEY ; NATIONAL INST ; NATIONAL INSTITUTES OF HEALTH ; NATIONAL INSTITUTES OF HEALTH NIH US DEPT OF HEALT ; RUTGERS THE STATE UNIVERSITY ; EDMOND J LAVOIE

Inventor(s): (std): RUCHELMAN ALEXANDER L ; LIU LEROY F ; LAVOIE EDMOND J

Inventor(s): LAVOIE EDMOND ; EDMOND J LAVOIE ; ALEXANDER L RUCHELMAN ; LIU LEROY ; LEROY F LIU ; RUCHELMAN ALEXANDER

Agent(s):

OFFICE FREYLINGER; VIKSNINS HARRIS AND PADYS PLLP; VIKNINS HARRIS AND PADY PLLP

Designated states:

AE AG AL AM AT AU AZ BA BB BE BF BG BJ BR BW BY BZ CA CF CG CH CI CM CN CO CR CU CY CZ DE DK DM DZ EC EE
EG ES FI FR GA GB GD GE GH GM GN GQ GR GW HR HU ID IE IL IN IS IT JP KE KG KP KR KZ LC LI LK LR LS LT LU LV MA
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TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

Title: BENZOQUINOLIZINE-2-CARBOXYLIC ACID-CONTAINING COMPOSITIONS

Abstract: Source: US2004176337A This invention relates to topical compositions of an **antibacterial** benzoquinolizine-2-carboxylic acid, incorporated either as the single therapeutic ingredient in hitherto undescribed pharmaceutical compositions, or as an ingredient in novel combination with at least one agent selected from a retinoid, an antifungal agent, another **antibacterial** compound and/or a steroid/non-steroid anti-inflammatory agent, to processes for preparation of the compositions, to use of the compositions in preparation of a medicament, and to a method of therapeutic or prophylactic use of such a composition for the treatment of dermal, ophthalmic, otic and nasal infections, with or without attendant inflammation.

Classifications:
International (IPC 8-9): A61K31/203 A61K31/4375 A61K31/4545 A61K31/473 A61K31/56 A61P31/04 (Advanced/Invention); A61K31/473 A61P31/00 (Core/Invention)
International (IPC 1-7): A61K31/07 A61K31/203 A61K31/473 A61K31/4745 A61K31/56 A61P31/04
CPC: A61K31/473
European: A61K31/473
US: 514/171 514/296 514/559 514/725

Family:

Publication number	Publication date	Application number	Application date	
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CA2512190 AA	20050629	CA20032512190	20031231	
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US2004176337 AA	20040909	US20030749933	20031231	
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Priority:
IN2002MU01170 20021231 WO2003IN00422 20031231

Probable Assignee: WOCKHARDT LTD

Assignee(s): (std): BHAGWAT SACHIN S ; DE SOUZA NOEL J ; GUPTA SHRIKANT V ; JHA RASENDRAKUMAR ; SAOJI DILIP G ; NAGORI RAJENDRA N ; SHUKLA MILIND C ; PATEL MAHESH V ; KUKREJA ANIL ; SOUZA NOEL J DE ; WOCKHARDT LTD

Assignee(s): WOCKHARDT LIMITED

Inventor(s): (std): BHAGWAT SACHIN ; BHAGWAT SACHIN S ; DE SOUZA NOEL J ; GUPTA SHRIKANT V ; JHA RASENDRAKUMAR ; KUKREJA ANIL ; PATEL MAHESH V ; NAGORI RAJENDRA N ; SAOJI DILIP G ; SHUKLA MILIND C ; SOUZA NOEL J DE

Inventor(s): ANIL KUKREJA ; SHRIKANT V GUPTA ; SHRIKANT VINAYAK GUPTA ; NOEL J DE SOUZA ; NOEL JOHN DE SOUZA ; RAJENDRA N NAGORI ; RASENDRAKUMAR JHA ; SACHIN S BHAGWAT ; SACHIN SUBHASH BHAGWAT ; MAHESH V PATEL ; MAHESH VITHALBHAI PATEL ; MILIND C SHUKLA ; MILIND CHINTAMAN SHUKLA ; DILIP G SAOJI ; DILIP GOPALKRISHNA SAOJI

Designated states: AE AG AL AM AT AU AZ BA BB BE BF BG BJ BR BW BY BZ CA CF CG CH CI CM CN CO CR CU CY CZ DE DK DM DZ EC EE EG ES FI FR GA GB GD GE GH GM GN GQ GR GW HR HU ID IE IL IN IS IT JP KE KG KP KR KZ LC LI LK LR LS LT LU LV MA MC MD MG MK ML MN MR MW MX MZ NA NE NI NL NO NZ OM PG PH PL PT RO RU SC SD SE SG SI SK SL SN SY SZ TD TG TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

Title: ANTIMICROBIAL AND DEGERMING AGENT

Abstract: Source: JP2005002033A PROBLEM TO BE SOLVED: To obtain a degerming agent (**antibacterial** agent, antifungal agent, and antiviral agent) widely effective against methicillin-resistant staphylococcus aureus (MRSA), vancomycin-resistant enterococcus (VRE), gram-negative bacterium such as Pseudomonas aeruginosa having multiple resistance and other microorganisms, and a degerming product. SOLUTION: The degerming agent comprises an antimicrobial pigment agent and a metal. An article is obtained by treatment with the degerming agent. Gentian violet, malachite green, brilliant blue, ethacridine and an azo pigment are preferable as the antimicrobial pigment agent. Magnesium, aluminum, zinc, iron, cobalt, nickel, tin, chromium, lead, copper, silver, platinum, a salt of them and a complex of them are preferable as the metal. The degerming agent exhibits synergistic sterilization effect on both gram-positive bacteria and gram-negative bacteria by using the antimicrobial pigment agent and the metal. An article considered to have contamination is dyed to prevent contamination.

Classifications:

International (IPC 8-9): A61K31/14 A61K31/473 A61K33/06 A61K33/24 A61K33/26 A61K33/30 A61K33/34 A61K33/38 A61K45/00 A61K9/10

A61K9/14 A61P31/04 (Advanced/Invention);

A61K31/14 A61K31/473 A61K33/06 A61K33/24 A61K33/26 A61K33/30 A61K33/34 A61K33/38 A61K45/00 A61K9/10 A61K9/14

A61P31/00 (Core/Invention)

International (IPC 1-7): A61K31/14 A61K31/473 A61K33/06 A61K33/24 A61K33/26 A61K33/30 A61K33/34 A61K33/38 A61K45/00 A61K9/10

A61K9/14 A61P31/04

Family:

Publication number	Publication date	Application number	Application date
JP2005002033 A2	20050106	JP20030166305	20030611

Priority:

JP20030166305 20030611

Probable Assignee: NAGAYAMA ZAIMEI

Assignee(s): (std): NAGAYAMA ZAIMEI

Inventor(s): (std): HANAKI HIDEAKI ; NAGAYAMA ZAIMEI

Title: Potentiators of **antibacterial** activity

Abstract: Source: US2005090482A The present invention relates to compounds that potentiate the activity of **antibacterials**. The present invention also relates to compositions useful in treating bacterial infection in mammals, and methods therewith. The present invention also relates to a method of inhibiting bacterial efflux of an antibiotic, thereby increasing the efficacy of the antibiotic.

Classifications:

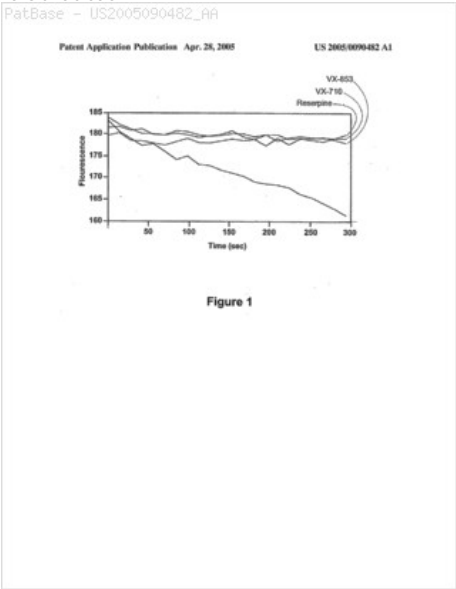
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International (IPC 1-7): A61K31/16 A61K31/195 A61K31/407 A61K31/43 A61K31/444 A61K31/4545 A61K31/496 A61K31/545 A61P31/04

CPC: A61K31/444 A61K31/4545 A61K31/496

European: A61K31/444 A61K31/4545 A61K31/496

US: 514/192 514/200 514/200S 514/210.09 514/210.090S 514/253.08 514/253.080P 514/254.01 514/255.01 514/298 514/298S 514/300 514/300S 514/318 514/332 514/332S 514/37 514/563 514/563S 514/616 514/616S



Family:

Publication number	Publication date	Application number	Application date
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US2009291964 AA	20091126	US20090534279	20090803
US7825136 BB	20101102	US20040887719	20040709
WO05007162 A1	20050127	WO2004US21973	20040709

Priority:

US20030486041P 20030710 US20030486046P 20030710 US20090534279 20090803
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Probable Assignee: VERTEX PHARMACEUTICALS INC

Assignee(s): (std): GROSSMAN TRUDY HOPE ; VERTEX PHARMA

Assignee(s): VERTEX PHARMACEUTICALS INC ; MACQUARIE US TRADING LLC ; GROSSMAN TRUDY H

Inventor(s): (std): GROSSMAN TRUDY H ; GROSSMAN TRUDY HOPE

Agent(s): FISH AND NEAVE IP GROUP, ROPES AND GRAY LLP; VERTEX PHARMACEUTICALS INC; MICHAEL J

Designated states: AE AG AL AM AT AU AZ BA BB BE BF BG BJ BR BW BY BZ CA CF CG CH CI CM CN CO CR CU CY CZ DE DK DM DZ EC EE EG ES FI FR GA GB GD GE GH GM GN GQ GR GW HR HU ID IE IL IN IS IT JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MC MD MG MK ML MN MR MW MX MZ NA NE NI NL NO NZ OM PG PH PL PT RO RU SC SD SE SG SI SK SL SN SY SZ TD TG TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

Title: DISINFECTANT

Abstract: Source: JP2005112801A PROBLEM TO BE SOLVED: To obtain a disinfectant widely effective for gram-positive bacteria such as methicillin-resistant Staphylococcus aureus and vancomycin-resistant enterococcus and a gram-negative bacteria such as Klebsiella pneumoniae and Pseudomonas aeruginosa and the other microorganisms including fungi. SOLUTION: This disinfectant comprises an **antibacterial** coloring agent, an **antibacterial** medicine and an organic acid. The disinfectant comprises, particularly preferably, gentiana violet, a citric acid-based buffering agent and polymixin. The disinfectant exhibits synergistic effect on the gram-negative bacteria, particularly by combination of three agents. The disinfectant is a pharmaceutical preparation which enables not only enhancement of sterilization effect and enlargement of **antibacterial** spectrum, but also pH adjustment by buffer action and can contribute to alleviation of pain due to by irritating property of pH and attenuation of corrosive action by pH.

Classifications:
International (IPC 8-9): A61K31/136 A61K31/19 A61K31/198 A61K31/255 A61K31/422 A61K31/4704 A61K31/473 A61K31/545 A61K31/65 A61K31/7036 A61K31/7048 A61K38/00 A61K45/06 A61K9/06 A61K9/08 A61K9/10 A61K9/14 A61K9/20 A61L2/16 A61L2/18 A61L2/22 A61P31/02 A61P43/00 (Advanced/Invention); A61K31/136 A61K31/185 A61K31/21 A61K31/422 A61K31/4704 A61K31/473 A61K31/545 A61K31/65 A61K31/7028 A61K31/7042 A61K38/00 A61K45/00 A61K9/06 A61K9/08 A61K9/10 A61K9/14 A61K9/20 A61L2/16 A61L2/18 A61L2/22 A61P31/00 A61P43/00 (Core/Invention)
International (IPC 1-7): A61K31/136 A61K31/19 A61K31/198 A61K31/255 A61K31/422 A61K31/4704 A61K31/473 A61K31/545 A61K31/65 A61K31/7036 A61K31/7048 A61K38/00 A61K45/06 A61K9/06 A61K9/08 A61K9/10 A61K9/14 A61K9/20 A61L2/16 A61L2/18 A61L2/22 A61P31/02 A61P43/00

Family:

Publication number	Publication date	Application number	Application date
JP2005112801 A2	20050428	JP20030350187	20031009

Priority:

JP20030350187 20031009

Probable Assignee: HANAKI HIDEAKI

Assignee(s): (std): HANAKI HIDEAKI ; NAGAYAMA ZAIMEI

Inventor(s): (std): HANAKI HIDEAKI ; NAGAYAMA ZAIMEI

Title: ACRIDINE DERIVATIVE

Abstract: Source: JP2005306773A PROBLEM TO BE SOLVED: To obtain a disinfectant having improved properties in any one of points such as (1) bactericidal action at a low concentration, (2) rapid bactericidal action in a short time, (3) bactericidal action having persistence, (4) low toxicity, and (5) stability without lowering the effect even when an organic substance is mixed, and an **antibacterial** compound of a new type against Gram-positive bacteria and Eumycetes in answer to the problem of appearance of a resistant bacterium, or the like. SOLUTION: A novel photodecomposition product (ANDP-8) of acrinol obtained by separating the main component in the photodecomposition product (ANDP) of acrinol and purifying it has an activity against Gram-positive bacteria of about 10-100 times the activity of acrinol as its original substance, and has also considerably strong **antibacterial** action against Eumycetes against which no **antibacterial** power is recognized with acrinol. The acridine derivative is represented by formula (I) or its pharmaceutically acceptable salt.

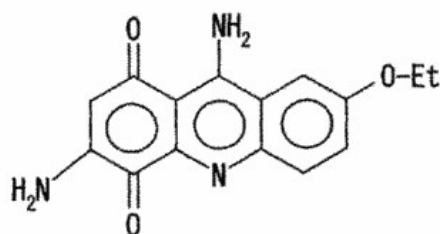
Classifications:

International (IPC 8-9): A61K31/473 A61P31/04 C07D219/10 (Advanced/Invention);

A61K31/473 A61P31/00 C07D219/00 (Core/Invention)

International (IPC 1-7): A61K31/473 A61P31/04 C07D219/10

PatBase - JP2005306773_R2



(I)

(式中、E t はエチル基を表す)

Family:

Publication number	Publication date	Application number	Application date
JP2005306773 A2	20051104	JP20040125101	20040421
JP4794136 B2	20111019	JP20040125101	20040421

Priority:

JP20040125101 20040421

Probable Assignee: UNIV KUMAMOTO

Assignee(s): (std): UNIV KUMAMOTO

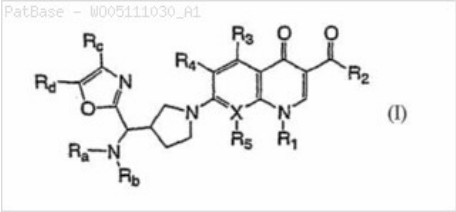
Assignee(s): KUMAMOTO UNIV

Inventor(s): (std): IIJIMA TOMONORI ; KIDO YUTAKA ; TANAKA SHIGEO ; TANAKA TOSHIJI

Title: QUINOLONE **ANTIBACTERIAL** AGENTS

Abstract: Compounds of formula (I) and methods for their preparation are disclosed. Further disclosed are methods of making biologically active compounds of formula (I) as well as pharmaceutically acceptable compositions comprising compounds of formula (I). Compounds of formula (I) as disclosed herein can be used in a variety of applications including use as **antibacterial** agents. A compound of formula (I):

Classifications:
International (IPC 8-9): A61K31/4353 A61K31/473 A61K31/4738 A61K31/5365 C07D401/04 C07D405/14 C07D413/14 C07D471/04 C07D498/06 (Advanced/Invention)
International (IPC 1-7): A61K31/4353 A61K31/473 A61K31/4738 A61K31/5365 A61P31/04 C07D413/14 C07D498/06
CPC: C07D405/14 C07D401/04 C07D413/14 C07D471/04
European: C07D401/04 C07D405/14 C07D413/14 C07D471/04 C07D498/06



Family:

Publication number	Publication date	Application number	Application date
WO05111030 A1	20051124	WO2005IB01213	20050502

Priority:

US20040570142P 20040512

Probable Assignee: WARNER LAMBERT CO

Assignee(s): (std): ELLSWORTH EDMUND LEE ; MURPHY SEAN TIMOTHY ; WARNER LAMBERT CO

Assignee(s): WARNER LAMBERT CO LLC ; WARNER LAMBERT COMPANY LLC

Inventor(s): (std): ELLSWORTH EDMUND LEE ; MURPHY SEAN TIMOTHY

Designated states: AE AG AL AM AT AU AZ BA BB BE BF BG BJ BR BW BY BZ CA CF CG CH CI CM CN CO CR CU CY CZ DE DK DM DZ EC EE EG ES FI FR GA GB GD GE GH GM GN GQ GR GW HR HU ID IE IL IN IS IT JP KE KG KM KP KR KZ LC LK LR LS LT LU LV MA MC MD MG MK ML MN MR MW MX MZ NA NE NI NL NO NZ OM PG PH PL PT RO RU SC SD SE SG SI SK SL SM SN SY SZ TD TG TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

Title: ADHESIVE PEEL-FORMING FORMULATIONS FOR DERMAL DELIVERY OF DRUGS AND METHODS OF USING THE SAME

Abstract: Source: US2005276842A The present invention is drawn to adhesive peel-forming formulations for dermal delivery of a drug. The formulation can include a drug, a solvent vehicle, and a peel-forming agent. The solvent vehicle can include a volatile solvent system having one or more volatile solvent, and a non-volatile solvent system having one or more non-volatile solvent, wherein the non-volatile solvent system has a solubility for the drug that is within a window of operable solubility for the drug such that the drug can be delivered at therapeutically effective rates over a sustained period of time. The formulation can have a viscosity suitable for application to a skin surface prior to evaporation of the volatile solvents system. When applied to the skin, the formulation can form a solidified peelable layer after at least a portion of the volatile solvent system is evaporated.

Classifications:

International (IPC 8-9): A01N37/12 A01N43/54 A61F13/00 A61F13/02 A61K31/00 A61K31/04S A61K31/07 A61K31/13 A61K31/13S A61K31/137 A61K31/16S A61K31/167 A61K31/19 A61K31/192 A61K31/195 A61K31/196 A61K31/203 A61K31/24 A61K31/24S A61K31/27S A61K31/327 A61K31/402S A61K31/40S A61K31/41S A61K31/416A A61K31/4168 A61K31/417A A61K31/437 A61K31/4439 A61K31/44S A61K31/473 A61K31/474S A61K31/48S A61K31/50S A61K31/51S A61K31/517 A61K31/52 A61K31/522 A61K31/541S A61K31/56 A61K31/566 A61K31/567 A61K31/568 A61K31/569 A61K31/57 A61K31/573 A61K31/58 A61K31/59 A61K31/60 A61K31/74 A61K35/64 A61K38/13 A61K38/21 A61K45/00 A61K47/04 A61K47/06 A61K47/08 A61K47/10 A61K47/12 A61K47/14 A61K47/18 A61K47/20 A61K47/22 A61K47/24 A61K47/30 A61K47/32 A61K47/34 A61K47/36 A61K47/38 A61K47/40 A61K47/42 A61K47/44 A61K47/46 A61K8/00 A61K8/02 A61K9/00 A61K9/06 A61K9/08 A61K9/10 A61K9/12 A61K9/14 A61K9/70 A61L15/16 A61L26/00 A61M37/00 A61P17/00 A61P17/06 A61P17/14 A61P21/00 A61P25/00 A61P25/04 A61P25/30 A61P29/00 A61P31/00 A61P31/04 A61P31/10 A61P31/12 A61P31/22 (Advanced/Invention); A61F13/00 A61F13/02 A61K9/70 (Advanced/Non-invention); A01N37/12 A61F13/00 A61F13/02 A61K31/00 A61K31/04 A61K31/04S A61K31/13 A61K31/13S A61K31/167 A61K31/18S A61K31/21 A61K31/416A A61K31/4427 A61K31/44S A61K31/4738 A61K31/519 A61K31/56 A61K31/568 A61K31/57 A61K31/59 A61K31/60 A61K31/74 A61K38/12 A61K45/00 A61K47/02 A61K47/06 A61K47/08 A61K47/10 A61K47/12 A61K47/14 A61K47/16 A61K47/20 A61K47/22 A61K47/24 A61K47/30 A61K47/32 A61K47/34 A61K47/36 A61K47/38 A61K47/40 A61K47/42 A61K47/44 A61K47/46 A61K8/02 A61K9/00 A61K9/06 A61K9/08 A61K9/12 A61K9/70 A61L15/16 A61M37/00 A61P17/00 A61P21/00 A61P25/00 A61P29/00 A61P31/00 (Core/Invention); A61F13/00 (Core/Non-invention)

International (IPC 1-7): A61F13/00 A61K9/12 A61K9/12 A61K9/70

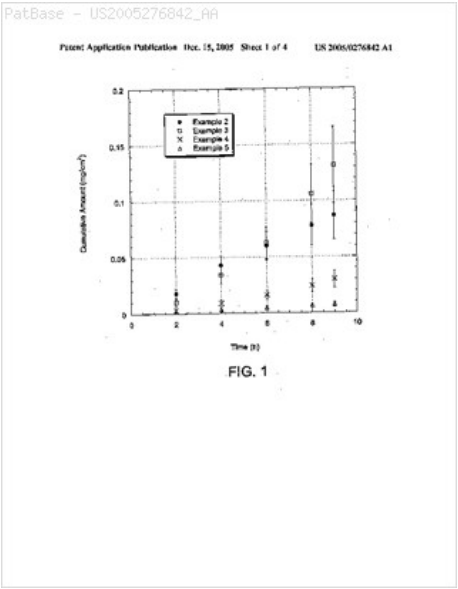
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European: A61K31/07 A61K31/16S A61K31/19 A61K31/192 A61K31/19S A61K31/24 A61K31/27S A61K31/41S A61K31/417A A61K31/4439 A61K31/44S A61K31/473 A61K31/474S A61K31/50S A61K31/522 A61K31/513 A61K31/522 A61K31/56 A61K31/568 A61K31/57 A61K31/573 A61K31/59 A61K31/74 A61K47/06 A61K47/10 A61K47/12 A61K47/14 A61K47/18 A61K47/32 A61K47/34 A61K47/38 A61K47/44 A61K9/00M3 A61K9/00M3B A61K9/06 A61K9/08 A61K9/70B A61K9/70D A61L26/00H2 K61K47/10 K61K47/18 K61K47/32 K61K47/38 K61K47/42 K61L300/402 K61L300/404 K61L300/602

US: 424/400 424/400P 424/443 424/443P 424/448 424/448P 424/449 424/45 424/45P 424/47 424/47P 424/487 424/539 424/539S 424/59 424/59P 424/61 424/770 424/770S 424/776 424/776S 424/78 424/78.02 424/78.02P 424/78.07 424/78.07P 514/11 514/159 514/159S 514/167 514/167S 514/168 514/168S 514/171 514/171S 514/174 514/174S 514/178 514/178S 514/18.7 514/18.700S 514/180 514/180S 514/182 514/182S 514/20.5 514/20.500S 514/226.5 514/226.500S 514/263.31 514/263.310S 514/263.38 514/263.380S 514/266.22 514/266.220S 514/269 514/269S 514/275 514/275S 514/282 514/284 514/284S 514/291 514/291S 514/292 514/292S 514/293 514/293S 514/303 514/330 514/330S 514/343 514/343S 514/383 514/383S 514/399 514/399S 514/401 514/401S 514/420 514/420S 514/422 514/422S 514/524 514/524S 514/536 514/536S 514/559 514/559S 514/563 514/563S 514/567 514/567S 514/568 514/568S 514/569 514/569S 514/570 514/570S 514/617 514/617S 514/626 514/626S 514/647 514/649 514/649S 514/654 514/654S 514/655 514/655S 514/656 514/714 514/714S 514/725 514/725S 514/772 514/772.2 514/772.5 514/772.6 514/772S 514/774 514/783 514/783S 514/784 514/784S 514/785 514/785S 514/788 514/788S 514/789 602/48 602/52 602/54 602/57

Family:

Publication number	Publication date	Application number	Application date
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Priority:

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Probable Assignee: NUVO RES INC

Assignee(s): (std):	ZARS INC ; ZHANG JIE ; WARNER KEVIN S ; RIGBY LARRY D ; SHARMA SANJAY ; WAMER KEVIN S ; SHARMA SANJA ; ZARS PHARMA INC ; SANJAY SHARMA ; ASHBURN MICHAEL A ; NIU SUYI ; NUVO RES INC
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Inventor(s):	ZHANG JIE WARNER KEVIN S ; ZHANG JIE WARNER KEVIN S ASHBURN MICHAEL A RIGBY L ; WARNER KEVIN ; WAMER KEVIN ; SUYI NIU ; KEVIN S WARNER ; LARRY D RIGBY ; MICHAEL A ASHBURN
Agent(s):	WOMBWELL FRANCIS ET AL; THORPE NORTH AND WESTERN LLP; OAKESON GARY P ET AL
Designated states:	AE AG AL AM AO AT AU AZ BA BB BE BF BG BH BJ BR BW BY BZ CA CF CG CH CI CM CN CO CR CU CY CZ DE DK DM DO DZ EC EE EG ES FI FR GA GB GD GE GH GM GN GQ GR GT GW HN HR HU ID IE IL IN IS IT JP KE KG KM KN KP KR KZ LA LC LI LK LR LS LT LU LV LY MA MC MD ME MG MK ML MN MR MT MW MX MY MZ NA NE NG NI NL NO NZ OM PG PH PL PT RO RS RU SC SD SE SG SI SK SL SM SN ST SV SY SZ TD TG TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

Title: BENZOQUINOLIZINE-2-CARBOXYLIC ACID CONTAINING COMPOSITIONS

Abstract: Source: IN01334MU2003A This invention relates to topical compositions of an **antibacterial** benzoquinolizine-2-carboxylic acid, incorporated either as the single therapeutic ingredient in hitherto undescribed pharmaceutical compositions, or as an ingredient in novel combination with at least one agent selected from a retinoid, an antifungal agent, another **antibacterial** compound and/or a steroid/non-steroid antiinflammatory agent, to processes for preparation of the compositions, to use of the compositions in preparation of a medicament, and to a method of therapeutic or prophylactic use of such a composition for the treatment of dermal, ophthalmic, otic and nasal infections, with or without attendant inflammation.

Classifications:

International (IPC 1-7): A61K31/473 A61P31/04

Family:

Publication number	Publication date	Application number	Application date
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Probable Assignee: WOCKHARDT LTD

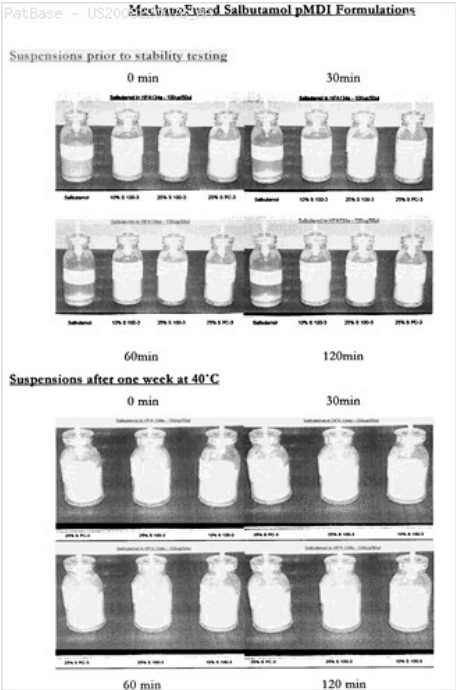
Assignee(s): WOCKHARDT LTD

Inventor(s): ANIL KUKREJA ; DILIP GOPALKRISHNA SAOJI1 ; MAHESH VITHALBHAI PATEL ; MILIND CHINTAMAN SHUKLA ; NOEL JOHN DE SOUZA ; RAJENDRA N NAGORI ; RASENDRAKUMAR JHA ; SACHIN SUBHASH BHAGWAT ; SHRIKANT VINAYAK GUPTA

Title: PHARMACEUTICAL FORMULATIONS

Abstract: Source: US2008220078A A pharmaceutical formulation for delivery in aerosol or spray form, comprising a liquefied propellant gas, a solid particulate pharmaceutically active agent and a dispersing agent, wherein the dispersing agent is fused to the surface of particles of the pharmaceutically active agent.

Classifications:
International (IPC 8-9): A61K31/13 A61K31/137 A61K31/357 A61K31/473 A61K31/522 A61K31/55 A61K39/395 A61K45/00 A61K47/06 A61K47/12 A61K47/18 A61K47/24 A61K9/00 A61K9/12 A61K9/14 A61K9/72 A61M11/00 A61P11/08 A61P25/02 A61P25/18 A61P25/24 A61P29/00 A61P31/04 A61P31/10 A61P31/12 A61P37/02 A61P37/08 A61P7/02 A61P9/06 A61P9/06 (Advanced/Invention); A61K31/13 A61K31/137 A61K31/357 A61K31/473 A61K31/519 A61K31/55 A61K39/395 A61K47/06 A61K47/12 A61K47/16 A61K47/24 A61K9/00 A61K9/12 A61K9/14 A61K9/72 A61M11/00 A61P11/00 A61P25/00 A61P29/00 A61P31/00 A61P37/00 A61P7/00 A61P9/00 (Core/Invention)
International (IPC 1-7): A61K9/72
CPC: A61K9/008 A61K31/137
European: A61K31/137 A61K9/00M20B A61K9/00M20B6
US: 424/130.1 424/43 424/45 424/490



Family:

Publication number	Publication date	Application number	Application date
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US2008220078 AA	20080911	US20050791670	20051130
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WO06059152 A3	20070111	WO2005GB50220	20051130

Priority:

GB20040026301 20041130 WO2005GB50220 20051130

Probable Assignee: VECTURA LTD

Assignee(s): (std): BEGAT PHILIPPE ; HARRIS HAGGIS ; MORTON DAVID ALEXANDER VODDEN ; PRICE ROBERT ; VECTURA LTD

Assignee(s): VECTURA LTD1 PROSPECT WESTWILTSHIRESN14 6FHCHIPPENHAMGB ; VECTURA LIMITED

Inventor(s): (std): BEGAT PHILIPPE ; HAGGIS HARRIS ; HARRIS HAGGIS ; MORTON DAVID ALEXANDER VODDEN ; PHILIPPE BEGAT ; PRICE ROBERT ; ROBERT PRICE ; VODDEN MORTON DAVID ALEXANDER

Inventor(s): PRICE ROBERTGB ; MORTON DAVID ALEXANDER VODDENG ; HARRIS HAGGISGB ; BEGAT PHILIPPEGB

Agent(s): DAVIDSON DAVIDSON AND KAPPEL LLC

Designated states: AE AG AL AM AT AU AZ BA BB BE BF BG BJ BR BW BY BZ CA CF CG CH CI CM CN CO CR CU CY CZ DE DK DM DZ EC EE EG ES FI FR GA GB GD GE GH GM GN GQ GR GW HR HU ID IE IL IN IS IT JP KE KG KM KN KP KR KZ LC LI LK LR LS LT LU LV LY MA MC MD MG MK ML MN MR MW MX MZ NA NE NG NI NL NO NZ OM PG PH PL PT RO RU SC SD SE SG SI SK SL SM SN SY SZ TD TG TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

Title: VIRUS-REMOVING AGENT OR FUNGUS-REMOVING AGENT

Abstract: Source: JP2006188499A PROBLEM TO BE SOLVED: To provide a degerming (**antibacterial**, antifungal, antiviral) agent widely effective against viruses, fungi and other microorganisms, and a degermed article. SOLUTION: The virus-removing agent and the fungus-removing agent comprise an antimicrobial dye agent and a metal. The articles are obtained by a treatment with the virus-removing agent and the fungus-removing agent. Preferably, the antimicrobial dye agent is gentian violet, malachite green, brilliant blue, ethacridine or an azo dye. Preferably, the metal is magnesium, aluminum, zinc, iron, cobalt, nickel, tin, chromium, lead, copper, silver or platinum, or a salt thereof or a complex thereof. The degerming agent comprises both the antimicrobial dye agent and the metal, and therefore exhibits cumulative and synergetic bactericidal effects on both viruses and fungi. Moreover, a dyeing treatment of articles liable to be contaminated can prevent contamination thereof.

Classifications:
International (IPC 8-9): A01N25/02 A01N25/04 A01N25/08 A01N25/12 A01N33/12 A01N41/06 A01N43/42 A01N43/78 A01N59/06 A01N59/16 A01N59/20 A01P3/00 A61K31/14 A61K31/473 A61K33/06 A61K33/24 A61K33/26 A61K33/30 A61K33/34 A61K33/38 A61K45/00 A61P31/10 A61P31/12 C09B11/00 C09B61/00 (Advanced/Invention); A61K31/473 (Core/Invention)

Family:

Publication number	Publication date	Application number	Application date
JP2006188499 A2	20060720	JP20050352875	20051207

Priority:

JP20040357522 20041210 JP20050352875 20051207

Probable Assignee: NAGAYAMA ZAIMEI

Assignee(s): (std): NAGAYAMA ZAIMEI

Inventor(s): (std): HANAKI HIDEAKI ; NAGAYAMA ZAIMEI

Title: 11,11-DIMETHYL-1-OXO-1,2,10,11-TETRAHYDROBENZO[h]PYRROLO-[2,1-a]-ISOQUINOLINE-2-SPIRO-2-(1-ARYL-3-AROYL-4-HYDROXY-5-OXO-2,5-DIHYDROPYRROLES) ELICITING **ANTIBACTERIAL** ACTIVITY AGAINST GRAM-POSITIVE MICROFLORA

Abstract: Source: RU2281286C

FIELD: organic chemistry, chemical technology.

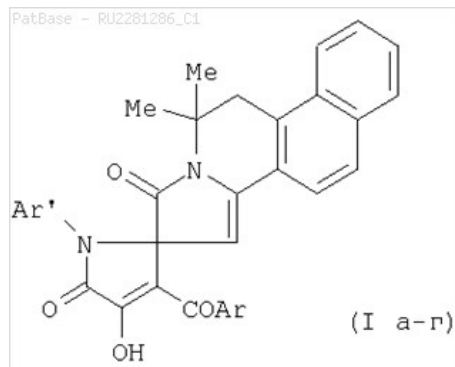
SUBSTANCE: invention relates to novel 11,11-dimethyl-1-oxo-1,2,10,11-tetrahydrobenzo[h]pyrrolo[2,1-a]-isoquinoline-2-spiro-2-(1-aryl-3-aro-4-hydroxy-5-oxo-2,5-dihydropyrroles) of the formulae (Ia-d): wherein Ar means Ph (Ia, b), C₆H₄OEt-4 (Ic), C₆H₄Cl-4 (Id); Ar' means C₆H₄Me-4 (Ia, c, d), C₆H₄Cl-4 (Ib) that elicit **antibacterial** activity against gram-positive microflora. Compounds of the formula (I) are prepared by interaction of 1-aryl-4-aro-5-methoxycarbonyl-2,3-dihydro-2,3-pyrrolidones with 1,3,3-trimethyl-3,4-dihydrobenzo[f]isoquinoline in absolute benzene medium at boiling for 2 min followed by isolation of end products by the known procedures. Synthesized compounds are not toxic practically.

EFFECT: improved preparing method, valuable biological properties of compounds.

1 tbl, 1 sch, 2 ex

Classifications:

International (IPC 8-9): A61K31/47 A61K31/473 C07D487/10 (Advanced/Invention); A61K31/47 A61K31/473 C07D487/00 (Core/Invention)



Family:

Publication number	Publication date	Application number	Application date
RU2281286 C1	20060810	RU20050119508	20050624

Priority:

RU20050119508 20050624

Probable Assignee: G OBRAZOVATEL NOE UCHREZHDENIE

Assignee(s): (std): G OBRAZOVATEL NOE UCHREZHDENIE

Assignee(s): GOSUDARSTVENNOE OBRAZOVATEL NOE UCHREZHDENIE VYSS ; GOSUDARSTVENNOE OBRAZOVATEL NOE UCHREZHDENIE VYSSH ; GOSUDARSTVENNOE OBRAZOVATEL'NOE UCHREZHDENIE VYSSHEGO PROFESSIONAL'NOGO OBRAZOVANIJA PERMSKIJ GOSUDARSTVENNYJ UNIVERSITET

Inventor(s): (std): BANNIKOVA JULIJA NIKOLAEVNA ; MASLIVETS ANDREJ NIKOLAEVICH ; ROZHKOVA JULIJA SERGEEVNA ; SHKLJAEV JURIJ VLADIMIROVICH ; SMIRNOVA ALEKSANDRA SERGEEVNA ; ALEKSANDROVA GALINA ARSENT EVN

Inventor(s): ALEKSANDROVA GALINA ARSENT EVNA ; ALEKSANDROVA GALINA ARSENT'EVNA

Title: DRIED MILLED GRANULATE AND METHODS

Abstract: Source: US2007048373A The present invention relates to a method of producing a dried wet granulate having a desirable average particle size and particle size distribution and dosage forms made from that granulate.

Classifications:

International (IPC 8-9): A61J3/06 A61K31/135 A61K31/16 A61K31/165 A61K31/44 A61K31/445 A61K31/4535 A61K31/47 A61K31/473 A61K31/48 A61K31/485 A61K31/551 A61K31/70 A61K31/7052 A61K9/16 A61K9/20 A61K9/26 A61K9/36 A61K9/50 B01J2/00 B02C23/06 (Advanced/Invention);

A61J3/06 A61K31/135 A61K31/16 A61K31/165 A61K31/44 A61K31/445 A61K31/4523 A61K31/47 A61K31/473 A61K31/48 A61K31/485 A61K31/551 A61K31/70 A61K31/7042 A61K9/16 A61K9/20 A61K9/30 B01J2/00 B02C23/00 (Core/Invention);

A61K (Subclass/Invention)

CPC: A61K9/1623 A61K9/1652 A61K9/1682 A61K31/165 A61K31/44 A61K31/473 A61K31/485 A61K31/7052

European: A61K31/165 A61K31/44 A61K31/473 A61K31/485 A61K31/7052 A61K9/16H4B A61K9/16H6F A61K9/16P

US: 241/16 424/464 514/28 514/282 514/290 514/317 514/618

Family:

Publication number	Publication date	Application number	Application date	
AT458475 E	20100315	AT20060813925T	20060829	
AT539739 E	20120115	AT20060001313T	20060829	
CA2621079 AA	20080229	CA20062621079	20060829	
CA2621079 C	20140218	CA20062621079	20060829	
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DK2198855 T3	20120402	DK20060001313T	20060829	
EP1919454 A2	20080514	EP20060813925	20060829	
EP1919454 B1	20100224	EP20060813925	20060829	
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EP2359811 A1	20110824	EP20110157456	20060829	
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ES2379333 T3	20120425	ES20100001313T	20060829	
ES2398637 T3	20130320	ES20110157456T	20060829	
HK1111622 A1	20100604	HK20080105730	20080523	
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HK1145146 A1	20120921	HK20100111702	20101215	
HK1160010 A1	20130712	HK20120100538	20120117	
JP2009505798 T2	20090212	JP20080529209T	20060829	
JP5144519 B2	20130213	JP20080529209T	20060829	
MX2008002779 A1	20080407	MX20080002779	20080227	
PT2198855 T	20120319	PT20100001313T	20060829	
US2007048373 AA	20070301	US20060507240	20060821	
WO07027720 A2	20070308	WO2006US33779	20060829	
WO07027720 A3	20070802	WO2006US33779	20060829	

Priority:

US20050712580P 20050830 US20060507240 20060821 WO2006US33779 20060829

EP20060813925 20060829 EP20100001313 20060829

Probable Assignee: CIMA LABS INC

Assignee(s): (std): CHASTAIN SARA J ; CIMA LABS INC ; HABIB WALID ; MOE DEREK

Inventor(s): (std): CHASTAIN SARA J ; HABIB WALID ; MOE DEREK ; CHASTAIN SARA

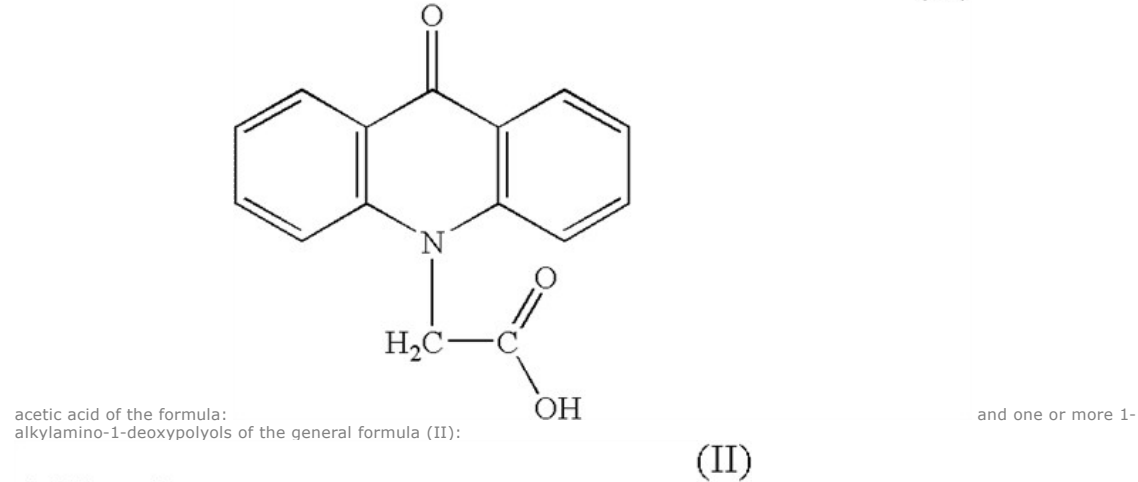
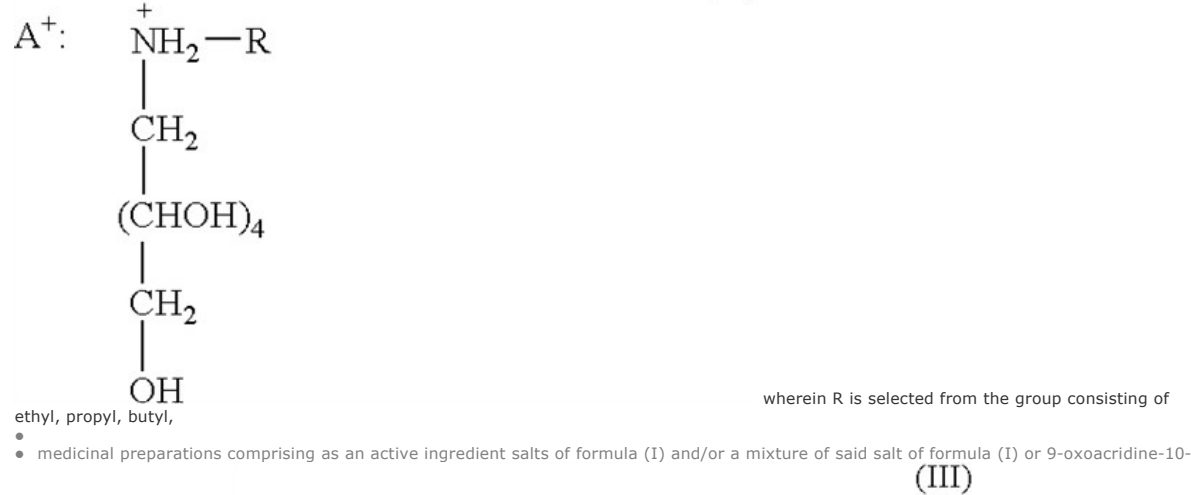
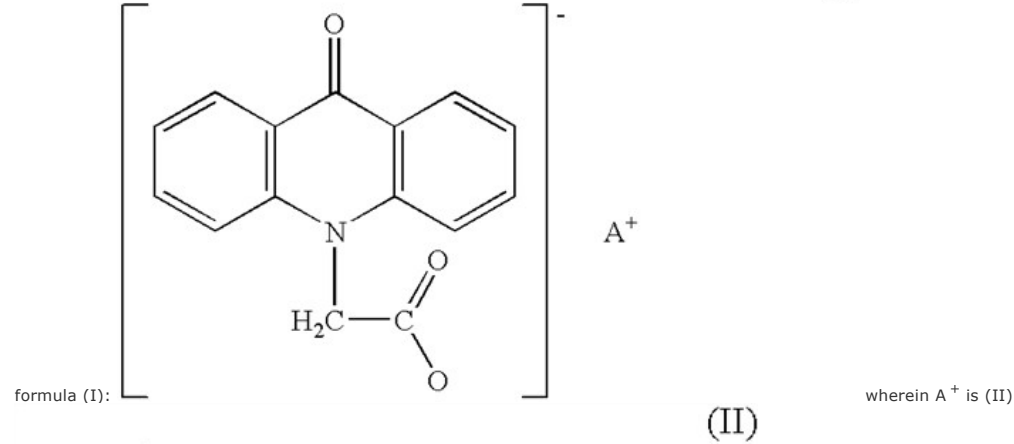
Inventor(s): WALID HABIB ; SARA J CHASTAIN ; DEREK MOE

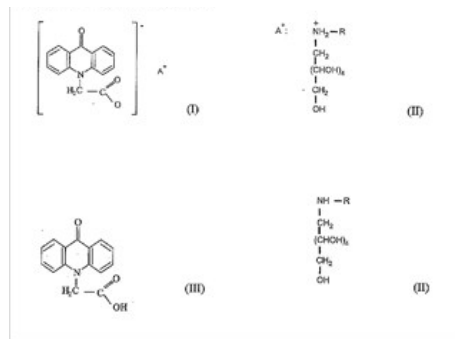
Agent(s): MAIWALD WALTER; HALLYBONE HUW GEORGE; CIMA, LERNER DAVID ET AL; CIMA LERNER DAVID ET AL

Designated states: AE AG AL AM AT AU AZ BA BB BE BF BG BJ BR BW BY BZ CA CF CG CH CI CM CN CO CR CU CY CZ DE DK DM DZ EC EE EG ES FI FR GA GB GD GE GH GM GN GQ GR GW HN HR HU ID IE IL IN IS IT JP KE KG KM KN KP KR KZ LA LC LI LK LR LS LT LU LV LY MA MC MD MG MK ML MN MR MW MX MY MZ NA NE NG NI NL NO NZ OM PG PH PL PT RO RS RU SC SD SE SG SI SK SL SM SN SV SY SZ TD TG TJ TM TN TR TT TZ UA UG US UZ VC VN ZA ZM ZW

Title: SALTS AND MIXTURE OF 9-OXOACRIDINE-10-ACETIC ACID WITH 1-ALKYLAMINO-1-DESOXY-POLYOLS, PHARMACEUTICAL COMPOSITIONS CONTAINING SAID AGENTS AND TREATMENT METHODS

Abstract: Source: US2010144780A The invention relates to salts of 1-alkylamino-1-deoxypolyols and 9-oxoacridine-10-acetic acid of the general (I)





Publication number	Publication date	Application number	Application date
AT486852 E	20101115	AT20060843969T	20061117
BRPI0620530 A2	20111116	BR2006PI20530	20061117
CA2631166 AA	20080520	CA20062631166	20061117
CN101370783 A	20090218	CN200780002701	20071117
CN101370783 B	20130327	CN200780002701	20061117
CN101370783 B	20130327	CN200780002701	20071117
DE602006018065 D1	20101216	DE200660018065T	20061117
DK1970372 T3	20110207	DK20060843969T	20061117
EP1970372 A2	20080917	EP20060843969	20061117
EP1970372 B1	20101103	EP20060843969	20061117
ES2355435 T3	20110325	ES20060843969T	20061117
IN03022CN2008 A	20090306	IN2008CN03022	20080616
KR20080071182 A	20080801	KR20087014671	20080617
MX2008006545 A1	20090116	MX20080006545	20080521
NO200802727 A	20080820	NO20080002727	20080619
RU2005136819 A	20070527	RU20050136819	20051121
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SI1970372 T1	20110429	SI20060030895T	20061117
UA93529 C2	20110225	UA20080008260	20061117
US2010144780 AA	20100610	US20060094479	20061117
US7846939 BB	20101207	US20060094479	20061117
WO07058568 A2	20070524	WO2006RU00614	20061117
WO07058568 A3	20071004	WO2006RU00614	20061117

RU20050136819 20051121 RU20050136819 20051121 WO2006RU00614 20061117
EP20060843969 20061117

Assignee(s): (std): EFAG AO ; EPHAG AS ; SURKOV KIRILL GENNADIEVICH

Assignee(s): M S EPHAG AS

Inventor(s): (std): GENNADIEVICH SURKOV KIRILL ; SURKOV KIRILL GENNADIEVICH

Inventor(s): KIRILL GENNADIEVICH SURKOV

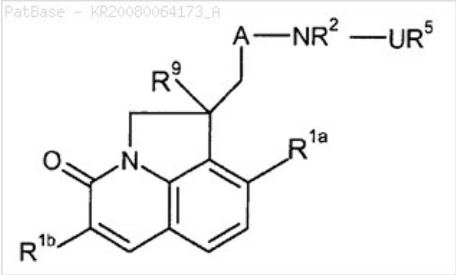
Agent(s): PFAU ANTON KONRAD; FROMMER LAWRENCE AND HAUG; FROMMER LAWRENCE AND HAUG LLP; RONALD R.

Designated states: AE AG AL AM AT AU AZ BA BB BE BF BG BJ BR BW BY BZ CA CF CG CH CI CM CN CO CR CU CY CZ DE DK DM DZ EC EE EG ES FI FR GA GB GD GE GH GM GN GQ GR GT GW HN HR HU ID IE IL IN IS IT JP KE KG KM KN KP KR KZ LA LC LI LK LR LS LT LU LV LY MA MC MD MG MK MN MR MW MX MY MZ NA NE NG NI NL NO NZ OM PG PH PL PT RO RS RU SC SD SE SG SI SK SL SM SN SV SY SZ TD TG TJ TM TN TR TT TZ UA UG US UZ VC VN ZA ZM ZW

Title: COMPOUNDS

Abstract: Source: US2008221110A Tricyclic nitrogen containing compounds and their use as **antibacterials**

Classifications:
International (IPC 8-9): A61K31/473 A61P31/04 C07D497/04 C07D498/04 A61K31/00 A61K31/436 A61K31/437 A61K31/4745 A61K31/495 A61K31/5025 A61K31/5365 A61K31/5383 A61K31/542 A61P31/00 C07D237/26 C07D471/04 C07D471/06 C07D491/056 C07D513/04 C07D519/00 (Advanced/Invention); A61K31/436 A61P31/00 C07D471/06 C07D519/00 (Advanced/Non-invention); A61K31/00 A61K31/4738 A61K31/5025 A61K31/5375 A61K31/542 A61P31/00 C07D471/00 C07D491/00 C07D519/00 (Core/Invention); A61K A61P C07D (Subclass/Invention)
International (IPC 1-7): A61K31/436 A61K31/437 A61K31/495 A61K31/542 A61P31/00 A61P31/04 C07D471/04 C07D471/06 C07D519/00
CPC: C07D471/06 C07D519/00
European: C07D471/06 C07D519/00
US: 514/228.2 514/228.200P 514/230.5 514/230.500S 514/248 514/248P 514/248S 514/294 514/294S 544/105 544/105S 544/235 544/235S 544/56 544/56S 546/94 546/94S



Family:

Publication number	Publication date	Application number	Application date
AR057981 AA	20080109	AR2006P104571	20061019
AT458737 E	20100315	AT20060849235T	20061017
AU2006335042 AA	20070719	AU20060335042	20061017
BRPI0617467 A2	20110726	BR2006P117467	20061017
CA2626641 AA	20080418	CA20062626641	20061017
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CY1110137 T1	20150114	CY20101100405T	20100510
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DK1954697 T3	20100614	DK20060849235T	20061017
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HK1118546 A1	20100618	HK20080110046	20080910
HK1118546 A3	20090213	HK20080110046	20080910
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HR20100194 T8	20100630	HR20100000194	20100407
IL190803 A0	20081229	IL20080190803	20080410
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NZ567315 A	20110128	NZ20060567315	20061017
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PT1954697 T	20100517	PT20060849235T	20061017
SI1954697 T1	20100531	SI20060030624T	20061017
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TW200736263 A	20071001	TW20060138495	20061019
US2008221110 AA	20080911	US20060550005	20061017
US2008280892 AA	20081113	US20060090947	20061017
WO07081597 A2	20070719	WO2006US60023	20061017
WO07081597 A3	20080612	WO2006US60023	20061017
ZA200803275 A	20090225	ZA20080003275	20080414

Priority:
US20050728975P 20051021 US20050728975 20051021 US20060826590P 20060922
WO2006US60023 20061017 US20060550005 20061017 US20060090947 20061017
EP20060849235 20061017

Probable Assignee: GLAXO GROUP LTD

Assignee(s): (std): GLAXO GROUP LTD ; HENNESSY ALAN JOSEPH ; MILES TIMOTHY JAMES ; MARKWELL ROGER EDWARD ; PEARSON NEIL DAVID ; KUSALAKUMARI SUKUMAR SENTHIL K ; KUSALAKUMARI SUKUMAR SENTHIL KUMAR ; CAILLEAU NATHALIE ; DAVIES DAVID THOMAS ; ESKEN JOEL MICHAEL ; GLAXO GROUP LIMIDED

Assignee(s): GLAXO GROUP LIMITED

Inventor(s): (std): DAVIES DAVID ; DAVIES DAVID THOMAS ; EDWARD MARKWELL ROGER ; ESKEN JOEL ; ESKEN JOEL MICHAEL ; HENNESSY ALAN ; HENNESSY ALAN JOSEPH ; JAMES MILES TIMOTHY ; JOSEPH HENNESSY ALAN ; KUMAR KUSALAKUMARI SUKUMAR SENTHIL ; KUSALAKUMARI SUKUMAR SENTHIL ; KUSALAKUMARI SUKUMAR SENTHIL K ; KUSALAKUMARI SUKUMAR SENTHIL KUMAR ; MARKWELL ROGER ; MARKWELL ROGER EDWARD ; MICHAEL ESKEN JOEL ; MILES TIMOTHY ; MILES TIMOTHY JAMES ; NATHALIE CAILLEAU ; PEARSON NEIL ; PEARSON NEIL DAVID ; SUKUMAR SENTHIL KUMAR KUSALAKU ; SUKUMAR SENTHIL KUMAR KUSALAKUMARI ; THOMAS DAVIES DAVID ; CAILLEAU NATHALIE ; DAVID PEARSON NEIL

Inventor(s): DAVID THOMAS DAVIES ; ALAN JOSEPH HENNESSY ; TIMOTHY JAMES MILES ; ROGER EDWARD MARKWELL ; SENTHIL KUMAR KUSALAKUMARI SUKUMAR ; NEIL DAVID PEARSON ; JOEL MICHAEL ESKEN ; ESKEN JOEL MICHAEL

Agent(s): VALENTINE JILL BARBARA; GLAXOSMITHKLINE, CORPORATE INTELLECTUAL PROPERTY - UW2220; GLAXOSMITHKLINE CORPORATE INTELLECTUAL PROPERTY UW2220; SMITHKLINE BEECHAM CORPORATE INTELLECTUAL PROPERTY US UW2220 CORP

Designated states: AE AG AL AM AT AU AZ BA BB BE BF BG BJ BR BW BY BZ CA CF CG CH CI CM CN CO CR CU CY CZ DE DK DM DZ EC EE EG ES FI FR GA GB GD GE GH GM GN GQ GR GT GW HN HR HU ID IE IL IN IS IT JP KE KG KM KN KP KR KZ LA LC LI LK LR LS LT LU LV LY MA MC MD MG MK ML MN MR MW MX MY MZ NA NE NG NI NL NO NZ OM PG PH PL PT RO RS RU SC SD SE SG SI SK SL SM SN SV SY SZ TD TG TJ TM TN TR TT TZ UA UG US UZ VC VN ZA ZM ZW

Title: METHODS OF WOUND CARE AND TREATMENT

Abstract: Source: US2008139674A Particular embodiments disclosed herein relate to gas-enriched fluids, methods of making the same, systems for making the same and/or methods of treatment utilizing the gas-enriched fluids for wound care related conditions and/or diseases. In certain embodiments, the gas-enriched fluid is oxygen-enriched water. Certain embodiments relate to cosmetic and/or therapeutic fluids and/or methods of treatment utilizing the fluids in order to treat a cosmetic and/or therapeutic symptom of wound care and/or increase proper wound healing.

Classifications:

International (IPC 8-9): A01N A01N1/02 A01N39/00 A23L2/38 A61F13/00 A61F9/007 A61J3/00 A61K A61K31/00 A61K31/135 A61K31/137 A61K31/138 A61K31/19 A61K31/192 A61K31/195 A61K31/196 A61K31/197 A61K31/198 A61K31/22 A61K31/27 A61K31/337 A61K31/365 A61K31/40 A61K31/405 A61K31/4152 A61K31/427 A61K31/43 A61K31/431 A61K31/436 A61K31/445 A61K31/4525 A61K31/4535 A61K31/4706 A61K31/473 A61K31/475 A61K31/496 A61K31/519 A61K31/522 A61K31/53 A61K31/5383 A61K31/5415 A61K31/545 A61K31/546 A61K31/56 A61K31/573 A61K31/58 A61K31/616 A61K31/63 A61K31/662 A61K31/70 A61K31/702 A61K31/7036 A61K31/704 A61K31/7048 A61K31/7052 A61K31/7135 A61K31/728 A61K31/74 A61K31/785 A61K33/00 A61K33/08 A61K33/14 A61K33/24 A61K33/40 A61K35/02 A61K38/00 A61K38/02 A61K38/12 A61K38/16 A61K38/21 A61K39/395 A61K41/00 A61K45/00 A61K45/06 A61K47/00 A61K47/02 A61K47/04 A61K50/00 A61K9/00 A61K9/08 A61K9/10 A61K9/14 A61K9/16 A61K9/72 A61L A61L15/44 A61L26/00 A61M1/00 A61M35/00 A61P1/00 A61P1/04 A61P1/06 A61P1/08 A61P1/10 A61P1/12 A61P11/00 A61P11/02 A61P11/04 A61P11/06 A61P11/08 A61P11/14 A61P13/12 A61P15/00 A61P17/00 A61P17/02 A61P17/04 A61P17/06 A61P17/08 A61P19/00 A61P19/02 A61P19/08 A61P21/00 A61P21/02 A61P25/00 A61P25/06 A61P25/14 A61P25/16 A61P25/28 A61P27/02 A61P27/06 A61P27/08 A61P27/14 A61P29/00 A61P3/00 A61P3/10 A61P31/00 A61P31/04 A61P31/06 A61P31/12 A61P31/16 A61P31/18 A61P35/00 A61P37/00 A61P37/06 A61P37/08 A61P39/00 A61P39/02 A61P43/00 A61P5/00 A61P9/00 A61P9/10 B01F B01F15/02 B01F3/00 B01F3/02 B01F3/04 B01F3/08 B01F5/00 B01F5/06 B01F7/00 B01F7/02 B01F7/12 B29D11/00 B32B27/04 B32B5/02 B82Y5/00 C02F1/46 C09K3/00 C12M1/02 C12M1/04 C12M3/00 C12N C12N1/14 C12N1/20 C12N13/00 C12N5/00 C12N5/02 C12N5/04 C12N5/07 C12N5/071 C12N5/078 C12N5/0783 C12N5/0787 C12N5/08 C12N9/04 C12P7/24 C12Q C12Q1/68 C25B15/08 C25B9/14 G01N G01N33/68 G02C13/00 G02C7/02 G02C7/04 G05D11/13 (Advanced/Invention);

A61F13/00 A61L12/08 B82Y30/00 B82Y5/00 C07K14/47 C07K14/705 C07K16/00 C12M1/34 C12N15/09 C12N9/02 C12P7/26 (Advanced/Non-invention); A61F9/007 A61K31/137 A61K31/21 A61K31/40 A61K31/427 A61K31/429 A61K31/496 A61K31/5375 A61K31/545 A61K31/546 A61K31/56 A61K31/58 A61K31/70 A61K31/7028 A61K31/7042 A61K31/74 A61K33/00 A61K33/14 A61K38/12 A61K38/16 A61K38/21 A61K39/395 A61K45/00 A61K47/00 A61K9/00 A61K9/14 A61M1/00 A61M35/00 A61P1/00 A61P11/00 A61P17/00 A61P19/00 A61P25/00 A61P27/00 A61P29/00 A61P31/00 A61P35/00 B01F3/00 B01F3/04 B01F3/08 B01F7/00 B01F7/02 B32B27/04 B32B5/02 C12N5/00 C12N5/02 C12N5/08 C12Q1/68 C25B15/00 C25B9/12 G02C7/02 G02C7/04 G05D11/00 (Core/Invention); C12N15/09 C12N9/02 (Core/Non-invention); A61K A61M B01F B32B C12N C12Q (Subclass/Invention)

International (IPC 1-7): A61K39/395 A61K45/00 A61K47/00 A61M1/00 B01F7/12 G02C7/02

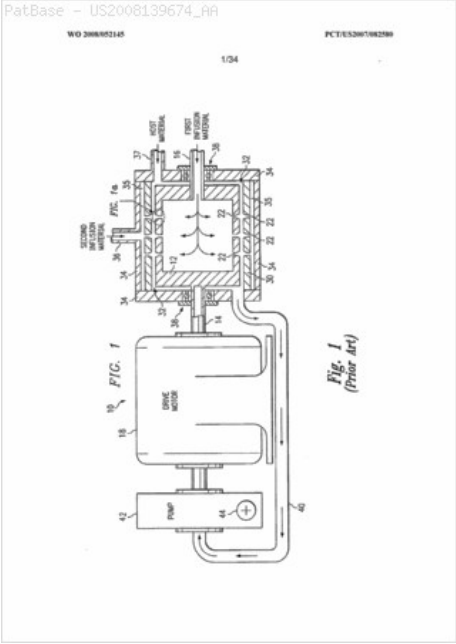
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Probable Assignee: REVALESIO CORP

Assignee(s): (std): ARCHAMBEAU GREGORY J ; REVALESIO CORP ; REVALESIO VORPORATION ; REVALESION CORP ; WATSON RICHARD L ; WOOD ANTHONY B

Inventor(s): (std): ANTHONY B WOOD ; ARCHAMBEAU GREGORY J ; GREGORY J ARCHAMBEAU ; RICHARD L WATSON ; WATSON RICHARD L ; WOOD ANTHONY B

Inventor(s): NA

Agent(s): HARTIG MICHAEL; GOWSHALL JONATHAN VALLANCE; TEALL CHARLOTTE; DAVIS WRIGHT TREMAINE LLP SEATTLE; DAVIS WRIGHT TREMAINE LLP; BARRY L; DAVISON BARRY L ET AL

Designated states: AE AG AL AM AO AT AU AZ BA BB BE BF BG BH BJ BR BW BY BZ CA CF CG CH CI CL CM CN CO CR CU CY CZ DE DK DM DO DZ EC EE EG ES FI FR GA GB GD GE GH GM GN GQ GR GT GW HN HR HU ID IE IL IN IS IT JP KE KG KM KN KP KR KZ LA LC LI LK LR LS LT LU LV LY MA MC MD ME MG MK ML MN MR MT MW MX MY MZ NA NE NG NI NL NO NZ OM PE PG PH PL PT RO RS RU SC SD SE SG SI SK SL SM SN ST SV SY SZ TD TG TH TJ TM TN TR TT TZ UA UG US UZ VC VN ZA ZM ZW

Title: AGENT FOR DEGRADING A NUCLEIC ACID AND METHOD OF DEGRADING A NUCLEIC ACID

Abstract: Source: US2010170777A The present invention provides an agent for degrading a nucleic acid, which includes ethidium monoazide as an active ingredient, and is useful as an **antibacterial** agent such as a bactericide or a disinfectant.

Classifications:

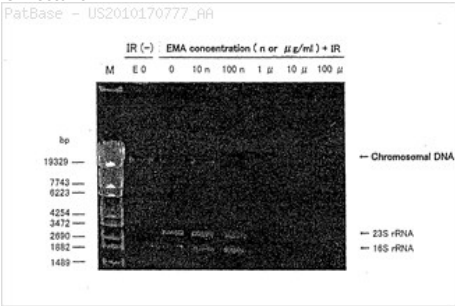
International (IPC 8-9): A01N33/04 A01N33/26 A01N43/34 A01N43/42 A01P3/00 A61K31/435 A61K31/473 A61K41/00 A61L12/00 A61L2/08 A61L2/16 A61P31/04 C07D221/12 (Advanced/Invention); A01N33/26 A61K31/473 A61K41/00 A61P31/04 (Advanced/Non-invention); A01N33/00 A01N43/34 A01P3/00 A61K31/435 A61K31/473 A61K41/00 A61L12/00 A61L2/08 A61L2/16 A61P31/00 C07D221/00 (Core/Invention); A61K31/473 A61K41/00 A61P31/00 (Core/Non-invention)

International (IPC 1-7): A01N43/42

CPC: A01N43/42 A61K31/473 A61K41/00H6

European: A01N43/42 A61K31/473 A61K41/00H6

US: 204/157.15 204/157.150P 514/298 514/298S 546/108 546/108S



Family:

Publication number	Publication date	Application number	Application date
AU2007302638 AA	20080619	AU20070302638	20070717
AU2007302638 BB	20100902	AU20070302638	20070717
CA2633591 AA	20080506	CA20072633591	20070717
CA2633591 C	20110215	CA20072633591	20070717
CN101378657 A	20090304	CN200780004456	20070717
CN101378657 B	20120530	CN200780004456	20070717
CN102389577 A	20120328	CN201110224527	20070717
EP2090169 A1	20090819	EP20070790835	20070717
EP2090169 A4	20100210	EP20070790835	20070717
IN02190CN2008 A	20090306	IN2008CN02190	20080502
JP2008137962 A2	20080619	JP20060326825	20061204
JP4113556 B2	20080709	JP20060326825	20061204
KR101017811 B1	20110228	KR20087011899	20070717
KR20080088581 A	20081002	KR20087011899	20080519
NO20082129 A	20080828	NO20080002129	20080507
RU2008124804 A	20091227	RU20080124804	20070717
RU2388473 C2	20100510	RU20080124804	20070717
US2010170777 AA	20100708	US20070092677	20070717
WO08068923 A1	20080612	WO2007JP64073	20070717

Priority:
JP20060326825 20061204 WO2007JP64073 20070717

Probable Assignee: MORINAGA MILK IND CO LTD

Assignee(s): (std): MORINAGA MILK IND CO LTD ; MORINAGA MILK INDUSTRY CO LTD ; YOSHIDA SHINICHI ; SOEJIMA TAKASHI ; UNIV KYUSHU ; MORINAGA MILK INDASTRI KO LTD

Assignee(s): MORINAGA MILK INDUSTRY CO ; MORINAGA MILK INDASTRI KO ; KYUSHU UNIV ; MORINAGA MILK IND CO

Inventor(s): (std): ESIDA SINITI ; SOEDZIMA TAKASI ; SOEJIMA TAKASHI ; YOSHIDA SHINICHI ; TAKASHI SOEJIMA ; SHINICHI YOSHIDA

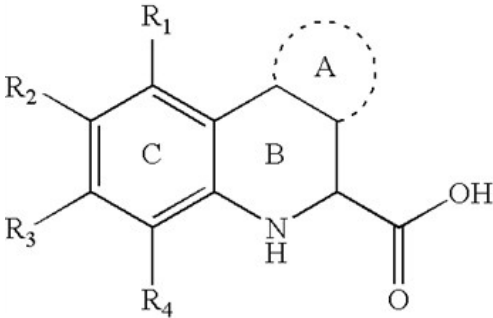
Agent(s): BANNERMAN DAVID GARDNER; KNOBBE MARTENS OLSON AND BEAR LLP; KAWAGUCHI YOSHIYUKI ET AL

Designated states: AE AG AL AM AT AU AZ BA BB BE BF BG BH BJ BR BW BY BZ CA CF CG CH CI CM CN CO CR CU CY CZ DE DK DM DO DZ EC EE EG ES FI FR GA GB GD GE GH GM GN GQ GR GT GW HN HR HU ID IE IL IN IS IT KE KG KM KN KP KR KZ LA LC LI LK LR LS LT LU LV LY MA MC MD ME MG MK ML MN MR MT MW MX MY MZ NA NE NG NI NL NO NZ OM PG PH PL PT RO RS RU SC SD SE SG SI SK SL SM SN SV SY SZ TD TG TJ TM TN TR TT TZ UA UG US UZ VC VN ZA ZM ZW

Title: SUBSTITUTED TETRAHYDROQUINOLINES AS ANTIBACTERIAL AGENTS

Abstract: Source: US2009203726A A method of treating a subject for a bacterial infection includes administering to a subject in need of treatment for a bacterial infection an effective amount of a compound represented by structural formula (I-a), or a pharmaceutically acceptable

I-a



salt, solvate, or hydrate thereof.
structural formula (I-a) are described herein.

Classifications:
International (IPC 8-9): A61K31/473 A61P31/04 C07D215/02 C07D215/04 C07D221/06 (Advanced/Invention);
A61K31/473 A61P31/00 C07D215/00 C07D221/00 (Core/Invention)
CPC: C07D221/16
European: C07D221/16
US: 514/290 546/79

The variables in



Family:

Publication number	Publication date	Application number	Application date
US2009203726 AA	20090813	US20080324496	20081126
WO09073550 A2	20090611	WO2008US84963	20081126
WO09073550 A3	20090730	WO2008US84963	20081126

Priority:

US20070991535P 20071130 US20080324496 20081126

Probable Assignee: BIOTA SCIENTIFIC MANAGEMENT PTY LTD

Assignee(s): (std): FRECHETTE ROGER ; MAXTHERA INC

Assignee(s): BIOTA SCIENTIFIC MANAGEMENT PTY LTD

Inventor(s): (std): FRECHETTE ROGER

Agent(s): MCCARTER AND ENGLISH LLP BOSTON; HANLEY ELIZABETH A ET AL

Designated states: AE AG AL AM AO AT AU AZ BA BB BE BF BG BH BJ BR BW BY BZ CA CF CG CH CI CM CN CO CR CU CY CZ DE DK DM DO DZ EC EE EG ES FI FR GA GB GD GE GH GM GN GQ GR GT GW HN HR HU ID IE IL IN IS IT JP KE KG KM KN KP KR KZ LA LC LK LR LS LT LU LV LY MA MC MD ME MG MK ML MN MR MW MX MY MZ NA NE NG NI NL NO NZ OM PG PH PL PT RO RS RU SC SD SE SG SI SK SL SM SN ST SV SY SZ TD TG TJ TM TN TR TT TZ UA UG US UZ VC VN ZA ZM ZW

Title: MEDICINE FOR TREATMENT OF ANIMALS WITH PUERPERAL ENDOMETRITIS

Abstract: Source: RU2367416C

FIELD: veterinary science.

SUBSTANCE: invention relates to veterinary science, precisely to obstetrics, genecology and biotechnology of reproduction, mainly to medicines for treatment of animals with puerperal endometritis. The medicine contains ethacridine lactate - 0.6, aloe - 50.4; cephatoxime - 2, urea - 15.0; neutral formalin - 10; distilled water - 5; glycerine - 17.0.

EFFECT: medicine has anti-inflammatory and **antibacterial** effects.

2 tbl

Classifications:

International (IPC 8-9): A61K31/047 A61K31/115 A61K31/17 A61K31/473 A61K36/886 A61P15/00 (Advanced/Invention); A61K31/045 A61K31/11 A61K31/17 A61K31/473 A61K36/88 A61P15/00 (Core/Invention)

Family:

Publication number	Publication date	Application number	Application date
RU2367416 C1	20090920	RU20080124999	20080619

Priority:

RU20080124999 20080619

Probable Assignee: FGOU VPO DONSKOJ G AGRARNYJ UN

Assignee(s): (std): FGOU VPO DONSKOJ G AGRARNYJ UN

Assignee(s): FGOU VPO DONSKOJ GOSUDARSTVENNYJ AGRARNYJ UNIVERSITET

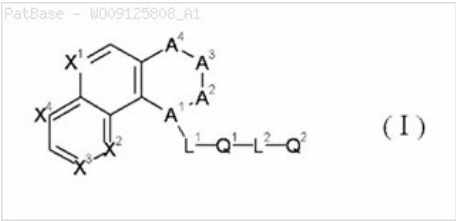
Inventor(s): (std): GRITSENKO BORIS PAVLOVICH ; KARNAUKHOVA OL GA MIKHAJLOVNA ; NIZHEL SKAJA ELENA IVANOVNA ; STEPANENKO NIKITA VLADIMIROVICH ; VERBINA EKATERINA BORISOVNA ; VOJTENKO LJUBOV GENNAD EVNA

Inventor(s): VOJTENKO LJUBOV' GENNAD'EVNA ; NIZHEL'SKAJA ELENA IVANOVNA ; KARNAUKHOVA OL'GA MIKHAJLOVNA

Title: AMINOCYCLOHEXYL DERIVATIVE

Abstract: It has been demanded to develop a substance which has a potent and wide-spectrum anti-bacterial activity against gram-positive bacteria, gram-negative bacteria and resistant bacteria thereof and is highly safe. Under these circumstances, extensive studies have been made, and it is now found that a compound represented by formula (I) or a salt thereof has a potent and wide-spectrum **antibacterial** activity against gram-positive bacteria and gram-negative bacteria and also has high safety at a level suitable for use as an **antibacterial** agent or a prophylactic or therapeutic agent for infectious diseases. Thus, disclosed is a compound represented by formula (I), a pharmacologically acceptable salt thereof, or a hydrate of the compound or the salt.

Classifications:
International (IPC 8-9): A61K31/4353 A61K31/4375 A61K31/473 A61K31/5383 A61K31/542 A61P31/04 C07D401/06 C07D413/14 C07D471/04 C07D498/04 C07D519/00 (Advanced/Invention); A61P31/04 (Advanced/Non-invention); A61K31/4353 A61K31/4375 A61K31/5383 A61P31/04 C07D471/04 C07D498/04 (Core/Non-invention)
CPC: C07D498/04
European: C07D498/04



Family:

Publication number	Publication date	Application number	Application date
TW200948817 A	20091201	TW20090111915	20090410
WO09125808 A1	20091015	WO2009JP57244	20090409

Priority:
JP20080103854 20080411

Probable Assignee: DAIICHI SANKYO CO LTD

Assignee(s): (std): FUJISAWA TETSUNORI ; HAYAKAWA MIHO ; INAGAKI HIROAKI ; ITOH MASAO ; TSUDA TOSHIFUMI ; DAIICHI SANKYO CO LTD

Assignee(s): DAIICHI SANKYO COMPANY LIMITED

Inventor(s): (std): FUJISAWA TETSUNORI ; HAYAKAWA MIHO ; INAGAKI HIROAKI ; ITOH MASAO ; TSUDA TOSHIFUMI

Agent(s): ISHIBASHI KOKI ET AL

Designated states: AE AG AL AM AO AT AU AZ BA BB BE BF BG BH BJ BR BW BY BZ CA CF CG CH CI CM CN CO CR CU CY CZ DE DK DM DO DZ EC EE EG ES FI FR GA GB GD GE GH GM GN GQ GR GT GW HN HR HU ID IE IL IN IS IT JP KE KG KM KN KP KR KZ LA LC LK LR LS LT LU LV LY MA MC MD ME MG MK ML MN MR MT MW MX MY MZ NA NE NG NI NL NO NZ OM PG PH PL PT RO RS RU SC SD SE SG SI SK SL SM SN ST SV SY SZ TD TG TJ TM TN TR TT TZ UA UG US UZ VC VN ZA ZM ZW

Title: COMPOSITIONS FOR THE TREATMENT OF VAGINAL INFECTIONS WITH CHRONIC INFLAMMATION

Abstract: Source: US2011104313A The present invention relates to compositions comprising benzofuran compounds and benzophenanthridine alkaloids, which possess anti-inflammatory, **antibacterial** and antifungal activity useful in the treatment of vaginal infections and the resulting inflammatory states.

Classifications:
International (IPC 8-9): A61K A61K31/343 A61K31/473 A61K31/4741 A61K36/18 A61K36/185 A61K36/28 A61K36/66 A61K36/75 A61K36/758 A61K9/02 A61K9/06 A61K9/08 A61K9/107 A61K9/14 A61K9/48 A61P13/00 A61P15/02 A61P29/00 A61P31/00 A61P31/04 A61P31/10 A61P43/00 C07D307/77 C07D307/78 (Advanced/Invention);
A61K31/343 A61P13/00 C07D307/77 C07D307/78 (Advanced/Non-invention);
A61K31/343 A61K31/473 (Core/Invention);
A61K (Subclass/Invention)
CPC: A61K36/28 A61K31/343 A61K31/473 A61K36/758
European: A61K31/343 A61K31/473 A61K36/28 A61K36/758
US: 424/737 424/737P 424/749 424/749S

Family:

Publication number	Publication date	Application number	Application date	
AT526968 E	20111015	AT20080425421T	20080612	
AU2009240295 AA	20091029	AU20090240295	20090406	
AU2009240295 BB	20140306	AU20090240295	20090406	
CA2722211 AA	20091029	CA20092722211	20090406	
CN102014906 A	20110413	CN200980114022	20090406	
DK2133079 T3	20111212	DK20080425421T	20080612	
EP2133079 A1	20091216	EP20080425421	20080612	
EP2133079 B1	20111005	EP20080425421	20080612	
EP2278971 A1	20110202	EP20090735815	20090406	
ES2371825 T3	20120110	ES20080425421T	20080612	
HK1136203 A1	20111230	HK20100102911	20100319	
IL208849 A0	20110131	IL20100208849	20101021	
IL208849 A1	20150331	IL20100208849	20101021	
IN03945KN2010 A	20111125	IN2010KN03945	20101021	
ITMI20080751 A1	20091025	IT2008MI00751	20080424	
JP2011518793 T2	20110630	JP20110505397T	20090406	
JP5677936 B2	20150225	JP20110505397T	20090406	
KR20100134686 A	20101223	KR20107023537	20101021	
PT2133079 T	20111128	PT20080425421T	20080612	
RU2010143226 A	20120527	RU20100143226	20090406	
RU2504379 C2	20140120	RU20100143226	20090406	
SI2133079 T1	20120131	SI20080030468T	20080612	
US2011104313 AA	20110505	US20090988897	20090406	
WO09129927 A1	20091029	WO2009EP02516	20090406	
WO09129927 A8	20091230	WO2009EP02516	20090406	

Priority:
IT2008MI00751 20080424 EP20080425421 20080612 WO2009EP02516 20090406
EP20090735815 20090406

Probable Assignee: INDENA SPA

Assignee(s): (std): BOMBARDELLI EZIO ; FONTANA GABRIELE ; GIORI ANDREA ; INDENA SPA ; RIVA ANTONELLA ; RONCHI MASSIMO ; MORAZZONI PAOLO

Assignee(s): INDENA S P A

Inventor(s): (std): ANDREA GIORI ; ANTONELLA RIVA ; BOMBARDELLI EHTSIO ; DZHIORI ANDREA ; EZIO BOMBARDELLI ; GABRIELE FONTANA ; MASSIMO RONCHI ; MORATSTSONI PAOLO ; PAOLO MORAZZONI ; RONKI MASSIMO ; RONCHI MASSIMO ; RIVA ANTONELLA ; MORAZZONI PAOLO ; GIORI ANDREA ; FONTANA GABRIELE ; BOMBARDELLI EZIO

Agent(s): MINOJA FABRIZIO; MINOJA FABRIZIO ET AL

Designated states: AE AG AL AM AO AT AU AZ BA BB BE BF BG BH BJ BR BW BY BZ CA CF CG CH CI CM CN CO CR CU CY CZ DE DK DM DO DZ EC EE EG ES FI FR GA GB GD GE GH GM GN GQ GR GT GW HN HR HU ID IE IL IN IS IT JP KE KG KM KN KP KR KZ LA LC LI LR LS LT LU LV LY MA MC MD ME MG MK ML MN MR MT MW MX MY MZ NA NE NG NI NL NO NZ OM PG PH PL PT RO RS RU SC SD SE SG SI SK SL SM SN ST SV SY SZ TD TG TJ TM TN TR TT TZ UA UG US UZ VC VN ZA ZM ZW

Title: COMPOSITIONS FOR THE TREATMENT AND PREVENTION OF INFECTIONS OF THE ORAL CAVITY

Abstract: Source: US2011091392A The present invention relates to compositions comprising benzophenanthridine alkaloids, benzofuran compounds and catechin polyphenols, which are useful in the treatment and prevention of infections of the oral cavity.

Classifications:

International (IPC 8-9): A61K31/343 A61K31/352 A61K31/353 A61K31/4355 A61K31/473 A61K31/4741 A61K36/00 A61K36/18 A61K36/185 A61K36/48 A61K8/49 A61K9/68 A61P1/02 A61P15/02 A61P31/02 C07D307/77 C07D307/78 (Advanced/Invention); A61K31/343 A61P1/02 C07D307/77 C07D307/78 (Advanced/Non-invention); A61K31/00 A61K31/343 (Core/Invention); A61K (Subclass/Invention)

International (IPC 1-7): A61K31/343

CPC: A61K31/343 A61K31/473 A61K45/06

European: A61K31/343 A61K31/473 A61K45/06

US: 424/48 424/48P 424/49 424/49S 424/58 424/725 424/734 424/749 424/776 424/777 424/778 424/779 514/279 514/279S 514/280 514/280S

Family:

Publication number	Publication date	Application number	Application date
AT550021 E	20120415	AT20080425422T	20080612
AU2009240294 AA	20091029	AU20090240294	20090406
AU2009240294 BB	20140410	AU20090240294	20090406
CA2722209 AA	20091029	CA20092722209	20090406
CN102014892 A	20110413	CN200980114023	20090406
DK2133076 T3	20120529	DK20080425422T	20080612
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EP2133076 B1	20120321	EP20080425422	20080612
EP2268276 A1	20110105	EP20090735454	20090406
ES2383223 T3	20120619	ES20080425422T	20080612
HK1136775 A1	20120803	HK20100102912	20100319
HR20120342 T1	20120531	HR20120000342	20120417
IL208848 A0	20110131	IL20100208848	20101021
IL208848 A1	20130627	IL20100208848	20101021
IN03946KN2010 A	20101224	IN2010KN03946	20101021
ITMI20080746 A1	20091025	IT2008MI00746	20080424
JP2011518792 T2	20110630	JP20110505396T	20090406
KR20100134685 A	20101223	KR20107023536	20101021
PT2133076 T	20120530	PT20080425422T	20080612
RU2010143220 A	20120527	RU20100143220	20090406
RU2504378 C2	20140120	RU20100143220	20090406
SI2133076 T1	20120629	SI20080030634T	20080612
US2011091392 AA	20110421	US20090988870	20090406
US8496975 BB	20130730	US20090988870	20090406
WO09129926 A1	20091029	WO2009EP02515	20090406
WO09129926 A8	20091230	WO2009EP02515	20090406

Priority:

IT2008MI00746 20080424 EP20080425422 20080612 WO2009EP02515 20090406

EP20090735454 20090406

Probable Assignee: INDENA SPA

Assignee(s): (std): BOMBARDELLI EZIO ; FONTANA GABRIELE ; GIORI ANDREA ; INDENA SPA ; RIVA ANTONELLA ; RONCHI MASSIMO ; MORAZZONI PAOLO

Assignee(s): INDENA S P A

Inventor(s): (std): ANDREA GIORI ; ANTONELLA RIVA ; BOMBARDELLI EHTSIO ; BOMBARDELLI EZIO ; DZHIORI ANDREA ; EZIO BOMBARDELLI ; FONTANA GABRIELE ; GABRIELE FONTANA ; GIORI ANDREA ; MASSIMO RONCHI ; MORATSTSONI PAOLO ; MORAZZONI PAOLO ; PAOLO MORAZZONI ; RIVA ANTONELLA ; RONCHI MASSIMO ; RONKI MASSIMO

Agent(s): MINOJA FABRIZIO; LUCAS AND MERCANTI LLP; MINOJA FABRIZIO ET AL

Designated states: AE AG AL AM AO AT AU AZ BA BB BE BF BG BH BJ BR BW BY BZ CA CF CG CH CI CM CN CO CR CU CY CZ DE DK DM DO DZ EC EE EG ES FI FR GA GB GD GE GH GM GN GQ GR GT GW HN HR HU ID IE IL IN IS IT JP KE KG KM KN KP KR KZ LA LC LI LK LR LS LT LU LV LY MA MC MD ME MG MK ML MN MR MT MW MX MY MZ NA NE NG NI NL NO NZ OM PG PH PL PT RO RS RU SC SD SE SG SI SK SL SM SN ST SV SY SZ TD TG TJ TM TN TR TT TZ UA UG US UZ VC VN ZA ZM ZW

Title: COMPOSITIONS FOR THE TREATMENT OF DISORDERS OF THE UPPER RESPIRATORY TRACT AND INFLUENZA SYNDROMES

Abstract: Source: US2011135769A The present invention relates to compositions based on benzophenanthridine alkaloids, extract of Hippophae rhamnoides and extract of Echinacea angustifolia which possess **antibacterial**, antiviral and anti-inflammatory activity, and are useful in the treatment of bacterial and viral infections of the upper respiratory tract, and in the treatment of influenza.

Classifications:

International (IPC 8-9): A61K31/366 A61K31/4355 A61K31/473 A61K36/00 A61K36/18 A61K36/185 A61K36/28 A61K36/36 A61K36/66 A61K9/06 A61K9/08 A61K9/20 A61K9/68 A61P11/00 A61P29/00 A61P31/04 A61P31/12 A61P31/16 (Advanced/Invention); A61K31/00 A61K31/473 A61K36/00 A61K36/185 A61P11/00 A61P31/00 (Core/Invention); A61K (Subclass/Invention)

International (IPC 1-7): A61K36/66

CPC: A61K36/66 A61K36/36 A61K31/473 A61K36/185 A61K36/28

European: A61K31/473 A61K36/185 A61K36/28 A61K36/36 A61K36/66

US: 424/764 424/764P

Family:

Publication number	Publication date	Application number	Application date	
AU2009254262 AA	20091210	AU20090254262	20090525	
AU2009254262 BB	20140213	AU20090254262	20090525	
CA2726872 AA	20091210	CA20092726872	20090525	
CN102056614 A	20110511	CN200980120908	20090525	
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EP2285393 A1	20110223	EP20090757190	20090525	
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ES2393239 T3	20121219	ES20090757190T	20090525	
HK1157662 A3	20120706	HK20110112154	20111110	
HR20120874 T1	20121130	HR20120000874	20121030	
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IL209714 A1	20140227	IL20100209714	20101202	
IN04632KN2010 A	20110204	IN2010KN04632	20101206	
ITMI20081029 A1	20091206	IT2008MI01029	20080605	
JP2011521982 T2	20110728	JP20110512001T	20090525	
KR20110027671 A	20110316	KR20107027256	20090525	
PT2285393 T	20121129	PT20090757190T	20090525	
RU2010153660 A	20120720	RU20100153660	20090525	
RU2518738 C2	20140610	RU20100153660	20090525	
SI2285393 T1	20121231	SI20090030377T	20090525	
US2011135769 AA	20110609	US20090996159	20090525	
WO09146807 A1	20091210	WO2009EP03673	20090525	
WO09146807 A8	20100204	WO2009EP03673	20090525	

Priority:

IT2008MI01029 20080605 EP20080425420 20080612 WO2009EP03673 20090525
EP20090757190 20090525

Probable Assignee: INDENA SPA

Assignee(s): (std): BOMBARDELLI EZIO ; INDENA SPA

Assignee(s): INDENA S P A

Inventor(s): (std): BOMBARDELLI EHTSIO ; BOMBARDELLI EZIO ; EZIO BOMBARDELLI

Agent(s): MINOJA FABRIZIO; MINOJA FABRIZIO ET AL

Designated states: AE AG AL AM AO AT AU AZ BA BB BE BF BG BH BJ BR BW BY BZ CA CF CG CH CI CM CN CO CR CU CY CZ DE DK DM DO DZ EC EE EG ES FI FR GA GB GD GE GH GM GN GQ GR GT GW HN HR HU ID IE IL IN IS IT JP KE KG KM KN KP KR KZ LA LC LI LK LR LS LT LU LV LY MA MC MD ME MG MK ML MN MR MT MW MX MY MZ NA NE NG NI NL NO NZ OM PG PH PL PT RO RS RU SC SD SE SG SI SK SL SM SN ST SV SY SZ TD TG TJ TM TN TR TT TZ UA UG US UZ VC VN ZA ZM ZW

Title: TOPICAL COMPOSITIONS COMPRISING 5-ALPHA REDUCTASE INHIBITORS

Abstract: Source: US2010048598A The present invention relates to topical compositions comprising 5a-reductase inhibitors. The present invention also includes processes for preparation of such topical compositions and methods of using them.

Classifications:

International (IPC 8-9): A61K31/00 A61K31/473 A61K31/506 (Advanced/Invention)

CPC: A61K9/0014 A61K9/06 A61K9/1075 A61K9/12 A61K31/473 A61K31/506

European: A61K31/473 A61K31/506 A61K9/00M3 A61K9/06 A61K9/107D A61K9/12

US: 514/275 514/284 514/284S

Family:

Publication number	Publication date	Application number	Application date	
IN02033CH2008 A	201111007	IN2008CH02033	20080821	
US2010048598 AA	20100225	US20090544737	20090820	

Priority:

IN2008CH02033 20080821 US20080106733P 20081020 US20090544737 20090820

Probable Assignee: DR REDDY S LABORATORIES INC

Assignee(s): (std): KANDAVILLI SATEESH ; PANDYA VISHVABHAVAN ; NALAMOTHU VIJENDRA

Assignee(s): DR REDDY S LABORATORIES INC ; DR REDDY S LABORATORIES LTD ; DR REDDY'S LABORATORIES INC ; DR REDDY'S LABORATORIES LTD

Inventor(s): (std): KANDAVILLI SATEESH ; NALAMOTHU VIJENDRA ; PANDYA VISHVABHAVAN

Inventor(s): VIJENDRA NALAMOTHU ; VISHVABHAVAN PANDYA ; SATESSH KANDAVILLI

Agent(s): DR REDDYS LABORATORIES INC

Title: PHARMACEUTICAL TOPICAL COMPOSITIONS

Abstract: Source: US2011263646A The invention provides pharmaceutical stable semisolid topical compositions comprising between 0.2 to 5 percent of a des-fluoroquinolone compound, and a suitable carrier to manufacture an ointment or a cream.

Classifications:

International (IPC 8-9): A61K31/01 A61K31/03 A61K31/122 A61K31/13 A61K31/185 A61K31/192 A61K31/47 A61K31/4709 A61K31/473 A61K47/06 A61K47/08 A61K47/10 A61K47/12 A61K47/14 A61K47/24 A61K47/34 A61K47/44 A61K9/06 A61K9/107 A61P11/00 A61P11/02 A61P15/00 A61P17/00 A61P31/00 A61P31/04 C07D215/233 C07D401/10 (Advanced/Invention); A61K31/4709 A61K9/06 A61P17/00 A61P31/04 (Advanced/Non-invention); A61K31/00 A61K31/4709 A61K9/00 A61K9/06 (Core/Invention); A61K (Subclass/Invention)

International (IPC 1-7): A61K31/4709 A61K9/06 A61P17/00 A61P31/04

CPC: A61K47/44 A61K31/4709 A61K47/12 A61K47/10 A61K47/14 A61K9/06 A61K9/0014 A61K47/06

European: A61K9/00M3 A61K9/06

US: 514/312 514/314

Family:

Publication number	Publication date	Application number	Application date	
AR073901 AA	20101209	AR2009P104005	20091019	
AU2009305360 AA	20100422	AU20090305360	20091016	
AU2009305360 BB	20150409	AU20090305360	20091016	
CA2738384 AA	20100422	CA20092738384	20091016	
CA2738384 C	20140708	CA20092738384	20091016	
CA2822167 AA	20100422	CA20092822167	20091016	
CN102186460 A	20110914	CN200980140860	20091016	
CN102186460 B	20130612	CN200980140860	20091016	
DK2344130 T3	20131209	DK20090736946T	20091016	
EP2177208 A1	20100421	EP20080166933	20081017	
EP2344130 A2	20110720	EP20090736946	20091016	
EP2344130 B1	20130904	EP20090736946	20091016	
EP2344130 B9	20131120	EP20090736946	20091016	
EP2570117 A1	20130320	EP20120192559	20091016	
ES2437967 T3	20140115	ES20090736946T	20091016	
HK1161552 A1	20140321	HK20120101885	20120224	
HK1161552 A3	20120727	HK20120101885	20120224	
IN01193KN2011 A	20110624	IN2011KN01193	20110321	
JP2012505867 T2	20120308	JP20110531512T	20091016	
JP2014088456 A2	20140515	JP20140031852	20140221	
JP5509209 B2	20140604	JP20110531512T	20091016	
KR20110071086 A	20110628	KR20117008243	20091016	
MX2011004052 A1	20110510	MX20110004052	20110415	
PT2344130 T	20131209	PT20090736946T	20091016	
RU2011119764 A	20121127	RU20110119764	20091016	
RU2478367 C2	20130410	RU20110119764	20091016	
SI2344130 T1	20131231	SI20090030749T	20091016	
TW201511779 A	20150401	TW20140134727	20091019	
TW201511779 A	20150401	TW20090134727	20091019	
US2011263646 AA	20111027	US20090124403	20091016	
US2014187578 AA	20140703	US20140197933	20140305	
UY32187 A1	20100430	UY20090032187	20091019	
WO10043717 A2	20100422	WO2009EP63625	20091016	
WO10043717 A3	20100729	WO2009EP63625	20091016	

Priority:

EP20080166933	20081017	WO2009EP63625	20091016	EP20090736946	20091016
EP20120192559	20091016	CA20092822167	20091016	CA20092738384	20091016
CA20132738384	20130812	CA20132738384	20130812	JP20110531512	20091016
US20110124403	20110712	US20140197933	20140305		

Probable Assignee: FERRER INTERNACIONAL SA

Assignee(s): (std): FERRER INTERNAC S A ; FERRER INTERNAC SA ; TARRAGO CRISTINA ; RAGA MANUEL ; SANTOS BENJAMIN ; GUGLIETTA ANTONIO ; FERRER INT ; FERRER INTERNASIONAL S A

Assignee(s): FERRER INTERNASIONAL SA ; FERRER INTERNACIONAL SAGRAN VIA CARLOS III 94E-08028BARCELONAES ; FERRER INT SA ; FERRER INTERNACIONAL S A ; FERRER INTERNACIONAL, S.A. ; FERRER INTERNACIONAL S A

Inventor(s): (std): TARRAGA CRISTINA ; TARRAGO KRISTINA ; TARRAGO CRISTINA ; SANTOS BENKHAMIN ; SANTOS BENJAMIN ; RAGA MANUEL ; GUGLIETTA ANTONIO ; CRISTINA TARRAGO ; BENJAMIN SANTOS ; ANTONIO GUGLIETTA ; MANUEL RAGA ; RAGA MANUEHL ; GUL ETTA ANTONIO

Inventor(s): GUGLIETTA ANTONIOES ; GUL'ETTA ANTONIO ; TARRAGO CRISTINAES ; SANTOS BENJAMINES ; RAGA MANUELES ; RAGA MANUEHL'

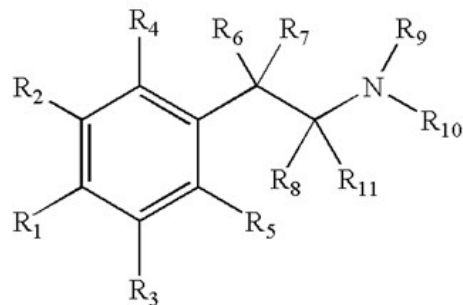
Agent(s): REITSTOETTER KINZEBACH; Reitstötter - Kinzebach

Designated states: AE AG AL AM AO AT AU AZ BA BB BE BF BG BH BJ BR BW BY BZ CA CF CG CH CI CL CM CN CO CR CU CY CZ DE DK DM DO DZ EC EE EG ES FI FR GA GB GD GE GH GM GN GQ GR GT GW HN HR HU ID IE IL IN IS IT JP KE KG KM KN KP KR KZ LA LC LI LK LR LS LT LU LV LY MA MC MD ME MG MK ML MN MR MT MW MX MY MZ NA NE NG NI NL NO NZ OM PE PG PH PL PT RO RS RU SC SD SE SG SI SK SL SM SN ST SV SZ TD TG TJ TM TN TR TT TZ UA UG US UZ VC VN ZA ZM ZW

Title: SUBSTITUTED HYDROXYPHENYLAMINE COMPOUNDS

Abstract: Source: US2010172916A The present invention relates to new substituted hydroxyphenylamine based modulators of hormone and/or pigment levels, pharmaceutical compositions thereof, and methods of use thereof.

Formula I



Classifications:
International (IPC 8-9): A61K31/122 A61K31/135 A61K31/165 A61K31/195 A61K31/197 A61K31/216 A61K31/355 A61K31/375 A61K31/381 A61K31/4045 A61K31/421 A61K31/428 A61K31/435 A61K31/437 A61K31/4409 A61K31/4415 A61K31/4545 A61K31/455 A61K31/473 A61K31/48 A61K31/4985 A61K31/506 A61K31/515 A61K31/519 A61K31/525 A61K31/5375 A61K31/55 A61K31/551 A61K31/66 A61K31/675 A61K31/7084 A61K31/714 A61K33/26 A61K36/48 A61K38/44 A61K39/395 A61P25/00 A61P25/16 A61P25/22 A61P25/24 A61P25/28 A61P25/30 A61P3/00 A61P3/04 A61P31/18 A61P5/00 C07C211/03 C07C229/36 (Advanced/Invention)
CPC: A61K31/135 A61K31/216 A61K45/06 C07C215/52 C07C229/36 A61K31/195
European: A61K31/135 A61K31/195 A61K31/216 A61K45/06 C07C215/52 C07C229/36
US: 424/158.1 424/158.100P 424/648 424/648S 424/757 424/757S 424/94.1 424/94.100S 424/94.4 424/94.400S 514/129 514/129S 514/217.02 514/217.020S 514/221 514/221S 514/237.8 514/237.800S 514/249 514/249S 514/250 514/250S 514/251 514/251S 514/252.16 514/252.160S 514/252.19 514/252.190S 514/270 514/270S 514/284 514/284S 514/288 514/288S 514/289 514/289S 514/293 514/293S 514/318 514/318S 514/348 514/348S 514/355 514/355S 514/357 514/357S 514/367 514/367S 514/376 514/376S 514/418 514/418S 514/438 514/438S 514/458 514/458S 514/47 514/474 514/474S 514/47S 514/52 514/52S 514/567 514/567S 514/620 514/620S 514/655 514/655S 514/689 514/689S 514/89 514/89S 560/40 560/40S 564/280 564/280S

Family:

Publication number	Publication date	Application number	Application date
US2010172916 AA	20100708	US20090614530	20091109
WO10054286 A2	20100514	WO2009US63685	20091109
WO10054286 A3	20100916	WO2009US63685	20091109

Priority:
US20080112788P 20081110 US20090614530 20091109

Probable Assignee: AUSPEX PHARMACEUTICALS INC

Assignee(s): (std): AUSPEX PHARMACEUTICALS INC ; GANT THOMAS G ; HODILUK CRAIG ; WOO SOON H

Inventor(s): (std): GANT THOMAS G ; HODILUK CRAIG ; HODULIK CRAIG ; WOO SOON ; WOO SOON H

Agent(s): GLOBAL PATENT GROUP - APX; GLOBAL PATENT GROUP APX; BENNETT DENNIS A

Designated states: AE AG AL AM AO AT AU AZ BA BB BE BF BG BH BJ BR BW BY BZ CA CF CG CH CI CL CM CN CO CR CU CY CZ DE DK DM DO DZ EC EE EG ES FI FR GA GB GD GE GH GM GN GQ GR GT GW HN HR HU ID IE IL IN IS IT JP KE KG KM KN KP KR KZ LA LC LK LR LS LT LU LV LY MA MC MD ME MG MK ML MN MR MT MW MX MY MZ NA NE NG NI NL NO NZ OM PE PG PH PL PT RO RS RU SC SD SE SG SI SK SL SM SN ST SV SY SZ TD TG TJ TM TN TR TT TZ UA UG US UZ VC VN ZA ZM ZW

Title: PHARMACEUTICAL COMPOSITION BASED ON ACRIDONACETIC ACID AND ITS COMPOUNDS FOR TREATMENT OF SUPPURATIVE-DESTRUCTIVE LESIONS OF MUCOUS MEMBRANE AND SKIN, GENERAL SYSTEM DISEASES IN CASE OF IMMUNODEFICIENCY STATES

Abstract: Source: RU2404773C

FIELD: medicine, pharmaceuticals.

SUBSTANCE: pharmaceutical composition contains acridonacetic acid or its therapeutically active compound, target additive and base, at the same time it contains at least one substance selected from the following row as additional target additive: immunomodulator, substance having **antibacterial** activity in respect of gram-positive and/or gram-negative bacteria, antimycotic agent, anesthetic agent, biogenic element, vitamin, preservative or their mixture at a certain ratio of components. Therapeutically active compound of acridonacetic acid - cyclophosphorone or cridanimod or anandin - is used. Composition is arranged in the form of suppositories or capsules for rectal and vaginal use or in the form of soft dosage form: ointment, cream, gel or in the form of fluid dosage form for topical and local administration.

EFFECT: composition of invention has immunomodulatory action, antiviral and **antibacterial** effect, higher therapeutical activity and preservation of therapeutical activity during long service life.

13 cl, 6 tbl, 37 ex
Classifications:
International (IPC 8-9): A61K31/473 A61K31/706 A61K9/00 A61P31/00 A61P37/00 (Advanced/Invention);
A61K31/473 A61K31/7042 A61K9/00 A61P31/00 A61P37/00 (Core/Invention)

Family:

Publication number	Publication date	Application number	Application date
RU2008147792 A	20100610	RU20080147792	20081204
RU2404773 C2	20101127	RU20080147792	20081204

Priority:

RU20080147792 20081204

Probable Assignee: BIOLOG I I SISTEMY AOZT
Assignee(s): (std): BIOLOG I I SISTEMY AOZT
Assignee(s): ZAKRYTOE AKTSIONERNOE OBSHCHESTVO BIOLOGICHESKIESSLEDOVANIJA I SISTEMY
Inventor(s): (std): KOSJAKOVA NINEL IVANOVNA ; MEZHBURD EVGENIJ VOL FOVICH ; MURASHEV ARKADIJ NIKOLAEVICH
Inventor(s): MEZHBURD EVGENIJ VOL'FOVICH ; KOSJAKOVA NINEL' IVANOVNA

Title: CYCLOPHERONE-BASED PHARMACEUTICAL COMPOSITION OF LOCAL OR EXTERNAL APPLICATION FOR TREATMENT OF PURULENT-DESTRUCTIVE AFFECTION OF MUCOUS MEMBRANE AND SKIN, GENERAL-SYSTEM DISEASES IN CASE OF IMMUNODEFICIENCY CONDITIONS (VERSIONS)

Abstract: Source: RU2414221C

FIELD: medicine, pharmaceuticals.

SUBSTANCE: invention relates to chemical-pharmaceutical industry and represents pharmaceutical composition of local, external and general-system application for treatment of purulent-destructive mucous membrane and skin lesions, as well as general-system diseases in case of immunodeficiency condition, which contains cyclopheron, target additive and base, which differs by the fact that as target additive it contains, at least one target additive, selected from line: immunomodulator, vitamin, substance, possessing **antibacterial** activity with respect to gram-positive and/or gram-negative bacteria, antimycotic, anesthetic, stimulator of reparative processes, biogenic element or their mixture with the following component content.

EFFECT: invention provides increase of efficiency of medications based on claimed pharmaceutical composition, convenience in application, increase of patient's motivation to treatment.

18 cl, 32 ex, 1 tbl

Classifications:
International (IPC 8-9): A61K31/473 A61K38/21 A61P17/02 (Advanced/Invention);
A61K38/21 A61P17/00 (Core/Invention)

Family:

Publication number	Publication date	Application number	Application date
RU2008147791 A	20100610	RU20080147791	20081204
RU2414221 C2	20110320	RU20080147791	20081204

Priority:

RU20080147791 20081204

Probable Assignee: BIOLOG I I SISTEMY AOZT

Assignee(s): (std): BIOLOG I I SISTEMY AOZT

Assignee(s): ZAKRYTOE AKTSIONERNOE OBSHCHESTVO BIOLOGICHESKIESSLEDOVANIJA I SISTEMY

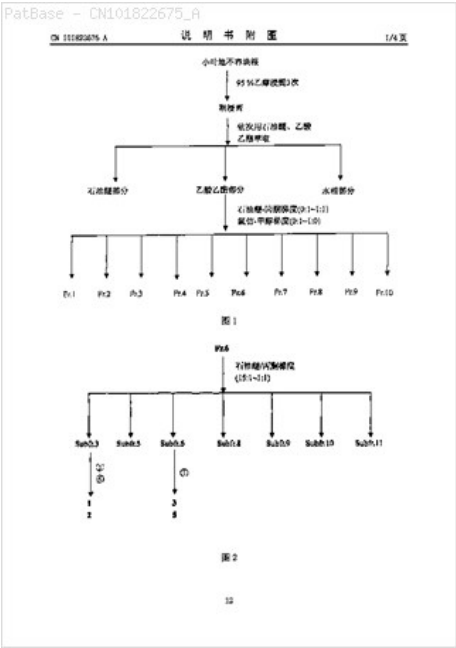
Inventor(s): (std): KOSJAKOVA NINEL IVANOVNA ; MEZHBURD EVGENIJ VOL FOVICH ; MURASHEV ARKADIJ NIKOLAEVICH

Inventor(s): MEZHBURD EVGENIJ VOL'FOVICH ; KOSJAKOVA NINEL' IVANOVNA

Title: APPLICATION OF APORPHINE ALKALOID, OXOAPORPHINE ALKALOID AND DERIVATIVES THEREOF IN PREPARING **ANTIBACTERIAL** MEDICINES

Abstract: Source: CN101822675A The invention discloses application of aporphine alkaloid, oxoaporphine alkaloid and derivatives thereof in preparing **antibacterial** medicines. The invention provides a new medical usage and develops a new application field for the known aporphine alkaloid, the oxoaporphine alkaloid, the derivatives thereof and pharmaceutically acceptable salts thereof. The compounds, such as the aporphine alkaloid, the oxoaporphine alkaloid, the derivatives thereof and the pharmaceutically acceptable salts thereof, have remarkable **antibacterial** activity for staphylococcus aureus and methicillin-resistant staphylococcus aureus, and the invention provides a new compound for seeking for a new **antibacterial** medicine.

Classifications:
International (IPC 8-9): A61K31/473 A61K31/4741 A61P31/04 (Advanced/Invention); A61K31/473 A61K31/4738 A61P31/00 (Core/Invention)



Title: Analgesic medicine compound containing hydrochloric acid isocorydine hydri

Abstract: Source: CN101843666A The invention relates to an analgesic medicine compound containing hydrochloric acid isocorydine hydri, which comprises antispasmodic hydrochloric acid isocorydine hydri, **antibacterial** agent tetracycline and the extract of Chinese medicine clove; and the formula calculates the ratio by the weight of 1g: 0.1 to 0.3g of hydrochloric acid isocorydine hydri, 0.05 to 0.1g of tetracycline and 0.1 to 0.3g of clove extract. The analgesic medicine compound containing hydrochloric acid isocorydine hydri has good curative effect, small toxic and side effect, integrates prevention and curing, and is convenient to be taken by a patient.

Classifications:
International (IPC 8-9): A61K36/61 A61P1/06 A61P29/02 C07D221/18 (Advanced/Invention); A61K31/473 A61K31/65 (Advanced/Non-invention)

Family:

Publication number	Publication date	Application number	Application date
CN101843666 A	20100929	CN201010200639	20100611

Priority:
CN201010200639 20100611

Probable Assignee: YUNNAN HONGHE PHARMACEUTICAL CO LTD

Assignee(s): (std): YUNNAN HONGHE PHARMACEUTICAL CO LTD

Assignee(s): YUNNAN HONGHE PHARMACEUTICAL CO

Inventor(s): (std): ZHENQUAN LIU ; GENHUAI ZHANG

Inventor(s): ZHANG GENHUAI ; LIU ZHENQUAN

Title: ANTIMICROBIAL AGENTS

Abstract: Source: US2012059026A The invention provides a compound of formula (I): or a salt or prodrug thereof, wherein Y, W, Z, Z1, Z2, Z3, Z4, and R1-R12 have any of the values described in the specification, as well as compositions comprising a compound of formula (I). The compounds are useful as **antibacterial** agents.

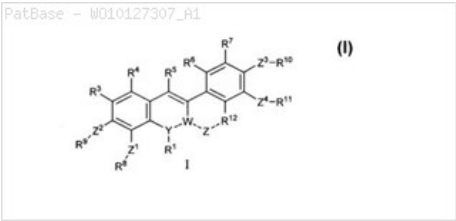
Classifications:

International (IPC 8-9): A01N43/42 A01P1/00 A61K31/472 A61K31/473 A61P31/04 C07D217/02 C07D217/10 C07D217/12 C07D221/18 C07D405/04 C07D455/03 (Advanced/Invention)

CPC: C07D455/03 C07D217/02 C07D217/10 C07D217/12 C07D405/04 C07D455/03

European: C07D217/02 C07D217/10 C07D217/12 C07D405/04 C07D455/03

US: 514/284 514/307 514/307S 546/144 546/144S 546/71 546/73 546/73S



Family:

Publication number	Publication date	Application number	Application date
CA2760526 AA	201011104	CA20102760526	20100430
US2012059026 AA	20120308	US20100266740	20100430
US2014315939 AA	20141023	US20140186516	20140221
WO10127307 A1	201011104	WO2010US33278	20100430

Priority:

US20090174337P 20090430 WO2010US33278 20100430 US20100266740 20100430

US20140186516 20140221 US20110266740 20111027

Probable Assignee: OF MEDICINE AND DENTISTRY OF NEW JERSEY UNIV

Assignee(s): (std): KAUL MALVIKA ; LAVOIE EDMOND J ; PARHI AJIT ; UNIV RUTGERS ; UNIV NEW JERSEY MED ; PILCH DANIEL S

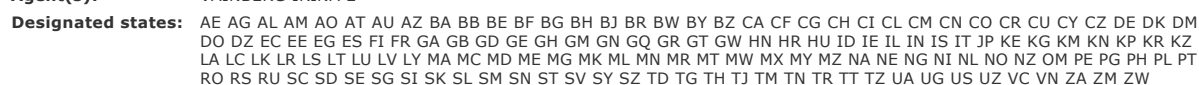
Assignee(s): RUTGERS STATE UNIV OF NEW JERSEY ; RUTGERS THE STATE UNIVERSITY OF NEW JERSEY ; UNIVERSITY OF MEDICINE AND DENTISTRY OF NEW JERSEY ; OF MEDICINE AND DENTISTRY OF NEW JERSEY UNIV

Inventor(s): (std): KAUL MALVIKA ; LAVOIE EDMOND J ; PARHI AJIT ; PILCH DANIEL S

Agent(s): MICKELSON JOHN W ET AL

Designated states: AE AG AL AM AO AT AU AZ BA BB BE BF BG BH BJ BR BW BY BZ CA CF CG CH CI CL CM CN CO CR CU CY CZ DE DK DM DO DZ EC EE EG ES FI FR GA GB GD GE GH GM GN GQ GR GT GW HN HR HU ID IE IL IN IS IT JP KE KG KM KN KP KR KZ LA LC LK LR LS LT LU LV LY MA MC MD ME MG MK ML MN MR MT MW MX MY MZ NA NE NG NI NL NO NZ OM PE PG PH PL PT RO RS RU SC SD SE SG SI SK SL SM SN ST SV SY SZ TD TG TH TJ TM TN TR TT TZ UA UG US UZ VC VN ZA ZM ZW

CPC: A61K31/198 A61K31/397 A61K31/47 A61K31/473 A61K31/4995 A61K45/06
European: A61K31/198 A61K31/397 A61K31/47 A61K31/473 A61K31/4995 A61K45/06
US: 514/154 514/154S 514/19.3 514/19.300S 514/196 514/196S 514/2.3 514/2.300S
 514/202 514/202S 514/203 514/203S 514/207 514/207S 514/209 514/209S 514/210.08
 514/210.080S 514/225.8 514/225.800S 514/226.2 514/226.200S 514/255.02
 514/255.020S 514/27 514/27S 514/283 514/283S 514/292 514/292S 514/297 514/297S
 514/311 514/311S 514/34 514/34S 514/4.4 514/4.400P 514/40 514/40S 514/449
 514/449S



Title: SALES FARMACEUTICAS DEL ACIDO 1-CICLOPROPIL-8-METIL-7-[5-METIL-6-(METILAMINO)-3-PIRIDINIL]-4-OXO-1,4-DIHIIDRO-3-QUINOLINCARBOXILICO, COMPOSICIONES FARMACEUTICAS QUE LAS CONTIENEN Y SU USO COMO AGENTES ANTIBACTERIANOS. ACID PHARMACEUTICAL SALES Pharmaceutical compositions containing them and their use as **antibacterial** agents. (Machine translation)

Abstract: Source: AR076206A La solicitud se refiere a una sal del acido 1-ciclopropil-8-metil-7-[5-metil-6-(metilamino)-3-piridinil]-4-oxo-1,4-dihidro-3-quinolincarboxilico seleccionada del grupo que consiste en las sales de citrato, hemifumarato, maleato, L-tartrato, mesilato, clorhidrato, potasio y sodio.

Machine translation: The application relates to an acid salt of 1-cyclopropyl-8-methyl-7-[5-methyl-6-(methylamino)-3-pyridinyl]-4-oxo-1,4-dihydro-3 -quinolinecarboxylic selected from the group consisting of citrate salts, hemifumarate, maleate, L-tartrate, mesylate, hydrochloride, potassium and sodium.

Classifications:
International (IPC 1-7): A61K31/473 A61P31/04 C07D401/06 C07D401/10

Family:

Publication number	Publication date	Application number	Application date
AR076206 AA	20110526	AR2010P101137	20100406

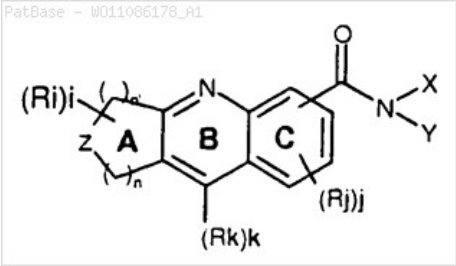
Priority:
AR2010P101137 20100406

Probable Assignee: FERRER INTERNAC SA
Assignee(s): (std): FERRER INTERNAC SA
Assignee(s): FERRER INTERNACIONAL S A
Inventor(s): (std): ANGLADA LUIS ; PALOMER ALBERT

Title: NOVEL SELECTIVE INHIBITORS OF UBIQUITIN SPECIFIC PROTEASE 7, THE PHARMACEUTICAL COMPOSITIONS THEREOF AND THEIR THERAPEUTIC APPLICATIONS

Abstract: Source: US2011177105A The present invention concerns the discovery of new selective inhibitors of ubiquitin specific proteases, their process of preparation and their therapeutic use.

Classifications:
International (IPC 8-9): A61K31/435 A61K31/473 A61K31/496 A61K31/55 A61K39/00 A61K45/00 A61K45/06 A61P19/02 A61P19/08 A61P19/10 A61P25/00 A61P25/16 A61P25/28 A61P29/00 A61P31/00 A61P31/04 A61P31/12 A61P31/14 A61P31/16 A61P31/20 A61P31/22 A61P35/00 A61P35/04 A61P37/00 A61P37/02 A61P37/06 A61P39/06 A61P43/00 A61P7/02 A61P7/10 A61P9/00 A61P9/12 C07D C07D219/04 C07D219/06 C07D221/16 C07D401/10 C07D401/12 C07D401/14 C07D403/06 (Advanced/Invention); A61K31/00 A61P35/00 C07D219/00 C07D401/00 (Core/Invention)
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European: C07D219/04 C07D219/06 C07D401/12 C07D401/14
US: 424/184.1 424/184.100P 514/217.07 514/217.070S 514/253.03 514/253.030S 514/297 514/297S 540/597 540/597S 544/361 544/361S 546/103 546/103S 546/104 546/104S 546/79



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CA2786957 AA	20110721	CA20112786957	20110117
CN102781919 A	20121114	CN201180010555	20110117
DK2523938 T3	20141027	DK20110701220T	20110117
EP2357176 A1	20110817	EP20100172844	20100813
EP2523938 A1	20121121	EP20110701220	20110117
EP2523938 B1	20140903	EP20110701220	20110117
ES2523383 T3	20141125	ES20110701220T	20110117
IL220902 A0	20120924	IL20120220902	20120712
IN06380DN2012 A	20140207	IN2012DN06380	20120719
JP2013517257 T2	20130516	JP20120548453T	20110117
KR20120125629 A	20121116	KR20127021238	20110117
PT2523938 T	20141125	PT20110701220T	20110117
SI2523938 T1	20141231	SI20110030305T	20110117
US2011177105 AA	20110721	US20100855983	20100813
US2013023521 AA	20130124	US20110521978	20110117
US2015072973 AA	20150312	US20140488601	20140917
WO11086178 A1	20110721	WO2011EP50523	20110117

Priority:

US20100295399P 20100115	US20100855983 20100813	US20100885983 20100813
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Inventor(s): (std): COLLAND FREDERIC ; FREDERIC COLLAND ; LOPEZ ROMAN ; ROMAN LOPEZ

Agent(s): BLOT PHILIPPE ROBERT EMILE; BLOT PHILIPPE ET AL

Designated states: AE AG AL AM AO AT AU AZ BA BB BE BF BG BH BJ BR BW BY BZ CA CF CG CH CI CL CM CN CO CR CU CY CZ DE DK DM DO DZ EC EE EG ES FI FR GA GB GD GE GH GM GN GQ GR GT GW HN HR HU ID IE IL IN IS IT JP KE KG KM KN KP KR KZ LA LC LI LK LR LS LT LU LV LY MA MC MD ME MG MK ML MN MR MT MW MX MY MZ NA NE NG NI NL NO NZ OM PE PG PH PL PT RO RS RU SC SD SE SG SI SK SL SM SN ST SV SY SZ TD TG TH TJ TM TN TR TT TZ UA UG US UZ VC VN ZA ZM ZW

Title: TRANSCRIPTION FACTOR DECOYS

Abstract: Source: US2013252881A Decoy nucleic acid sequences comprising a sequence encoding all or part of a binding site for bacterial sigma alternative sigma54 factor are described. Uses of the decoys in **antibacterial** complexes and for the treatment of bacterial infections are also described.

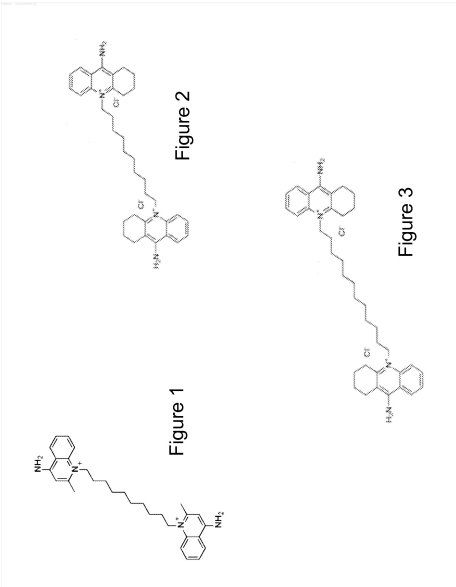
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Family:

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AU2011234231 AA	20111006	AU20110234231	20110330
CA2794392 AA	20111006	CA20112794392	20110330
CN103002900 A	20130327	CN201180027336	20110330
EP2552455 A2	20130206	EP20110714380	20110330
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JP2013523111 T2	20130617	JP20130501949T	20110330
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Agent(s): Boxall Sarah Jane; BOXALL IPM LTD
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A Facile Synthesis of [1]Benzopyrano[4,3-*b*]pyridin-5-ones

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The title compounds **5a-c** and **7a-m** have been prepared by Vilsmeier formylation of 4-aminocoumarins **1** yielding aldehydes **2**, and subsequent condensation of **2** with C-H acids in the presence of piperidine. This condensation probably pro-

ceeds via the intermediate ylidemalonic esters **4**. By means of detailed ¹H- and ¹³C-NMR studies a Dimroth-type rearrangement of intermediates **6f-m** has been found to take place in the course of the formation of products **7f-m**.

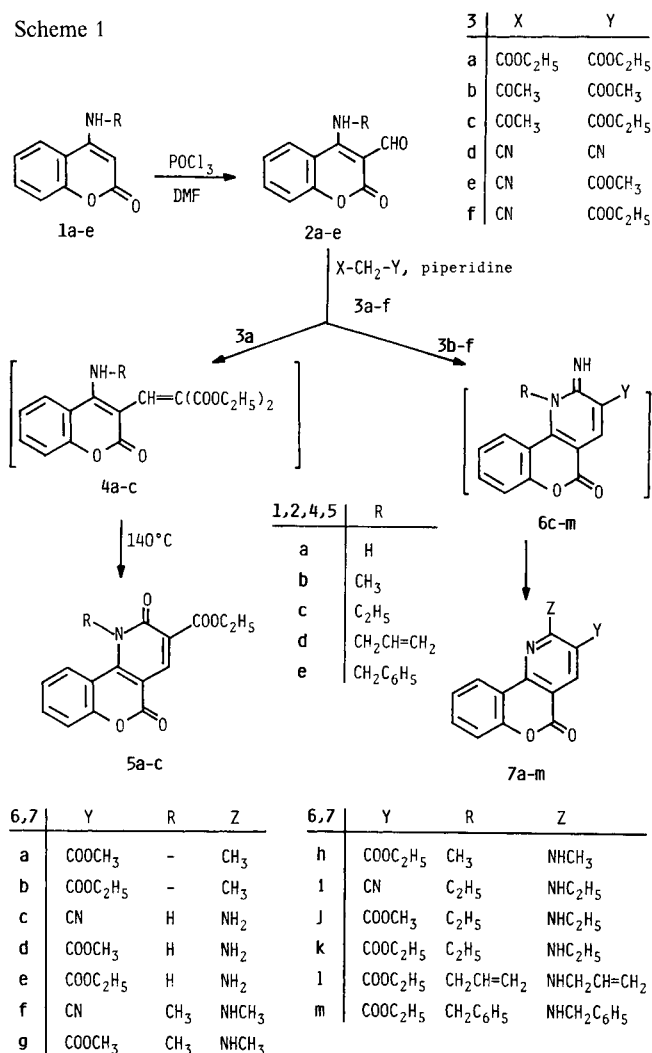
A variety of approaches^[1-9] has been employed for the preparation of numerous 5*H*-[1]benzopyrano[4,3-*b*]pyridine derivatives by starting mainly from salicylaldehyde^[1,8], 3-acylchromones^[3,6], or 4-hydroxycoumarins^[1,5,7]. In most cases the corresponding 4-amino[1]benzopyranes have been obtained as intermediates^[3e,5,7,9]. The known methods are mostly based on a Vilsmeier-Haack^[3,7,9], Wittig^[3] or "AN-RORC"-type^[3b,e] reaction in the step prior to the closure of the pyridine ring. Representatives of this class of compounds have been found to display biological activity or fluorescent properties^[1,3,6].

Recently, we have developed a simple method for the preparation of 4-amino- and some 4-(alkylamino)coumarins **1a-e**^[10]. Now we report on their application as starting compounds for a general synthesis of the title compounds **5a-c** and **7a-m**^(*) substituted in the positions 1-3 (Scheme 1).

The Vilsmeier formylation of **1a-e** occurs smoothly to give **2a-e** in very high yields (*cf. ref.*^[3d]). These compounds are then allowed to react with C-H acids **3a-f** in boiling alcohol or pyridine in the presence of an excess of piperidine (Knoevenagel conditions). In most trials spontaneous formation of the corresponding target compounds **5a** and **7a-m** has been found. Only when diethyl malonate (**3a**) reacts with **2b, c** the probable intermediate ylidemalonic esters **4b, c** can be detected by TLC and, without isolation, further cyclized at 140°C to give **5b, c**.

When malononitrile (**3d**) or cyanoacetic esters **3e, f** are allowed to react with *N*-alkyl-4-amino-3-formylcoumarins **2b-e** (Scheme 1), only the fully aromatized derivatives **7f-m** can be isolated as major products. The structures of all 2-amino derivatives **7c-m** have been confirmed by the equal pattern of their UV spectra (*cf. Experimental*). This aromatization is obviously accompanied by a Dimroth-type rearrangement of the formerly cyclized intermediates **6f-m**

Scheme 1



(Scheme 1). The yields of the rearranged products **7f-1** (17–56%) are markedly lower than those of **7a-e** (80–91%) and **5a-c** (68–88%); the highest yield of rear-

^(*) Compounds **7l** and **7m** have been added in a revised version of the manuscript (October 22, 1991).

ranged product has been achieved for the *N*-benzyl derivative **7m** (75%).

The structures of all compounds **2a–e**, **5a–c**, and **7a–m** have been confirmed by means of spectral (UV, IR, NMR, MS) and elemental analyses. The product **7b** (solely mentioned in the literature without any experimental details) has been earlier obtained by oxidation of the corresponding 5-hydroxy derivative^[6], and we have identified it by a comparison with an authentic sample^[11]. All compounds **5** and **7** show intense blue to violet fluorescence on UV irradiation.

The 1-D ¹H-, ¹³C-, DEPT- and proton-coupled ¹³C-NMR spectra (Tables 1 and 2, cf. Experimental) are quite compatible with the structures **5** and **7** proposed above. For example, the observed additional splitting of the NH proton signal and that of the *N*-methyl protons in **7f**, **g**, and **h** as well as of the *N*-methylene protons in **7i**, **j**, and **k** furnishes evidence of the position of the *N*-alkyl groups. The 1-D NOED experiments provide further support for an unambiguous assignment.

The structure assignments have been further confirmed by 2-D NMR experiments with compounds **5c**, **7b**, and **7k** in CDCl₃ solution. A precise structural description of the 3-carboxylic esters **7d**, **e**, **g**, **h**, and **j–m** should also take into account the formation of an intramolecular hydrogen bond and hence the hindered rotation of the 2-amino group (cf. Figure 1 and Table 2). For instance, compounds **7d** and **e** show different chemical shifts for each NH₂ proton in CDCl₃ so that one of them is strongly deshielded (to δ = 8.27 and 8.30, respectively) due to its participation in internal hydrogen bonding.

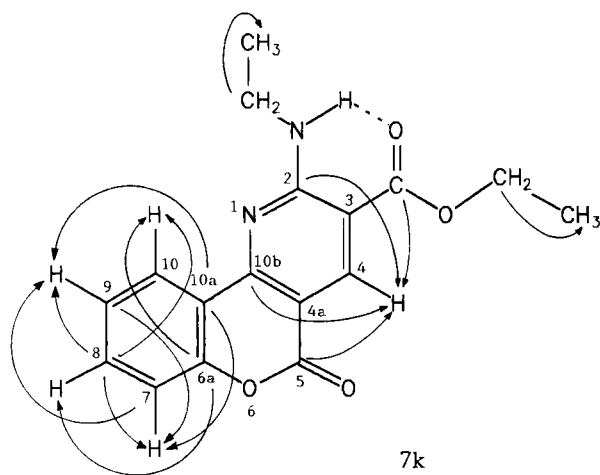


Figure 1. ¹H-¹³C long-range correlation from LR HETCOR of **7k** in CHCl₃

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Experimental

General: TLC: precoated plates Kieselgel 60 F₂₅₄ Merck (Germany), layer thickness 0.25 mm, eluent hexane/chloroform/acetone

(5:3:2), detection by UV (254 nm). Yields of TLC-homogenous isolated products are given. — M.p.: Boëtius hot-plate microscope (Germany). — IR (nujol): C. Zeiss UR-20 spectrophotometer (Jena, Germany). — UV (methanol): C. Zeiss Specord UV-VIS spectrophotometer (Jena, Germany). — EI-MS (70 eV): JEOL JMS D 300 (Japan). — NMR: The 1-D and 2-D NMR spectra were measured with a Bruker WM 250 spectrometer operating at 250.135 MHz (¹H) using a 5-mm ¹H/¹³C dual probe head. All chemical shifts were referenced to the solvent peaks: δ = 7.26 and 77.10 in CDCl₃ or δ = 2.52 and 3.95 in [D₆]DMSO, for ¹H- and ¹³C-NMR spectra, respectively. The 1-D nuclear Overhauser effect difference (NOED) spectra were measured with an irradiation time of 0.7 s, delay of 7 s, and 90° observation pulse. The 2-D ¹³C-¹H shift-correlated (HETCOR) spectra were recorded by an initial (t₁, t₂) matrix of 64 × 2048 points with a delay of 3.33 ms and 2.22 ms. After zero filling in the F1 (¹H) domain a sine-bell nonshifted weighting was used in both dimensions. The 2-D ¹³C-¹H long-range shift correlated (LR-HETCOR) spectra were performed with delays of 40 ms and 20 ms, optimized for *trans* three-bond proton-carbon configuration. The measured NMR data are given in Tables 1 and 2.

Formylation of 4-Aminocoumarins 1a–c: Accomplished according to ref.^[13d] to give **2a–c**.

4-Amino-2-oxo-2H-1-benzopyran-3-carbaldehyde (2a): Yield 70%, m.p. 267–268 °C (ethanol), R_f = 0.23.

C₁₀H₇NO₃ (189.2) Calcd. C 63.49 H 3.73 N 7.41
Found C 63.59 H 3.74 N 7.36
Mol. mass 189 (MS)

4-(Methylamino)-2-oxo-1-benzopyran-3-carbaldehyde (2b): Yield 97%, m.p. 215–216 °C (ethanol), R_f = 0.28

C₁₁H₉NO₃ (203.2) Calcd. C 65.02 H 4.46 N 6.89
Found C 64.83 H 4.54 N 6.77
Mol. mass 203 (MS)

4-(Ethylamino)-2-oxo-1-benzopyran-3-carbaldehyde (2c): Yield 98%, m.p. 180–181 °C (ethanol), R_f = 0.36.

C₁₂H₁₁NO₃ (217.2) Calcd. C 66.36 H 5.10 N 6.45
Found C 66.45 H 5.17 N 6.43
Mol. mass 217 (MS)

4-(Allylamino)-2-oxo-1-benzopyran-3-carbaldehyde (2d): From 4.05 g (25.0 mmol) of 4-hydroxycoumarin and 14.3 g (250 mmol) of allylamine according to ref.^[10] the corresponding 4-(allylamino)-coumarin (**1d**) [3.61 g, m.p. 133–134 °C (benzene)] was obtained and further formylated^[13d] to give **2d**; yield 3.20 g (56% referred to 4-hydroxycoumarin), m.p. 174–175 °C (ethanol).

C₁₃H₁₁NO₃ (229.3) Calcd. C 68.11 H 4.84 N 6.11
Found C 68.00 H 4.77 N 6.06
Mol. mass 229 (MS)

4-(Benzylamino)-2-oxo-1-benzopyran-3-carbaldehyde (2e): Prepared as described in ref.^[13d].

Ethyl 1,5-Dihydro-2,5-dioxo-2H-[1]benzopyrano[4,3-b]pyridine-3-carboxylate (5a): A mixture of 0.38 g (2.0 mmol) of **2a**, 3.20 g (20 mmol) of **3a**, 1.20 g (14 mmol) of piperidine, and 0.51 g (8.5 mmol) of glacial acetic acid in 10 ml of ethanol was refluxed for 2 h. After cooling, the separated crystals were filtered and washed with ethanol; yield 0.56 g (98%) of colorless **5a**, m.p. 313–315 °C (dimethylformamide), R_f = 0.16. — IR: ν̄ = 3100 cm⁻¹ (NH), 1710 (lactone C=O), 1696 (br., ester and lactam C=O). — UV: λ_{max} = 256 nm, 287, 355.

C₁₅H₁₁NO₅ Calcd. 285.06364 Found 285.0636 (MS)

Ethyl 1,5-Dihydro-1-methyl-2,5-dioxo-2H-[1]benzopyrano[4,3-b]pyridine-3-carboxylate (5b): A mixture of 0.41 g (2.0 mmol) of **2b**,

Table 1. ¹H-NMR chemical shifts^[a] (δ values) of **5a–c** and **7a–k** in [D₆]DMSO (CDCl₃)^[b]

Compd.	4-H	7-H	8-H	9-H	10-H	1-NR ^[c]	2-Z ^[c]	3-Y
5a	8.39	7.38	7.65	7.40	8.43	3.38	—	1.29t, 4.23q
5b	8.54	7.55	7.79	7.48	8.44	3.92	—	1.31t, 4.29q
5c	8.56 (8.84)	7.55 7.44	7.79 7.71	7.54 7.47	8.18 (8.17)	1.61t, 4.39q (1.79t, 4.53q)	— —	1.31t, 4.29q (1.43t, 4.40q)
7a	8.84	7.50	7.74	7.52	8.54	—	2.96	3.94
7b	8.79	7.50	7.74	7.49	8.50	—	2.93	1.38t, 4.39q
7c	8.62 (8.62)	7.42 7.34	7.70 7.61	7.45 7.36	8.31 (8.38)	— —	8.17 (5.80)	— —
7d	8.72 (9.04)	7.42 7.32	7.69 7.57	7.44 7.33	8.34 (8.40)	— —	8.10, 8.38 (5.94, 8.27)	3.90 (3.93)
7e	8.65 (8.99)	7.37 7.29	7.66 7.55	8.40 7.31	8.29 (8.35)	— —	7.32, 8.07 (6.00, 8.30)	1.36t, 4.33q (1.43t, 4.38q)
7f	8.59	7.42	7.72	7.46	8.43	—	8.30, 3.10	—
7g	8.69	7.42	7.70	7.45	8.44	—	8.75, 3.19	3.90
7h	8.71	7.43	7.71	7.45	8.45	—	8.75, 3.20	1.37t, 4.37q
7i	8.57 (8.52)	7.42 7.33	7.70 7.60	7.45 7.35	8.37 (8.42)	— —	8.35, 1.26, 3.65 (5.82, 1.38, 3.77)	— —
7j	8.66	7.40	7.69	7.43	8.38	—	8.70, 1.28, 3.72	3.89
7k	8.67 (8.86)	7.43 7.24	7.69 7.51	7.46 7.28	8.37 (8.34)	— —	8.74, 1.29, 3.72 (8.63, 1.27, 3.71)	1.37t, 4.35q (1.40t, 4.35q)

^[a] Examples of coupling constants *J* [Hz]: **7g**: 7-H, d, *J* = 8.36; 8-H, t, *J* = 8.00; 9-H, td, *J* = 8.36, *J* = 1.82; 10-H, dd, *J* = 7.63, *J* = 1.11; NHCH₃, d, *J* = 4.72; NHCH₃, br.q. **7j**: 7-H, d, *J* = 8.35; 8-H, t, *J* = 7.63; 9-H, td, *J* = 7.61, *J* = 1.42; 10-H, dd, *J* = 7.63, *J* = 1.09; NHCH₂CH₃, dq, *J* = 6.90, *J* = 5.80; NHCH₂CH₃, t, *J* = 6.90; NHCH₂CH₃, t, *J* = 5.27. — ^[b] Data in CDCl₃ of compounds with sufficient solubility are given in parentheses. — ^[c] The chemical shifts of NH or NH₂ are given in *italics*.

3.20 g (20 mmol) of **3a**, 0.72 g (8.5 mmol) of piperidine, and 260 mg (4.3 mmol) of glacial acetic acid in 5 ml of ethanol was refluxed for 10 h. The condenser was then removed and the mixture heated at 140 °C for 3 h. After cooling, the separated crystals were treated with 5 ml of ethanol, filtered, and washed with ethanol; yield 0.50 g (84%) of almost colorless **5b**, m.p. 202–203 °C (ethanol), *R*_f = 0.18. — IR: $\tilde{\nu}$ = 1743 cm^{−1} (lactone C=O), 1725 (ester C=O), 1673 (lactam C=O). — UV: λ_{max} = 227 nm, 266, 286, 364.

C₁₆H₁₃NO₅ (299.3) Calcd. C 64.21 H 4.38 N 4.68
Found C 64.00 H 4.38 N 4.70
Mol. mass 299 (MS)

*Ethyl 1-Ethyl-1,5-dihydro-2,5-dioxo-2H-[1]benzopyrano[4,3-*b*]pyridine-5-carboxylate (5c)*: Prepared as described for **5b** from 0.43 g (2.0 mmol) of **2c** and 3.20 g (20 mmol) of **3a**; yield 0.42 g (67%) of colorless **5c**, m.p. 211–212 °C (ethanol); *R*_f = 0.20. — IR: $\tilde{\nu}$ = 1747 cm^{−1} (lactone C=O), 1726 (ester C=O), 1676 (lactam C=O). — UV: λ_{max} = 228 nm, 267, 287, 365.

C₁₇H₁₅NO₅ (313.3) Calcd. C 65.17 H 4.82 N 4.47
Found C 64.97 H 4.81 N 4.40
Mol. mass 313 (MS)

*Methyl 2-Methyl-5-oxo-5H-[1]benzopyrano[4,3-*b*]pyridine-3-carboxylate (7a)*: A mixture of 0.57 g (3.0 mmol) of **2a**, 3.48 g (30 mmol) of **3b**, 1.80 g (21.7 mmol) of piperidine, and 0.80 g (13 mmol) of glacial acetic acid in 15 ml of methanol was refluxed for 16 h.

After cooling, the separated crystals were filtered and washed with methanol; yield 0.73 g (91%) of pale yellow **7a**, m.p. 214–216 °C (ethanol), *R*_f = 0.60. — IR: $\tilde{\nu}$ = 1729 cm^{−1} (br., lactone C=O), 1710 (sh, ester C=O). — UV: λ_{max} = 227 nm (sh.), 279, 311.

C₁₅H₁₁NO₄ (269.3) Calcd. C 66.91 H 4.12 N 5.20
Found C 66.72 H 4.15 N 5.16
Mol. mass 269 (MS)

*Ethyl 2-Methyl-5-oxo-5H-[1]benzopyrano[4,3-*b*]pyridine-3-carboxylate (7b)*: Prepared as described above for **7a** but using 0.57 g (3.0 mmol) of **2a** and 3.90 g (30 mmol) of **3c** in 15 ml of ethanol; yield 0.73 g (86%) of colorless **7b**, m.p. 166–167 °C (ethanol), *R*_f = 0.64. Identified by a comparison of m.p., mixed m.p., *R*_f, and IR data with those of authentic sample^[11]. — IR: $\tilde{\nu}$ = 1733 cm^{−1} (lactone C=O), 1720 (ester C=O). — UV: λ_{max} = 228 nm (sh), 281, 310.

C₁₆H₁₃NO₄ (283.3) Calcd. C 67.84 H 4.63 N 4.95
Found C 67.79 H 4.53 N 4.85
Mol. mass 283 (MS)

*2-Amino-5-oxo-5H-[1]benzopyrano[4,3-*b*]pyridine-3-carbonitrile (7c)*: A mixture of 0.57 g (3.0 mmol) of **2a**, 0.20 g (3.0 mmol) of **3d**, 0.36 g (4.2 mmol) of piperidine, and 0.20 g (3.3 mmol) of glacial acetic acid in 25 ml of ethanol was refluxed for 8 h. After cooling the separated crystals were filtered and washed with ethanol; yield 0.62 g (87%) of almost colorless **7c**, m.p. 288–289 °C

Table 2. ^{13}C -NMR chemical shifts (δ values) of **5a**, **c** and **7a**, **b**, **d**–**g**, **i**–**k** in $[\text{D}_6]\text{DMSO}$ (CDCl_3)^[a]

Compd.	5a	5c	7a	7b	7d	7e	7f	7g	7i	7j	7k
C-2	164.7	(160.0)	190.6	206.0 (166.8)	159.4	161.1 (161.0)	158.8	n.o.	158.7	159.4	(159.7)
C-3	116.1	(120.4)	125.0	125.5 (125.6)	107.1	107.1 (107.2)	n.o.	n.o.	93.0	107.5	(107.8)
C-4	141.1	(142.0)	139.9	139.9 (140.6)	142.1	142.0 (143.2)	144.4	141.4	144.7	141.5	(142.5)
C-4a	100.2	(103.6)	n.o.	114.9 (114.7)	106.2	106.1 (107.6)	105.5	n.o.	105.6	105.2	(105.8)
C-5	159.4	(158.8)	161.9	164.5 (164.8)	161.0	159.4 (160.6)	159.2	n.o.	158.8	158.8	(160.8)
C-6a	153.0	(153.8)	158.1	151.8 (153.2)	153.2	153.2 (153.3)	153.2	n.o.	153.2	153.2	(153.8)
C-7 (ar.)	116.8	(119.1)	117.5	117.0 (117.1)	116.9	116.9 (117.1)	116.8	116.9	116.9	116.9	(117.0)
C-8 (ar.)	132.6	(133.8)	134.9	133.2 (132.9)	133.1	133.0 (132.9)	133.3	133.1	133.3	133.1	(132.5)
C-9 (ar.)	124.0	(124.6)	124.2	124.6 (124.8)	124.4	124.3 (124.4)	124.5	124.5	124.6	124.4	(124.2)
C-10 (ar.)	124.3	(126.1)	124.8	124.9 (125.2)	124.5	124.5 (125.1)	124.8	124.8	124.8	124.7	(125.2)
C-10a	118.5	(113.2)	117.2	118.1 (118.5)	118.1	118.1 (118.4)	118.1	n.o.	118.2	118.3	(119.0)
C-10b	151.8	(150.6)	n.o.	165.3 (160.3)	154.7	154.6 (155.3)	154.1	n.o.	154.7	154.4	(155.2)
2-Z	—	—	30.6	30.4 (25.8)	—	—	28.3	28.0	13.9 36.2	14.0 35.7	(14.1) (36.1)
3-Y	14.0 59.8 164.9	(14.2) (61.4) (163.2)	52.5 n.o.	13.8 (14.2) 61.4 (61.7) 152.8 (152.5)	52.3 165.5	13.8 (14.2) 61.1 (61.6) 165.0 (165.9)	115.2 (CN)	52.3 n.o.	115.2 (CN)	52.3 165.7	(14.3) (61.3) (166.5)
1-NR	—	(14.2) (44.8)	—	—	—	—	—	—	—	—	—

^[a] n.o.: not observed because of poor solubility.

(acetonitrile), $R_f = 0.32$. — IR: $\tilde{\nu} = 3500\text{ cm}^{-1}$, 3418, 3390, 3320, 3208 (NH_2), 2230 (CN), 1720 cm^{-1} (lactone $\text{C}=\text{O}$), 1640, 1608. — UV: $\lambda_{\text{max}} = 260\text{ nm}$, 280, 291, 352.

$\text{C}_{13}\text{H}_7\text{N}_3\text{O}_2$ (237.2) Calcd. C 65.82 H 2.97 N 17.72
Found C 65.54 H 3.04 N 17.73
Mol. mass 237 (MS)

Methyl 2-Amino-5-oxo-5H-[1]benzopyrano[4,3-b]pyridine-3-carboxylate (7d): A mixture of 0.57 g (3.0 mmol) of **2a**, 1.49 g (15 mmol) of **3e**, 1.80 g (21 mmol) of piperidine, and 0.80 g (13 mmol) of glacial acetic acid in 15 ml of methanol was refluxed for 9 h. After cooling, the separated crystals were filtered and washed with methanol; yield 0.71 g (88%) of colorless **7d**, m.p. $263\text{--}265^\circ\text{C}$ (ethanol), $R_f = 0.46$. — IR: $\tilde{\nu} = 3358\text{ cm}^{-1}$, 3491 (NH_2), 1718 (lactone $\text{C}=\text{O}$), 1695 (ester $\text{C}=\text{O}$), 1620. — UV: $\lambda_{\text{max}} = 259\text{ nm}$, 278, 287, 351.

$\text{C}_{14}\text{H}_{10}\text{N}_2\text{O}_4$ (270.2) Calcd. C 62.22 H 3.73 N 10.37
Found C 62.39 H 3.88 N 10.38
Mol. mass 270 (MS)

Ethyl 2-Amino-5-oxo-5H-[1]benzopyrano[4,3-b]pyridine-3-carboxylate (7e): Prepared as described above for **7d** but starting from 0.57 g (3.0 mmol) of **2a**, 1.70 g (15 mmol) of **3f** and 15 ml of ethanol (instead of methanol); yield 0.74 g (87%) of colorless **7e**, m.p. $191\text{--}192^\circ\text{C}$ (ethanol), $R_f = 0.52$. — IR: $\tilde{\nu} = 3495\text{ cm}^{-1}$, 3356 (NH_2), 1728 (lactone $\text{C}=\text{O}$), 1695 (ester $\text{C}=\text{O}$), 1620, 1608. — UV: $\lambda_{\text{max}} = 260\text{ nm}$, 279, 289, 354.

$\text{C}_{15}\text{H}_{12}\text{N}_2\text{O}_4$ (284.3) Calcd. C 63.38 H 4.26 N 9.86
Found C 63.41 H 4.26 N 9.76
Mol. mass 284 (MS)

2-(Methylamino)-5-oxo-5H-[1]benzopyrano[4,3-b]pyridine-3-carbonitrile (7f): A mixture of 0.41 g (2.0 mmol) of **2b**, 0.14 g (2.1 mmol) of **3d**, and 0.96 g (11 mmol) of piperidine in 6 ml of pyridine was refluxed for 4 h. After cooling, 9 ml of 33% (v/v) aqueous ethanol was added, and the mixture was kept at $0\text{--}4^\circ\text{C}$ for 24 h. The separated crystals were filtered, thoroughly washed with water, and recrystallized from acetonitrile; yield 0.17 g (34%), of pale yellow **7f**, m.p. $298\text{--}299^\circ\text{C}$, $R_f = 0.48$. — IR: $\tilde{\nu} = 3332\text{ cm}^{-1}$ (NH), 2233 (CN), 1729 (lactone $\text{C}=\text{O}$), 1609. — UV: $\lambda_{\text{max}} = 267\text{ nm}$, 283, 295, 358.

$\text{C}_{14}\text{H}_9\text{N}_3\text{O}_2$ (251.2) Calcd. C 66.92 H 3.61 N 16.73
Found C 66.68 H 3.59 N 16.55
Mol. mass 251 (MS)

Methyl 2-(Methylamino)-5-oxo-5H-[1]benzopyrano[4,3-b]pyridine-3-carboxylate (7g): A mixture of 0.20 g (1.0 mmol) of **2b**, 0.69 g (7.0 mmol) of **3e**, 1.80 g (21 mmol) of piperidine, and 0.73 g (12 mmol) of glacial acetic acid in 3 ml of methanol was refluxed for 5 h. After cooling, 5 ml of 50% (v/v) aqueous methanol was added, and the mixture was kept at $0\text{--}4^\circ\text{C}$ for 24 h. The separated crystals were filtered and washed thoroughly with water; yield 0.05 g (18%) of colorless **7g**, m.p. $241\text{--}243^\circ\text{C}$ (acetone), $R_f = 0.57$. — IR: $\tilde{\nu} = 3349\text{ cm}^{-1}$ (NH), 1725 (lactone $\text{C}=\text{O}$), 1698 (ester $\text{C}=\text{O}$), 1613. — $\lambda_{\text{max}} = 265\text{ nm}$, 282, 293, 361.

$\text{C}_{15}\text{H}_{12}\text{N}_2\text{O}_4$ (284.3) Calcd. C 63.38 H 4.26 N 9.86
Found C 63.27 H 4.25 N 9.76
Mol. mass 284 (MS)

Ethyl 2-(Methylamino)-5-oxo-5H-[1]benzopyrano[4,3-b]pyridine-3-carboxylate (7h): A mixture of 0.20 g (1.0 mmol) of **2b**, 0.08

g (7.0 mmol) of **3f**, 1.80 g (21 mmol) of piperidine, and 0.81 g (14 mmol) of glacial acetic acid in 3 ml of ethanol was refluxed for 5 h. After cooling, the separated crystals were filtered and washed with water; yield 0.08 g (27%) of colorless **7h**, m.p. 232–233 °C (acetone), $R_f = 0.62$. — IR: $\tilde{\nu} = 3345 \text{ cm}^{-1}$ (NH), 1724 (lactone C=O), 1682 (ester C=O), 1615. — UV: $\lambda_{\text{max}} = 267 \text{ nm}$, 283, 293, 362.

$\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}_4$ (298.3) Calcd. C 64.42 H 4.73 N 9.39
Found C 64.36 H 4.75 N 9.39
Mol. mass 298 (MS)

*2-(Ethylamino)-5-oxo-5H-[1]benzopyrano[4,3-*b*]pyridine-3-carbonitrile (7i)*: A mixture of 0.22 g (1.0 mmol) of **2c**, 0.07 g (1.1 mmol) of **3d**, and 0.48 g (5.7 mmol) of piperidine in 3 ml of pyridine was refluxed for 2 h. After cooling, 5 ml of 50% (v/v) aqueous ethanol was added, and the mixture was kept at 0–4 °C for 24 h. The separated crystals were filtered and washed with water; yield 0.14 g (53%) of colorless **7i**, m.p. 287–288 °C (acetonitrile), $R_f = 0.53$. — IR: $\nu = 3352 \text{ cm}^{-1}$ (NH), 3068 (Ar-H), 2227 (CN), 1725 (lactone C=O), 1610. — UV: $\lambda_{\text{max}} = 268 \text{ nm}$, 284, 296, 360.

$\text{C}_{15}\text{H}_{11}\text{N}_3\text{O}_2$ (265.3) Calcd. C 67.91 H 4.18 N 15.84
Found C 67.86 H 4.15 N 15.62
Mol. mass 265 (MS)

*Methyl 2-Ethylamino-5-oxo-5H-[1]benzopyrano[4,3-*b*]pyridine-3-carboxylate (7j)*: A mixture of 0.22 g (1.0 mmol) of **2c**, 0.69 g (7.0 mmol) of **3e**, 1.81 g (21 mmol) of piperidine, and 0.73 g (12 mmol) of glacial acetic acid in 3 ml of methanol was refluxed for 3 h. After cooling, the separated crystals were collected by filtration and dried at 105 °C; yield 0.13 g (44%) of colorless **7j**, m.p. 209 to 210 °C (acetone), $R_f = 0.59$. — IR: $\tilde{\nu} = 3300 \text{ cm}^{-1}$, 1728 (lactone C=O), 1696 (ester C=O), 1610. — UV: $\lambda_{\text{max}} = 268 \text{ nm}$, 284, 296, 360.

$\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}_4$ (298.3) Calcd. C 64.42 H 4.73 N 9.39
Found C 64.37 H 4.72 N 9.36
Mol. mass 298 (MS)

*Ethyl 2-(Ethylamino)-5-oxo-5H-[1]benzopyrano[4,3-*b*]pyridine-3-carboxylate (7k)*: Prepared as described for **7j** from 0.22 g (1.0 mmol) of **2c** and 0.79 g (7.0 mmol) of **3f** in 3 ml of ethanol; yield 0.14 g (45%) of colorless **7k**, m.p. 185–186 °C (ethanol), $R_f = 0.66$. — IR: $\tilde{\nu} = 3362 \text{ cm}^{-1}$ (NH), 1735 (lactone C=O), 1700 (ester C=O), 1615. — UV: $\lambda_{\text{max}} = 266 \text{ nm}$, 283, 294, 364.

$\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_4$ (312.3) Calcd. C 65.37 H 5.16 N 8.97
Found C 65.22 H 5.20 N 8.91
Mol. mass 312 (MS)

*Ethyl 2-(Allylamino)-5-oxo-5H-[1]benzopyrano[4,3-*b*]pyridine-3-carboxylate (7l)*: A mixture of 0.23 g (1.0 mmol) of **2d**, 0.57 g (5.0 mmol) of **3f**, 0.60 g (7.1 mmol) of piperidine, and 0.28 g (4.7 mmol) of glacial acetic acid in 5 ml of ethanol was refluxed for 5 h. After cooling, the separated crystals were filtered, washed with water, and dried at 105 °C; yield 0.18 g (56%) of yellowish **7l**, m.p. 157–159 °C (2-propanol), $R_f = 0.63$. — IR: $\tilde{\nu} = 3323 \text{ cm}^{-1}$ (NH), 1723 (lactone

C=O), 1693 (ester C=O), 1611. — UV: $\lambda_{\text{max}} = 268 \text{ nm}$, 284, 295, 360.

$\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}_4$ (324.3) Calcd. C 66.66 H 4.97 N 8.64
Found C 66.42 H 4.96 N 8.61
Mol. mass 324 (MS)

*Ethyl 2-(Benzylamino)-5-oxo-5H-[1]benzopyrano[4,3-*b*]pyridine-3-carboxylate (7m)*: A mixture of 0.28 g (1.0 mmol) of **2e**, 0.57 g (5.0 mmol) of **3f**, 0.62 g (7.1 mmol) of piperidine, and 0.28 g (4.7 mmol) of glacial acetic acid in 5 ml of ethanol was refluxed for 4 h. After cooling, the separated crystals were filtered, washed with ethanol, and dried at 105 °C; yield 0.28 g (75%) of colorless **7m**, m.p. 192–194 °C (ethanol), $R_f = 0.61$. — IR: $\nu = 3337 \text{ cm}^{-1}$ (NH), 1729 (lactone C=O), 1692 (ester C=O), 1613, 1584. — UV: $\lambda_{\text{max}} = 269 \text{ nm}$, 284, 295, 360.

$\text{C}_{22}\text{H}_{18}\text{N}_2\text{O}_4$ (374.4) Calcd. C 70.58 H 4.85 N 7.48
Found C 70.40 H 4.79 N 7.41
Mol. mass 374 (MS)

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