Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 07-094650- -00004-0000
Fecha: 2008-06-27 13:02:07 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 55

206

FORMULARIO ÚNICO DE OPOSICIÓN

① OPOSICIÓN A :

- [x] Patente de Invención.
- [ ] Patente de Modelo de Utilidad.
- [ ] Diseño Industrial.
- [ ] Esquema de Trazado para Circuitos Integrados.
- [ ] Marcas de Productos o Servicios.
- [ ] Marca Colectiva.
- [ ] Marca de Certificación.
- [ ] Lema Comercial.

② SOLICITUD PUBLICADA

Número del expediente: **07-94650**
Solicitante: GRACEWAY PHARMACEUTICALS, LLC
Apoderado: JUAN PABLO CADENA SARMIENTO
Título de la nueva creación o denominación del signo: "METODO PARA TRATAR QUERATOSIS ACTINICA".
Gaceta: **590**

③ OPOSICIÓN PRESENTADA POR:

SOLICITANTE

Nombre: **GYNOPHARM S.A**
Dirección: **CALLE 80 No. 78B -201**
Nacionalidad o Domicilio:
Lugar de Constitución: **COLOMBIA BARRANQUILLA**
Teléfono: **(571)3719900** Fax: **(571)3730818**
E-mail:

IDENTIFICACIÓN
C.C. [ ] NIT [x]
C.E. [ ] Otro [ ]
Cual ____
Número **802.006.279-4**

REPRESENTANTE O APODERADO

Nombre: **ELIANA ISAURA MORENO BOHORQUEZ**
Dirección: **CARRERA 13 No. 119-95 104**
Teléfono: **(571) 2131213** Fax: **(571) 6121979**
E-mail: **negocios@optimum-co.com**

IDENTIFICACIÓN
C.C. [x] NIT [ ]
C.E. [ ] Otro [ ]
Cual ____
Número **51`975.664** TP **83823**

④ FUNDAMENTOS DE LA OPOSICIÓN:

Causal: **Art.14, 16, 18, 20 y 30 de la Decisión 486 de la CAN**
No cumple con los requisitos de patentabilidad.
Signo opositor:
Justificación:
La presente solicitud no cumple con los requisitos de patentabilidad dado que lo revelado, ya se encontraba en el estado de la técnica o es posible derivarlo de la misma tal y como se demostrará en el capítulo "Fundamento de Hechos".

⑤ **Comprobante de pago No.** _____ **Fecha** _____

⑥ **ANEXOS**

- [x] Comprobante de pago de la tasa.
- [x] Poderes, si fuere el caso.
- [x] Pruebas de los fundamentos de la oposición.
- [ ] Documentos que acrediten el legítimo interés, si fuere el caso.
- [x] Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas.

⑦

NOMBRE: **ELIANA ISAURA MORENO BOHORQUEZ**

FIRMA:

C.C. **51.975.664** **TP.** **83823**

Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.

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Derecho de la Competencia, Propiedad Industrial y Comercio Exterior

Señora Jefe,

DIVISIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Referencia	: Expediente N° 07 094.650
Asunto	: Oposición a la solicitud de patente de Invención titulada "METODO PARA TRATAR QUERATOSIS ACTINICA"
Solicitante	: GRACEWAY PHARMACEUTICALS, LLC.
Opositora	: GYNOPHARM S.A.

Publicada en la Gaceta de la Propiedad Industrial

N° 590 del 31 de marzo de 2008

Yo, ***ELIANA ISAURA MORENO BOHORQUEZ,*** abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 del Consejo Superior de la Judicatura, en mi condición de apoderada de la sociedad ***GYNOPHARM S.A.*** conformada bajo las leyes de la República de Colombia y domiciliada en la ciudad de Barranquilla, Colombia, atentamente manifiesto que estando dentro del término de ley y por orden expresa de mi representada, presento oposición a la concesión del registro de la Patente de Invención titulada "**MÉTODO PARA TRATAR QUERATOSIS ACTÍNICA**", cuyo titular es **GRACEWAY PHARMACEUTICALS, LLC,** y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

Carrera 13 Nº 119-95, Oficina 104. Tel. (571) 2 13 12 13 - Fax. (571) 6 12 19 79
E-mail: negocios@optimum-co.com - www.optimum-co.com
Bogotá Colombia

1. INTERÉS PARA ACTUAR

Conforme a lo dispuesto en el artículo 42 de la Decisión 486 de 2000 de la CAN, estando dentro del término estipulado por la ley, manifiesto el legitimo interés de nuestra representada para oponerse al registro de la patente de la referencia, atendiendo a que la solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizará más adelante y de ser concedida afectaría directamente la comercialización de algunos productos de mi representada, que contienen, en particular 2-metil-1-(2-metilpropil)-1h-imidazo[4,5-c][1,5]naftiridin-4-amina. Por lo tanto, solicito respetuosamente a ese Despacho se sirva tener en cuenta la presente oposición dentro del trámite administrativo que se surte en esta Superintendencia.

2. FUNDAMENTOS DE HECHOS

2.1. La solicitud objeto de la presente fue presentada el 13 de septiembre de 2007, reivindicando prioridad bajo la solicitud US20050661661P del 2005-03-14; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial Nº 590 del 31 de marzo de 2008, cuya publicación internacional corresponde a la WO2006099275 del 2006-09-21.

2.2. La solicitud colombiana **07 094.650** objeto de la presente oposición, se refiere a un método para tratar queratosis actínica, el método caracterizado porque comprende aplicar tópicamente a una lesión de queratosis actínica dos veces por semana por una duración de aproximadamente 8 semanas una formulación que comprende 2-metil1-(2-metilpropil)-1H-imidazo[4,5-c] [1,5]-naftiridin-4-amina en una cantidad de 0.3% en peso, basado en el peso total de la formulación; donde el método está caracterizado porque la 2-metil-1-(2-metilpropil) -1H-imidazo [4, 5-c] [1, 5] naftiridin-4 -amina se adiciona a la formulación como una sal; donde el método está

caracterizado porque la 2-metil-1-(2-metilpropil)-1H-imidazo [4,5-c] [1,5]naftiridin-4 - amina se adiciona a la formulación como una base libre; donde la formulación además comprende un sistema conservador, un antioxidante, un agente quelante, un ácido graso, un componente hidrofóbico, un agente aumentador de viscosidad, un emulsificante, un ajustador del pH, o combinaciones de los mismos; donde la formulación comprende un sistema conservador.

2.3. En primera instancia, se debe advertir que las reivindicaciones se refieren al uso y a un método de tratamiento y no sólo a la composición farmacológica o a un método de fabricación mediante la cual se obtenga un producto tangible y según la legislación, decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- "*Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento (...)*", los usos no están contemplados como patentables; y, Artículo 20.- "*No serán patentables (...) d) los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales*". Solo serán patentables los productos o procedimientos. Por lo tanto a luz de la norma, dicha materia referente al uso y a un método de tratamiento no seria patentable.

2.4. Ahora bien, con base en el artículo 14 de la Decisión 486 de la CAN consagra lo siguiente: "*Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial*". Así las cosas, las invenciones objeto de patente deben ser nuevas y tener nivel inventivo. Bien, pues antes de la fecha de prioridad de esta solicitud se encuentran los siguientes documentos que afecta la patentabilidad de la presente solicitud:

- D1: US2003199538 publicada el 23 de octubre de 2003.

2.5. Ahora bien, el documento D1, particularmente en la descripción revela formulaciones farmacéuticas que comprenden un modificante de respuesta inmune (IRM) escogido de aminas imidazoquinolina, aminas imidazotetrahidroquinolina, aminas imidazopiridina, aminas 6,7-fundidas cicloalquillimidazopiridina, aminas 1,2-acortadas imidazoquinolina, tiazolo-quinolineaminas, oxazolo-quinolinaminas, tiazolo-piridinaminas, oxazolo-piridinaminas, aminas imidazonaftiridina, aminas tetrahidroimidazonaftiridina y aminas tiazolonaftiridina; un ácido graso; y un hidrófobo, como componente aprótico miscible con el ácido graso útil para el tratamiento dermal y condiciones asociadas. Según esta anterioridad D1, se proporcionan formulaciones nuevas tópicas, ventajosas para el tratamiento de keratosis actínico, cicatrices postquirúrgicas, carcinoma de célula básica, dermatitis atópica, y verrugas. Como tal, estas anterioridad D1 revela formulaciones que comprenden IRM partiendo desde una amina imidazonaftiridina, un ácido graso y un componente hidrofóbico. Según estas anteroridades, las formulaciones tópicas son ventajosas para el tratamiento de keratosis actinico. Según esta anterioridad, las formulaciones incluyen un sistema conservador compuesto a partir de etilparaben, propilparaben y ácido ascórbico. También se define en D1 que puede tener dietilenglicol. Así las cosas, como lo evidencia dicho documento D1, la presente solicitud además de comprender una materia de exclusión a la patentabilidad por ser un método terapéutico, tampoco es novedosa pues lo revelado ya se encontraba en el estado de la técnica.

2.6. Por lo tanto, este documento objeto de oposición a la luz del documento D1 carece evidentemente de NOVEDAD.

2.7. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana **07-094650** no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con dos los tres requisitos necesarios para su protección.

2.8. Que por consiguiente, respecto a la solicitud pretendida se tiene que:

2.8.1. CARECE DE NOVEDAD: Según la decisión 486 de la Comunidad Andina de Naciones, Artículo 16.- *"Una invención se considerará nueva cuando no está comprendida en el estado de la técnica. El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida.".* A la fecha de prioridad, 14 de marzo de 2005 ya era conocido, pues como se demostró, era parte del arte anterior con base en el documento D1, un método para tratar queratosis actínica, sobre el cual busca protección en el capítulo reivindicatorio.

2.8.2. CARENCIA DE APLICACIÓN INDUSTRIAL La Decisión 486 de la CAN consagra en su artículo 14 lo siguiente: *"Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial"*. La presente solicitud carece de aplicación Industrial ya que como se demostró anteriormente, algunas cláusulas reclaman el método terapéutico y estos no son aplicables industrialmente porque primero no se obtiene un producto o proceso; y segundo no es reproducible o repetible a escala industrial. Por lo tanto, el objeto de la presente invención referido a los usos y métodos terapéuticos, no cumplen con el requisito de la aplicación industrial.

2.9. Dado lo anterior, es posible deducir que la solicitud y lo reivindicado no es objeto de patentabilidad pues es contrario a lo que dicta la Decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- *"Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación*

industrial.". La solicitud pretendida no cumple con dos de los tres requisitos de patentabilidad.

2.10. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente oposición y negar el registro Patente de invención denominada **"MÉTODO PARA TRATAR QUERATOSIS ACTÍNICA"**, cuyo titular es **GRACEWAY PHARMACEUTICALS, LLC,** solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° **590 del 31 de marzo de** 2008.

3. PRUEBAS

De conformidad con lo dispuesto por las normas vigentes, solicito a usted tener como prueba en este asunto los siguientes:

- D1: US2003199538 publicada el 23 de octubre de 2003.

4. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes:

4.1. Numeral 1 del artículo 586 del Código de Comercio.

4.2. Artículo 42 de la Decisión 486 de la Comisión del Acuerdo de Cartagena.

4.3. En las demás normas concordantes.

5. ANEXOS

Para los efectos correspondientes anexo al presente escrito los siguientes documentos:

1. Poder para actuar en el presente.
2. Documento que acredita al representante legal de **GYNOPHARM S.A.**
3. Recibo de caja del respectivo pago de tasa.
4. Copias de los documentos:

- D1: US2003199538 publicada el 23 de octubre de 2003.

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Derecho de la Competencia, Propiedad
Industrial y Comercio Exterior

6. NOTIFICACIONES

Para efectos de notificaciones que por disposición del artículo 50 del Decreto 01 de 1984 debe hacer su Despacho, informo que mi representada y la suscrita recibiremos notificaciones en la Secretaría de su Despacho o en mis oficinas situadas en la Carrera 13 Nº 119-95, Of. 104 de esta ciudad de Bogotá.

Señor Superintendente,

ELIANA ISAURA MORENO BOHÓRQUEZ
C.C. 51'975.664 de Bogotá
T.P.A. 83823 del C.S. de la J.

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PODER ESPECIAL

Yo, **LUIS PALACIOS ARAGON,** mayor de edad y vecino de la ciudad de Barranquilla (Colombia), identificado como aparece al pie de mi firma, quien en el presente documento actúa en calidad de Representante Legal de la sociedad **GYNOPHARM S.A.** sociedad legalmente constituida y domiciliada en la ciudad de Barranquilla (Colombia), por el presente documento otorgo a la doctora **ELIANA ISAURA MORENO BOHORQUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 del C.S. de la J., poder especial, amplio y suficiente, para formular oposiciones ú observaciones a la solicitud de patente No. **07. 94650,** titulada **"MÉTODO PARA TRATAR QUERATOSIS ACTINICA",** cuyo titular es **GRACEWAY PHARMACEUTICALS, LLC.,** publicada en la gaceta No. 590 del 31 de marzo de 2008.

Nuestro apoderado queda facultado, de manera expresa, para realizar todo tipo de actos necesarios para llevar a cabo el trámite de la oposición, incluyendo, sin limitación, preparar y presentar solicitudes, hacer declaraciones, pagar tasas, contribuciones e impuestos, recabar los títulos o certificados. Asimismo quedan autorizados para impugnar administrativa y judicialmente todo lo que fuere resuelto en el expediente a que se hace expresa referencia en el presente poder, con todas las facultades generales y específicas que fuera requerido para ella.

De la misma manera, además de las facultades que le confiere la naturaleza del presente mandato, se encuentran facultados para recibir, desistir, transigir, sustituir, y reasumir el presente poder, incoar acciones, interponer recursos y demás facultades conferidas por la ley.

Dado y Firmado en Barranquilla (Colombia) a los 19 días del mes de mayo de 2008.

GYNOPHARM S.A.

C.C. Nº 3197[illegible]
NIT: 802006279
Representante Legal

Acepto:

ELIANA ISAURA MORENO BOHORQUEZ
C.C. 51'975.664 de Bogotá
T.P.A. 83823 del C.S. de la J.

RECONOCIMIENTO DE DOCUMENTO PRIVADO

Ante mi, NIBARDO AGUSTIN FUERTES MORALES, Notario Veinticinco del Círculo de Bogotá (E), comparece Luis Alberto Palacios Aragon identificado con cédula de ciudadanía No 819.798 y declara que la firma puesta en el presente instrumento privado es suya y que el contenido del mismo es cierto.

Bogotá D.C. 03 JUN. 2008

FIRMA

NIBARDO AGUSTIN FUERTES MORALES
NOTARIO VEINTICINCO(E)

COMPARECENCIA PERSONAL Y AUTENTICACION DE FIRMA

El Notario Treinta y Nueve (39) de Bogotá, da fé que el anterior escrito dirigido a: Quien Corresponda

fué presentado personalmente por: Eliana Tsouro Moreno Bolaños

quien eshibió la C.C. No. 51975664 de Bogotá.

y T.P. No. 83823 C.S. y manifestó que la firma que aparece en el presente documento es suya, y que acepta el contenido del mismo.

03 JUN. 2008

FIRMA

MIGUEL ARTURO LINERO DE CAMBIL
NOTARIO

Notaría 39

01

7095239 2

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

Fecha : 20080529 Hora Certificado 11:49:33

Operacion : 02CP20529010 PAGINA No. 1

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CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.
EN ?JUNIO DE ESTE A?O SE ELEGIR? JUNTA DIRECTIVA DE LA C?MARA DE COMERCIO. LAS INSCRIPCIONES DE CANDIDATOS DEBEN HACERSE EN LA PRIMERA QUINCENA DE MAYO. PARA INFORMACI?N DETALLADA DIRIGIRSE A LA SEDE PRINCIPAL O COMUNICARSE AL SIGUIENTE TELEFONO: 3303911.

EL SUSCRITO SECRETARIO DE LA CAMARA DE COMERCIO DE BARRANQUILLA, CON FUNDAMENTO EN LAS INSCRIPCIONES DEL REGISTRO MERCANTIL:

C E R T I F I C A

Que por Escritura P?blica No. 3,551 del 17 de Dic/bre de 1997, otorgada en la Notaria 3a. de Barranquilla, inscrito(as) en esta C?mara de Comercio, el 18 de Dic/bre de 1997 bajo el No. 72,965 del libro respectivo, fue constituida la sociedad----------
anonima denominada GYNOPHARM S.A ----------

C E R T I F I C A

Que dicha sociedad ha sido reformada por las siguientes escrituras y/o documentos privados:

Numero	aaaa/mm/dd	Notaria	No. Insc o Reg	aaaa/mm/dd
532	1999/03/25	Notaria 3a. de Barranquilla	80,373	1999/04/13

C E R T I F I C A

Que de acuerdo con la(s) escritura(s) arriba citada(s), la sociedad se rige por las siguientes disposiciones:
DENOMINACION O RAZON SOCIAL:
GYNOPHARM S.A.----------
DOMICILIO PRINCIPAL: Barranquilla.
NIT No: 802.006.279-4.
MATRICULA MERCANTIL: 245,470.

C E R T I F I C A

Direccion para notificaciones judiciales:
CL 80 No 78 B - 201.
De la ciudad de Barranquilla.

C E R T I F I C A

DURACION: El t?rmino de duraci?n de la sociedad se fij? hasta el 16 de Dic/bre de 2047.

C E R T I F I C A

*** CONTINUA ***

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

Fecha : 20080529 Hora Certificado 11:49:33

Operacion : 02CP20529010 PAGINA No. 2

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OBJETO SOCIAL: a) La fabricacion de capsulas y otro productos similares a partir de materiales tales como gelatinas u otros de distinta naturaleza, que puedan ser utilizados como envases o recipientes de productos y sustancias quimicas, farmaceuticas y cosmeticas, para uso y consumo humano y veterinario. b) La investigacion, desarrollo y fabricacion de toda clase de productos y sustancias quimicas, farmaceuticas y cosmeticas para uso y consumo humano, animal y vegetal. c) La compra y venta de meterias primas , insumos y productos intermedios necesarios para los procesos de fabricacion de sustancias quimicas, farmaceuticas y cosmeticas, asi como la comercializacion interna y externa de los productos terminados. d) La compra, venta, importacion, exportacion y distribucion de toda clase de elementos instrumentales y equipos, medicos, quirurgicos, odontologicos y hospitalarios para la salud humana y animal. e) Actuar como representante o agente de personas naturales y juridicas nacionales y extranjeras en la realizacion de operaciones o transacciones relacionadas con la industria farmaceutica y en especial con cualesquiera de las actividades descritas en los literales a), b), c) y d) antes transcritos. f) Prestar los servicios de asesoria y consultoria en las areas administrativa, de mercadeo, analisis clinico, asistencia tecnica, investigacion, costos y produccion exportaciones, importaciones, ventas, relacionadas con iguales o similares actividades a las que constituyen el objeto de GYNOPHARM S.A., asi como los de publicidad y promocion de productos quimicos, cosmeticos y farmaceuticos para uso humano, animal o industrial. g) Adquirir, operar, administrar y explotar, a cualquier titulo,empresas o establecimientos dedicados a la investigacion, desarrollo, fabricacion o comercializacion de productos quimicos, farmaceuticos, hospitalarios o cosmeticos. En desarrollo de su objeto principal, la sociedad podra tomar interes social como accionista, socio o fundador de empresas que tengan igual o similar objeto; comprar, vender, importar y exportar maquinarias, insumos y repuestos requeridos para el desarrollo de sus actividades; tomar dinero en prestamo,financiar y garantizar las operaciones comerciales que celebre con terceros relativas a su objeto; celebrar y ejecutar todo tipo de actos y contratos necesarios para desarrollar sus operacioes; girar, aceptar, otorgar y protestar todo tipo de titulos valores e instrumentos negociables; comprar, vender y constituir gravamenes sobre bienes muebles e inmuebles; designar representantes o apoderados en el pais y en el exterior y, en general, realizar cualquier acto o negocio que sea necesario o conveniente para el desarrollo de su objeto social y para la mejor proteccion de sus intereses corporativos o lo de sus socios.----------

C E R T I F I C A

CAPITAL	Nro Acciones	Valor Acci?n
Autorizado		
$**********4,000,000,000	**********4,000,000	**********1,000

*** CONTINUA ***

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Suscrito
$**********2,672,646,000 ************2,672,646 ****************1,000
Pagado
$**********2,672,646,000 ************2,672,646 ****************1,000

C E R T I F I C A

ADMINISTRACION: Seran funciones de la junta directiva, entre otras: Autorizar cualquier acto o contrato cuya cuantia sea superior al equivalente en pesos Colombianos a cincuenta mil dolares de los Estados Unidos de America (US$50.000.oo), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion y para enajenar o gravar bienes inmuebles y demas activos fijos de la sociedad, cualquiera que sea la cuantia de la transaccion. Las demas que le sean propias y no esten atribuidas a otro organo social y las que le correspondan en virtud de la ley. la sociedad tendra un Gerente General, quien ejercera la administracion y representacion legal de la sociedad y tendra las siguientes atribuciones, entre otras: Ejercer la representacion legal de la sociedad en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos Colombianos a cincuenta mil dolares de los Estados Unidos de America (US$50.000.oo), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto. Para enajenar, a cualquier titulo, bienes inmuebles de la sociedad o constituir gravamenes sobre los mismos, debera obtener la aprobacion de la junta directiva, cualquiera que sea la cuantia de la transaccion; o las demas funciones que le correspondan como representante legal por disposicion de la ley, de estos estatutos o de la junta directiva. El Gerente General tendra un suplente, designado por la junta directiva, quien lo reemplazara con identicas facultades en sus faltas temporales, absolutas o meramente acciedentales, sin que sea necesario para ello acreditar la ausencia del principal.----------

C E R T I F I C A

Que seg?n Acta No. 15 del 18 de Febrero de 2008 correspondiente a la Asamblea de Accionistas en Bogota, de la sociedad:
GYNOPHARM S.A.----------
cuya parte pertinente se inscribi? en esta C?mara de Comercio, el 25 de Febrero de 2008 bajo el No. 137,919 del libro respectivo, fueron hechos los siguientes nombramientos:

CLASE: JUNTA DIRECTIVA

*** CONTINUA ***

****

Principales

1.	Llobet Poal Manuel	CC.******14,670,196
2.	Zanatta Reherman Leonardo Andres	CC.*******2,760,271
3.	Munoz Marroquin Diego	CC.*******7,688,292
4.	Montealegre Gonzalez Andres Leonardo	CC.******79,950,262

Suplentes

1.	Agudelo Pelaez Luis Hernando	CC.******14,238,997
2.	Aroca Almanza Arleth Ayelina	CC.******36,718,415
3.	Penaranda Urbina Adriana Paola	CC.******53,120,683
4.	tovar Vasquez Ruth	CC.******52,175,756

C E R T I F I C A

Que seg?n Acta No. 18 del 30 de Octubre de 2003 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: GYNOPHARM S.A. cuya parte pertinente se inscribi? en esta C?mara de Comercio, el 06 de Nov/bre de 2003 bajo el No. 107,783 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificaci?n
Gerente General.	
Palacios Aragon Luis Alberto	CE.*********319,788

C E R T I F I C A

Que seg?n Acta No. 49 del 03 de Marzo de 2008 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: GYNOPHARM S.A. cuya parte pertinente se inscribi? en esta C?mara de Comercio, el 11 de Marzo de 2008 bajo el No. 138,342 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificaci?n
Suplente del Gerente.	
Mollajoli Centurion Andres Fernando	CE.*********351,283

C E R T I F I C A

Que seg?n Acta No. 16 del 08 de Mayo de 2008 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: GYNOPHARM S.A. cuya parte pertinente se inscribi? en esta C?mara de Comercio, el 22 de Mayo de 2008 bajo el No. 140,053 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificaci?n
Revisor Fiscal	
Marroquin Sepulveda Edgar	CC.******17,147,542

C E R T I F I C A

Que segun Documento Privado de fecha 10 de Octubre del 2.000, ins-

*** CONTINUA ***

****

crito en esta Camara de Comercio el 23 de Noviembre del 2.000 bajo el No. 1.872 del libro repectivo, consta que el senor RUBEN MINSKI GONTOVNIK C.C. No. 7.463.982, actuando como Presidente y representante legal de la sociedad GYNOPHARM S.A., otorga Poder Especial, Amplio y Suficienta a KAREN JENNIFER FIGUEROA GARCIA C.C. No. 32.-732.070, para que en nombre y representacion de la sociedad suscriba todas las declaraciones cambiarias a que esta obligada GYNOPHARM S.A., en el giro normal de sus negocios y operaciones sociales.-----

C E R T I F I C A

Que segun Documento Privado de fecha 10 de Octubre del 2.000, inscrito en esta Camara de Comercio el 12 de junio del 2.002, bajo el 2.164 del libro respectivo,consta que el senor JORGE CASTELLANOS MARTINEZ,identificado con C.C.No.19.460.089,actuando como representante legal de la sociedad GYNOPHARM S.A, otorga Poder Especial Amplio y Suficiente a KAREN FIGUEROA GARCIA, identificada con la cedula de ciudadania No.32.732.070 de Barranquilla, mediante documento privado de octubre 10/2000, inscrito en la Camara de Comercio de Barranquilla bajo el No.1.872 del libro respectivo, para que en representacion de GYNOFARM S.A, suscriba las declaraciones cambiarias a los que esta obligada GYNOFARM S.A. en el giro ordinario de sus negocios y operaciones sociales.----------

C E R T I F I C A

Que en esta C?mara de Comercio no aparecen inscripciones posteriores de documentos referentes a reforma, disoluci?n, liquidaci?n o nombramientos de representantes legales de la expresada sociedad.

C E R T I F I C A

Que su ?ltima Renovaci?n fue el: 23 de Abril de 2008.

La informaci?n sobre embargos de establecimiento se suministra en Certificados de Matr?cula, la de contratos sujetos a registro, en Certificados Especiales.

C E R T I F I C A

Que los actos de registro aqu? certificados quedan en firme cinco d?as h?biles despues de la correspondiente inscripci?n, siempre que, dentro de dicho t?rmino, no sean objeto de los recursos de reposici?n ante esta entidad, y/o de apelaci?n para ante la Superintendencia de Industria y Comercio.

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720 219 15

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 07-094650- -00004-0000

Fecha: 2008-06-27 13:02:07 Dep. 2020 NUECREACIONE
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Act. 400 OPOSIOBSERVTER Folios: 55

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 43,781
FECHA : JUNIO 3 DE 2008

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
GYNOPHARM S.A.	CONSIGNACION	BANCO DE BOGOTA	062754387	4638384	29/04/2008	798,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-04 PRESENTACION DE OBSERVACIONES	12 MARCAS Y LEMAS COMERCIALES	266,000.00
		TOTAL : $	266,000.00

SON: DOSCIENTOS SESENTA Y SEIS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

ANEXO 1

Carrera 13 N° 119-95, Oficina 104. Tel. (571) 2 13 12 13 - Fax. (571) 6 12 19 79
E-mail: negocios@optimum-co.com - www.optimum-co.com
Bogotá Colombia

US 20030199538A1

(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2003/0199538 A1**

Skwierczynski et al. (43) **Pub. Date: Oct. 23, 2003**

(54) **PHARMACEUTICAL FORMULATION COMPRISING AN IMMUNE RESPONSE MODIFIER**

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(73) Assignee: **3M Innovative Properties Company**

(21) Appl. No.: **10/306,019**

(22) Filed: **Nov. 27, 2002**

Related U.S. Application Data

(60) Provisional application No. 60/340,605, filed on Nov. 29, 2001. Provisional application No. 60/378,452, filed on May 6, 2002.

Publication Classification

(51) **Int. Cl.**[7] **A61K 31/4745**; A61K 31/20

(52) **U.S. Cl.** **514/291**; 514/292; 514/558

(57) **ABSTRACT**

Pharmaceutical formulations comprising an immune response modifier (IRM) chosen from imidazoquinoline amines, imidazotetrahydroquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, 1,2-bridged imidazoquinoline amines, thiazolo-quinolineamines, oxazolo-quinolinamines, thiazolo-pyridinamines, oxazolo-pyridinamines, imidazonaphthyridine amines, tetrahydroimidazonaphthyridine amines, and thiazolonaphthyridine amines; a fatty acid; and a hydrophobic, aprotic component miscible with the fatty acid are useful for the treatment of dermal associated conditions. Novel topical formulations are provided. In one embodiment, the topical formulations are advantageous for treatment of actinic keratosis, postsurgical scars, basal cell carcinoma, atopic dermatitis, and warts.

PHARMACEUTICAL FORMULATION COMPRISING AN IMMUNE RESPONSE MODIFIER

CROSS REFERENCE TO RELATED APPLICATION

[0001] This application claims priority to Provisional Patent Application Serial No. 60/340,605, filed Nov. 29, 2001 and Provisional Patent Application Serial No. 60/378,452, filed May 6, 2002.

FIELD OF THE INVENTION

[0002] The present invention is directed to pharmaceutical formulations comprising at least one immune response modifier chosen from imidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, 1,2-bridged imidazoquinoline amines, thiazoloquinoline amines, oxazoloquinoline amines, thiazolopyridine amines, oxazolopyridine amines, imidazonaphthyridine amines, imidazotetrahydronaphthyridine amines, and thiazolonaphthyridine amines. Embodiments of the present invention are directed to topical formulations for application to the skin of a mammal. Other embodiments of the present invention are directed to methods for treating dermal diseases.

BACKGROUND

[0003] Many imidazoquinoline amine, imidazopyridine amine, 6,7-fused cycloalkylimidazopyridine amine, 1,2-bridged imidazoquinoline amine, thiazoloquinoline amine, oxazoloquinoline amine, thiazolopyridine amine, oxazolopyridine amine, imidazonaphthyridine amine, imidazotetrahydronaphthyridine amine, and thiazolonaphthyridine amine compounds have demonstrated potent immunostimulating, antiviral and antitumor (including anticancer) activity, and have also been shown to be useful as vaccine adjuvants. These compounds are hereinafter collectively referred to as "IRM" (immune response modifier) compounds. One of these IRM compounds, known as imiquimod, has been commercialized in a topical formulation, Aldara™, for the treatment of anogenital warts associated with human papillomavirus.

[0004] The mechanism for the antiviral and antitumor activity of these IRM compounds is thought to be due in substantial part to enhancement of the immune response by induction of various important cytokines (e.g., interferons, interleukins, tumor necrosis factor, etc.). Such compounds have been shown to stimulate a rapid release of certain monocyte/macrophage-derived cytokines and are also capable of stimulating B cells to secrete antibodies which play an important role in these IRM compounds' antiviral and antitumor activities. One of the predominant immunostimulating responses to these compounds is the induction of interferon (IFN)-α production, which is believed to be very important in the acute antiviral and antitumor activities seen. Moreover, up regulation of other cytokines such as, for example, tumor necrosis factor (TNF), Interleukin-1 (IL-1) and IL-6 also have potentially beneficial activities and are believed to contribute to the antiviral and antitumor properties of these compounds.

[0005] Although some of the beneficial effects of IRMs are known, the ability to provide therapeutic benefit via topical application of an IRM compound for treatment of a particular condition at a particular location may be hindered by a variety of factors. These factors include irritation of the skin to which the formulation is applied, formulation wash away, insolubility and/or degradation of the IRM compound in the formulation, physical instability of the formulation (e.g., separation of components, thickening, precipitation/agglomerization of active ingredient, and the like), poor permeation, and undesired systemic delivery of the topically applied IRM compound. Accordingly, there is a continuing need for new methods and formulations to provide the greatest therapeutic benefit from this class of compounds.

SUMMARY OF THE INVENTION

[0006] At several locations throughout the specification, guidance is provided through lists of examples. In each instance, the recited list serves only as a representative group; it is not meant that the list is exclusive.

[0007] In one aspect, the present invention is directed to a pharmaceutical formulation comprising an immune response modifier selected from imidazoquinoline amines, imidazotetrahydroquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, 1,2-bridged imidazoquinoline amines, thiazoloquinoline amines, oxazoloquinoline amines, thiazolopyridine amines, oxazolopyridine amines, imidazonaphthyridine amines, imidazotetrahydronaphthyridine amines, and thiazolonaphthyridine amines; a fatty acid; a hydrophobic, aprotic component miscible with the fatty acid and comprising a hydrocarbyl group of 7 or more carbon atoms; and a hydrophilic viscosity enhancing agent selected from cellulose ethers and carbomers.

[0008] In one embodiment, the pharmaceutical formulation comprises an immune response modifier selected from imidazonaphthyridine amines, imidazotetrahydronaphthyridine amines, and thiazolonaphthyridine amines; a fatty acid; and a hydrophobic, aprotic component miscible with the fatty acid and comprising a hydrocarbyl group of 7 or more carbon atoms.

[0009] The formulation can further comprise one or more of a preservative system, an emulsifier, and water.

[0010] In another aspect, the present invention is directed to a method of treatment of a dermal associated condition comprising applying to skin a topical formulation comprising an immune response modifier selected from imidazoquinoline amines, imidazotetrahydroquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, 1,2-bridged imidazoquinoline amines, thiazoloquinoline amines, oxazoloquinoline amines, thiazolopyridine amines, oxazolopyridine amines, imidazonaphthyridine amines, imidazotetrahydronaphthyridine amines, and thiazolonaphthyridine amines; a fatty acid; a hydrophobic, aprotic component miscible with the fatty acid and comprising a hydrocarbyl group of 7 or more carbon atoms; and a hydrophilic viscosity enhancing agent selected from cellulose ethers and carbomers.

[0011] In one embodiment, the method of treatment of a dermal associated condition comprises applying to skin a formulation comprising an immune response modifier selected from imidazonaphthyridine amines, imidazotetrahydronaphthyridine amines, and thiazolonaphthyridine amines; a fatty acid; and a hydrophobic, aprotic component

miscible with the fatty acid and comprising a hydrocarbyl group of 7 or more carbon atoms.

[0012] In other embodiments, the method of treatment of a dermal associated condition comprises applying to skin a formulation comprising an immune response modifier selected from imidazonaphthyridine amines, imidazotetrahydronaphthyridine amines, and thiazolonaphthyridine amines; a fatty acid; a hydrophobic, aprotic component miscible with the fatty acid and comprising a hydrocarbyl group of 7 or more carbon atoms; and further comprising one or more of a preservative system, an emulsifier, and water.

[0013] In one embodiment, the dermal associated condition is selected from actinic keratosis, postsurgical scars, basal cell carcinoma, atopic dermatitis, and warts.

[0014] In another aspect, the present invention is directed to a method for delivering an immune response modifier to a dermal surface, the method comprising the steps of selecting a formulation comprising a compound selected from imidazoquinoline amines, imidazotetrahydroquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, 1,2-bridged imidazoquinoline amines, thiazoloquinoline amines, oxazolo-quinoline amines, thiazolopyridine amines, oxazolopyridine amines, imidazonaphthyridine amines, imidazotetrahydronaphthyridine amines, and thiazolonaphthyridine amines; a fatty acid; a hydrophobic, aprotic component miscible with the fatty acid and comprising a hydrocarbyl group of 7 or more carbon atoms; and a hydrophilic viscosity enhancing agent selected from cellulose ethers and carbomers; and applying the selected formulation to the dermal surface for a time sufficient to allow the formulation to deliver the IRM to the dermal surface.

[0015] In one embodiment, the selected formulation comprises an immune response modifier selected from imidazonaphthyridine amines, imidazotetrahydronaphthyridine amines, and thiazolonaphthyridine amines; a fatty acid; and a hydrophobic, aprotic component miscible with the fatty acid and comprising a hydrocarbyl group of 7 or more carbon atoms.

[0016] Unless otherwise indicated, all numbers expressing quantities, ratios, and numerical properties of ingredients, reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term "about".

[0017] As used herein, "a" or "an" or "the" are used interchangeably with "at least one", to mean "one or more" of the element being modified.

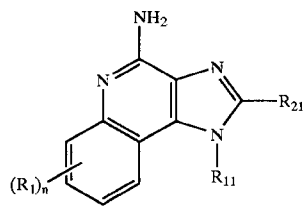
DETAILED DESCRIPTION

[0018] In one aspect, the present invention is directed to a formulation comprising an immune response modifier compound selected from imidazoquinoline amines, imidazotetrahydroquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, 1,2-bridged imidazoquinoline amines, thiazoloquinoline amines, oxazoloquinoline amines, thiazolopyridine amines, oxazolopyridine amines, imidazonaphthyridine amines, imidazotetrahydronaphthyridine amines, and thiazolonaphthyridine amines; a fatty acid; a hydrophobic, aprotic component miscible with the fatty acid and comprising a hydrocarbyl group of 7 or more carbon atoms, and a hydrophilic viscosity enhancing agent selected from cellulose ethers and carbomers.

[0019] These immune response modifier compounds, methods of making them, methods of using them and compositions containing them are disclosed in U.S. Pat. Nos. 4,689,338; 4,929,624; 4,988,815; 5,037,986; 5,175,296; 5,238,944; 5,266,575; 5,268,376; 5,346,905; 5,352,784; 5,367,076; 5,389,640; 5,395,937; 5,446,153; 5,482,936; 5,693,811; 5,741,908; 5,756,747; 5,939,090; 6,039,969; 6,083,505; 6,110,929; 6,194,425; 6,245,776; 6,331,539; 6,376,669; and 6,451,810; European Patent 0 394 026; US Publication 2002/0055517; and PCT Publications WO 00/47719; WO 00/76518; WO 01/74343; WO 02/46188; WO 02/46189; WO 02/46190; WO 02/46191; WO 02/46192; WO 02/46193; WO 02/46194; and WO 02/46749 the disclosures of which are incorporated by reference herein.

[0020] As noted above, many of the IRM compounds useful in the present invention have demonstrated significant immunomodulating activity. In certain embodiments of the present invention, the IRM compound can be chosen from imidazoquinoline amines, for example, 1H-imidazo[4,5-c]quinolin-4-amines defined by one of Formulas I-V below:

I



[0021] wherein

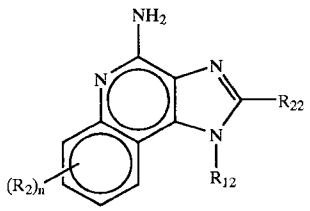
[0022] R_{11} is chosen from alkyl of one to ten carbon atoms, hydroxyalkyl of one to six carbon atoms, acyloxyalkyl wherein the acyloxy moiety is alkanoyloxy of two to four carbon atoms or benzoyloxy, and the alkyl moiety contains one to six carbon atoms, benzyl, (phenyl)ethyl and phenyl, said benzyl, (phenyl)ethyl or phenyl substituent being optionally substituted on the benzene ring by one or two moieties independently chosen from alkyl of one to four carbon atoms, alkoxy of one to four carbon atoms and halogen, with the proviso that if said benzene ring is substituted by two of said moieties, then said moieties together contain no more than six carbon atoms;

[0023] R_{21} is chosen from hydrogen, alkyl of one to eight carbon atoms, benzyl, (phenyl)ethyl and phenyl, the benzyl, (phenyl)ethyl or phenyl substituent being optionally substituted on the benzene ring by one or two moieties independently chosen from alkyl of one to four carbon atoms, alkoxy of one to four carbon atoms and halogen, with the proviso that when the benzene ring is substituted by two of said moieties, then the moieties together contain no more than six carbon atoms; and

[0024] each R_1 is independently chosen from alkoxy of one to four carbon atoms, halogen, and alkyl of

one to four carbon atoms, and n is an integer from 0 to 2, with the proviso that if n is 2, then said R_1 groups together contain no more than six carbon atoms;

II



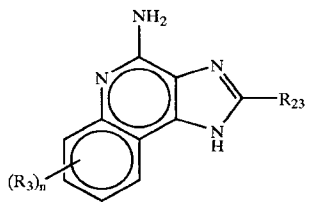
[0025] wherein

[0026] R_{12} is chosen from straight chain or branched chain alkenyl containing two to ten carbon atoms and substituted straight chain or branched chain alkenyl containing two to ten carbon atoms, wherein the substituent is chosen from straight chain or branched chain alkyl containing one to four carbon atoms and cycloalkyl containing three to six carbon atoms; and cycloalkyl containing three to six carbon atoms substituted by straight chain or branched chain alkyl containing one to four carbon atoms; and

[0027] R_{22} is chosen from hydrogen, straight chain or branched chain alkyl containing one to eight carbon atoms, benzyl, (phenyl)ethyl and phenyl, the benzyl, (phenyl)ethyl or phenyl substituent being optionally substituted on the benzene ring by one or two moieties independently chosen from straight chain or branched chain alkyl containing one to four carbon atoms, straight chain or branched chain alkoxy containing one to four carbon atoms, and halogen, with the proviso that when the benzene ring is substituted by two such moieties, then the moieties together contain no more than six carbon atoms; and

[0028] each R_2 is independently chosen from straight chain or branched chain alkoxy containing one to four carbon atoms, halogen, and straight chain or branched chain alkyl containing one to four carbon atoms, and n is an integer from zero to 2, with the proviso that if n is 2, then said R_2 groups together contain no more than six carbon atoms;

III

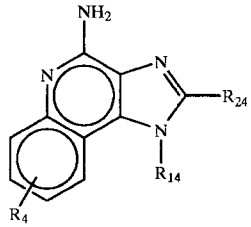


[0029] wherein

[0030] R_{23} is chosen from hydrogen, straight chain or branched chain alkyl of one to eight carbon atoms, benzyl, (phenyl)ethyl and phenyl, the benzyl, (phenyl)ethyl or phenyl substituent being optionally substituted on the benzene ring by one or two moieties independently chosen from straight chain or branched chain alkyl of one to four carbon atoms, straight chain or branched chain alkoxy of one to four carbon atoms, and halogen, with the proviso that when the benzene ring is substituted by two such moieties, then the moieties together contain no more than six carbon atoms; and

[0031] each R_3 is independently chosen from straight chain or branched chain alkoxy of one to four carbon atoms, halogen, and straight chain or branched chain alkyl of one to four carbon atoms, and n is an integer from zero to 2, with the proviso that if n is 2, then said R_3 groups together contain no more than six carbon atoms;

IV



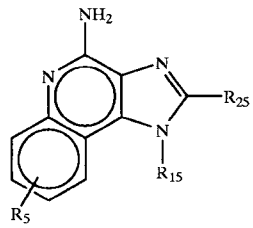
[0032] wherein

[0033] R_{14} is —CHR_xR_y wherein R_y is hydrogen or a carbon-carbon bond, with the proviso that when R_y is hydrogen R_x is alkoxy of one to four carbon atoms, hydroxyalkoxy of one to four carbon atoms, 1-alkynyl of two to ten carbon atoms, tetrahydropyranyl, alkoxyalkyl wherein the alkoxy moiety contains one to four carbon atoms and the alkyl moiety contains one to four carbon atoms, or 2-, 3-, or 4-pyridyl, and with the further proviso that when R_y is a carbon-carbon bond R_y and R_x together form a tetrahydrofuranyl group optionally substituted with one or more substituents independently chosen from hydroxy and hydroxyalkyl of one to four carbon atoms;

[0034] R_{24} is chosen from hydrogen, alkyl of one to four carbon atoms, phenyl, and substituted phenyl wherein the substituent is chosen from alkyl of one to four carbon atoms, alkoxy of one to four carbon atoms, and halogen; and

[0035] R_4 is chosen from hydrogen, straight chain or branched chain alkoxy containing one to four carbon atoms, halogen, and straight chain or branched chain alkyl containing one to four carbon atoms;

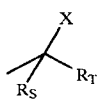
V



[0036] wherein

[0037] R_{15} is chosen from: hydrogen; straight chain or branched chain alkyl containing one to ten carbon atoms and substituted straight chain or branched chain alkyl containing one to ten carbon atoms, wherein the substituent is chosen from cycloalkyl containing three to six carbon atoms and cycloalkyl containing three to six carbon atoms substituted by straight chain or branched chain alkyl containing one to four carbon atoms; straight chain or branched chain alkenyl containing two to ten carbon atoms and substituted straight chain or branched chain alkenyl containing two to ten carbon atoms, wherein the substituent is chosen from cycloalkyl containing three to six carbon atoms and cycloalkyl containing three to six carbon atoms substituted by straight chain or branched chain alkyl containing one to four carbon atoms; hydroxyalkyl of one to six carbon atoms; alkoxyalkyl wherein the alkoxy moiety contains one to four carbon atoms and the alkyl moiety contains one to six carbon atoms; acyloxyalkyl wherein the acyloxy moiety is alkanoyloxy of two to four carbon atoms or benzoyloxy, and the alkyl moiety contains one to six carbon atoms; benzyl; (phenyl)ethyl; and phenyl; said benzyl, (phenyl-)ethyl or phenyl substituent being optionally substituted on the benzene ring by one or two moieties independently chosen from alkyl of one to four carbon atoms, alkoxy of one to four carbon atoms, and halogen, with the proviso that when said benzene ring is substituted by two of said moieties, then the moieties together contain no more than six carbon atoms;

[0038] R_{25} is



[0039] wherein

[0040] R_S and R_T are independently chosen from hydrogen, alkyl of one to four carbon atoms, phenyl, and substituted phenyl wherein the substituent is chosen from alkyl of one to four carbon atoms, alkoxy of one to four carbon atoms, and halogen;

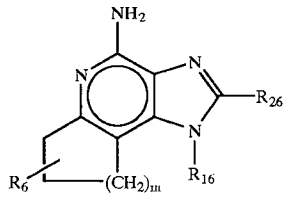
[0041] X is chosen from alkoxy containing one to four carbon atoms, alkoxyalkyl wherein the alkoxy moiety contains one to four carbon atoms and the alkyl moiety contains one to four carbon atoms, hydroxyalkyl of one to four carbon atoms, haloalkyl of one to four carbon atoms, alkylamido wherein the alkyl group contains one to four carbon atoms, amino, substituted amino wherein the substituent is alkyl or hydroxyalkyl of one to four carbon atoms, azido, chloro, hydroxy, 1-morpholino, 1-pyrrolidino, alkylthio of one to four carbon atoms; and

[0042] R_5 is chosen from hydrogen, straight chain or branched chain alkoxy containing one to four carbon atoms, halogen, and straight chain or branched chain alkyl containing one to four carbon atoms;

[0043] and a pharmaceutically acceptable salt of any of the foregoing.

[0044] The IRM compound can also be chosen from 6,7 fused cycloalkylimidazopyridine amines defined by Formula VI below:

VI



[0045] wherein m is 1, 2, or 3;

[0046] R_{16} is chosen from hydrogen; cyclic alkyl of three, four, or five carbon atoms; straight chain or branched chain alkyl containing one to ten carbon atoms and substituted straight chain or branched chain alkyl containing one to ten carbon atoms, wherein the substituent is chosen from cycloalkyl containing three to six carbon atoms and cycloalkyl containing three to six carbon atoms substituted by straight chain or branched chain alkyl containing one to four carbon atoms; fluoro- or chloroalkyl containing from one to ten carbon atoms and one or more fluorine or chlorine atoms; straight chain or branched chain alkenyl containing two to ten carbon atoms and substituted straight chain or branched chain alkenyl containing two to ten carbon atoms, wherein the substituent is chosen from cycloalkyl containing three to six carbon atoms and cycloalkyl containing three to six carbon atoms substituted by straight chain or branched chain alkyl containing one to four carbon atoms; hydroxyalkyl of one to six carbon atoms; alkoxyalkyl wherein the alkoxy moiety contains one to four carbon atoms and the alkyl moiety contains one to six carbon atoms; acyloxyalkyl wherein the acyloxy moiety is alkanoyloxy of two to four carbon atoms or benzoyloxy, and the alkyl moiety contains one to six carbon atoms, with the proviso that any such alkyl, substituted alkyl, alkenyl, substituted alkenyl, hydroxyalkyl, alkoxyalkyl, or acyloxyalkyl group does not have a fully carbon substituted carbon atom bonded directly to the nitrogen atom; benzyl; (phenyl)ethyl; and phenyl; said benzyl, (phenyl)ethyl or phenyl substituent being optionally substituted on the benzene ring by one or two moieties independently chosen from alkyl of one to four carbon atoms, alkoxy of one to four carbon atoms, and halogen, with the proviso that when said benzene ring is substituted by two of said moieties, then the moieties together contain no more than six carbon atoms;

[0047] and $—CHR_xR_y$

[0048] wherein

[0049] R_y is hydrogen or a carbon-carbon bond, with the proviso that when R_y is hydrogen R_x is alkoxy of one to four carbon atoms, hydroxyalkoxy of one to

four carbon atoms, 1-alkynyl of two to ten carbon atoms, tetrahydropyranyl, alkoxyalkyl wherein the alkoxy moiety contains one to four carbon atoms and the alkyl moiety contains one to four carbon atoms, or 2-, 3-, or 4-pyridyl, and with the further proviso that when R_y is a carbon-carbon bond R_y and R_x together form a tetrahydrofuranyl group optionally substituted with one or more substituents independently chosen from hydroxy and hydroxyalkyl of one to four carbon atoms,

[0050] R_{26} is chosen from hydrogen, straight chain or branched chain alkyl containing one to eight carbon atoms, straight chain or branched chain hydroxyalkyl containing one to six carbon atoms, morpholinoalkyl, benzyl, (phenyl)ethyl and phenyl, the benzyl, (phenyl)ethyl or phenyl substituent being optionally substituted on the benzene ring by a moiety chosen from methyl, methoxy, and halogen; and

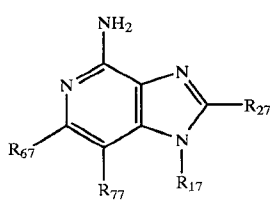
[0051] —$C(R_S)(R_T)(X)$ wherein R_S and R_T are independently chosen from hydrogen, alkyl of one to four carbon atoms, phenyl, and substituted phenyl wherein the substituent is chosen from alkyl of one to four carbon atoms, alkoxy of one to four carbon atoms, and halogen;

[0052] X is chosen from alkoxy containing one to four carbon atoms, alkoxyalkyl wherein the alkoxy moiety contains one to four carbon atoms and the alkyl moiety contains one to four carbon atoms, haloalkyl of one to four carbon atoms, alkylamido wherein the alkyl group contains one to four carbon atoms, amino, substituted amino wherein the substituent is alkyl or hydroxyalkyl of one to four carbon atoms, azido, alkylthio of one to four carbon atoms, and morpholinoalkyl wherein the alkyl moiety contains one to four carbon atoms, and

[0053] R_6 is chosen from hydrogen, fluoro, chloro, straight chain or branched chain alkyl containing one to four carbon atoms, and straight chain or branched chain fluoro- or chloroalkyl containing one to four carbon atoms and at least one fluorine or chlorine atom; and pharmaceutically acceptable salts thereof.

[0054] In other embodiments of the present invention, the IRM compound can be chosen from imidazopyridine amines defined by Formula VII below:

VII



[0055] wherein

[0056] R_{17} is chosen from hydrogen; —CH_2R_W wherein R_W is chosen from straight chain, branched chain, or cyclic alkyl containing one to ten carbon atoms, straight chain or branched chain alkenyl containing two to ten carbon atoms, straight chain or branched chain hydroxyalkyl containing one to six carbon atoms, alkoxyalkyl wherein the alkoxy moiety contains one to four carbon atoms and the alkyl moiety contains one to six carbon atoms, and phenylethyl; and —$CH{=}CR_ZR_Z$ wherein each R_Z is independently straight chain, branched chain, or cyclic alkyl of one to six carbon atoms;

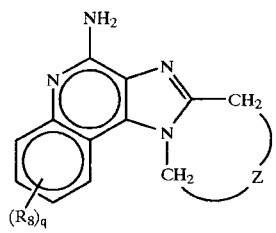
[0057] R_{27} is chosen from hydrogen; straight chain or branched chain alkyl containing one to eight carbon atoms; straight chain or branched chain hydroxyalkyl containing one to six carbon atoms; alkoxyalkyl wherein the alkoxy moiety contains one to four carbon atoms and the alkyl moiety contains one to six carbon atoms; benzyl, (phenyl)ethyl and phenyl, the benzyl, (phenyl)ethyl oand phenyl being optionally substituted on the benzene ring by a moiety chosen from methyl, methoxy, and halogen; and morpholinoalkyl wherein the alkyl moiety contains one to four carbon atoms;

[0058] R_{67} and R_{77} are independently chosen from hydrogen and alkyl of one to five carbon atoms, with the proviso that R_{67} and R_{77} taken together contain no more than six carbon atoms, and with the further proviso that when R_{77} is hydrogen then R_{67} is other than hydrogen and R_{27} is other than hydrogen or morpholinoalkyl, and with the further proviso that when R_{67} is hydrogen then R_{77} and R_{27} are other than hydrogen;

[0059] and pharmaceutically acceptable salts thereof.

[0060] In yet another embodiment of the present invention, the IRM compound can be chosen from 1,2-bridged imidazoquinoline amines defined by Formula VIII below:

VIII



[0061] wherein

[0062] Z is chosen from:

[0063] —$(CH_2)_p$— wherein p is 1 to 4;

[0064] —$(CH_2)_a$—$C(R_DR_E)(CH_2)_b$—, wherein a and b are integers and a+b is 0 to 3, R_D is hydrogen or alkyl of one to four carbon atoms, and R_E is chosen from alkyl of one to four carbon atoms, hydroxy, —OR_F wherein R_F is alkyl of one to four carbon atoms, and —$NR_GR'_G$ wherein R_G and R'_G are independently hydrogen or alkyl of one to four carbon atoms; and

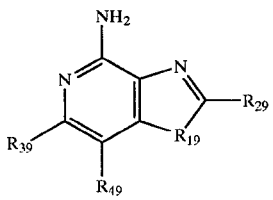
[0065] —$(CH_2)_a$—(Y)—$(CH_2)_b$— wherein a and b are integers and a+b is 0 to 3, and Y is O, S, or —NR_J— wherein R_J is hydrogen or alkyl of one to four carbon atoms;

[0066] and wherein q is 0 or 1 and R_8 is chosen from alkyl of one to four carbon atoms, alkoxy of one to four carbon atoms, and halogen,

[0067] and pharmaceutically acceptable salts thereof.

[0068] In a further embodiment, the IRM compound can be chosen from thiazoloquinoline amines, oxazoloquinoline amines, thiazolonaphthyridine amines, thiazolopyridine amines, and oxazolopyridine amines of Formula IX:

IX



[0069] wherein:

[0070] R_{19} is chosen from oxygen, sulfur and selenium;

[0071] R_{29} is chosen from

[0072] -hydrogen;

[0073] -alkyl;

[0074] -alkyl-OH;

[0075] -haloalkyl;

[0076] -alkenyl;

[0077] -alkyl-X-alkyl;

[0078] -alkyl-X-alkenyl;

[0079] -alkenyl-X-alkyl;

[0080] -alkenyl-X-alkenyl;

[0081] -alkyl-$N(R_{59})_2$;

[0082] -alkyl-N_3;

[0083] -alkyl-O—C(O)—$N(R_{59})_2$;

[0084] -heterocyclyl;

[0085] -alkyl-X-heterocyclyl;

[0086] -alkenyl-X-heterocyclyl;

[0087] -aryl;

[0088] -alkyl-X-aryl;

[0089] -alkenyl-X-aryl;

[0090] -heteroaryl;

[0091] -alkyl-X-heteroaryl; and

[0092] -alkenyl-X-heteroaryl;

[0093] R_{39} and R_{49} are each independently:

[0094] -hydrogen;

[0095] —X-alkyl;

[0096] -halo;

[0097] -haloalkyl;

[0098] —$N(R_{59})_2$;

[0099] or when taken together, R_{39} and R_{49} form a fused aromatic, heteroaromatic, cycloalkyl or heterocyclic ring;

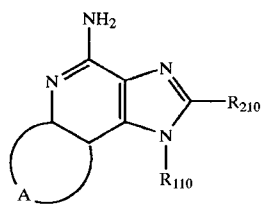
[0100] X is chosen from —O—, —S—, —NR_{59}—, —C(O)—, —C(O)O—, —OC(O)—, and a bond; and

[0101] each R_{59} is independently H or C_{1-8}alkyl;

[0102] and pharmaceutically acceptable salts thereof.

[0103] In another embodiment, the IRM compound can be chosen from imidazonaphthyridine amines and imidazotetrahydronaphthyridine amines of Formulae X and XI below:

X



[0104] wherein

[0105] A is =N—CR=CR—CR=; =CR—N=CR—CR—; =CR—CR=N—CR=; or =CR—CR=CR—N=;

[0106] R_{110} is chosen from:

[0107] -hydrogen;

[0108] —C_{1-20}alkyl or C_{2-20}alkenyl that is unsubstituted or substituted by one or more substituents chosen from:

[0109] -aryl;

[0110] -heteroaryl;

[0111] -heterocyclyl;

[0112] —O—C_{1-20}alkyl,

[0113] —O—$(C_{1-20}alkyl)_{0-1}$-aryl;

[0114] —O—$(C_{1-20}alkyl)_{0-1}$-heteroaryl;

[0115] —O—$(C_{1-20}alkyl)_{0-1}$-heterocyclyl;

[0116] —CO—O—C_{1-20}alkyl;

[0117] —$S(O)_{0-2}$—C_{1-20}alkyl;

[0118] —$S(O)_{0-2}$—$(C_{1-20}alkyl)_{0-1}$-aryl;

[0119] —$S(O)_{0-2}$—$(C_{1-20}alkyl)_{0-1}$-heteroaryl;

[0120] —$S(O)_{0-2}$—$(C_{1-20}alkyl)_{0-1}$-heterocyclyl;

[0121] —$N(R_{310})_2$;

[0122] —N_3;

[0123] oxo;

[0124] -halogen;

[0125] —NO_2;

[0126] —OH; and

[0127] —SH; and

[0128] —C_{1-20}alkyl-NR_{310}-Q-X—R_{410} or —C_{2-20}alkenyl-NR_{310}-Q-X—R_{410} wherein Q is —CO— or —SO_2—; X is a bond, —O— or —NR_{310}— and R_{410} is aryl; heteroaryl; heterocyclyl; or —C_{1-20} alkyl or C_{2-20}alkenyl that is unsubstituted or substituted by one or more substituents chosen from:

[0129] -aryl;

[0130] -heteroaryl;

[0131] -heterocyclyl;

[0132] —O—C_{1-20}alkyl,

[0133] —O—(C_{1-20}alkyl)$_{0-1}$-aryl;

[0134] —O—(C_{1-20}alkyl)$_{0-1}$-heteroaryl;

[0135] —O—(C_{1-20}alkyl)$_{0-1}$-heterocyclyl;

[0136] —CO—O—C_{1-20}alkyl;

[0137] —S(O)$_{0-2}$—C_{1-20}alkyl;

[0138] —S(O)$_{0-2}$—(C_{1-20}alkyl)$_{0-1}$-aryl;

[0139] —S(O)$_{0-2}$—(C_{1-20}alkyl)$_{0-1}$-heteroaryl;

[0140] —S(O)$_{0-2}$—(C_{1-20}alkyl)$_{0-1}$-heterocyclyl;

[0141] —$N(R_{310})_2$;

[0142] —NR_{310}—CO—O—C_{1-20}alkyl;

[0143] —N_3;

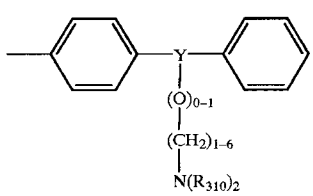
[0144] oxo;

[0145] -halogen;

[0146] —NO_2;

[0147] —OH; and

[0148] —SH; or R_{410} is



[0149] wherein Y is —N— or —CR—;

[0150] R_{210} is chosen from:

[0151] -hydrogen;

[0152] —C_{1-10}alkyl;

[0153] —C_{2-10}alkenyl;

[0154] -aryl;

[0155] —C_{1-10}alkyl-O—C_{1-10}alkyl;

[0156] —C_{1-10}alkyl-O—C_{2-10}alkenyl; and

[0157] —C_{1-10}alkyl or C_{2-10}alkenyl substituted by one or more substituents chosen from:

[0158] —OH;

[0159] -halogen;

[0160] —$N(R_{310})_2$;

[0161] —CO—$N(R_{310})_2$;

[0162] —CO—C_{1-10}alkyl;

[0163] —N_3;

[0164] -aryl;

[0165] -heteroaryl;

[0166] -heterocyclyl;

[0167] —CO-aryl; and

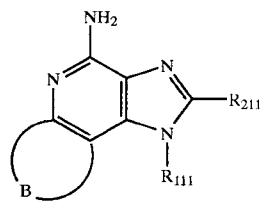
[0168] —CO-heteroaryl;

[0169] each R_{310} is independently chosen from hydrogen and C_{1-10}alkyl; and

[0170] each R is independently chosen from hydrogen, C_{1-10}alkyl, C_{1-10}alkoxy, halogen and trifluoromethyl,

[0171] and pharmaceutically acceptable salts thereof;

XI



[0172] wherein

[0173] B is —NR—$C(R)_2$—$C(R)_2$—$C(R)_2$—; —$C(R)_2$—NR—$C(R)_2$—$C(R)_2$—; —$C(R)_2$—$C(R)_2$—NR—$C(R)_2$— or —$C(R)_2$—$C(R)_2$—$C(R)_2$—NR—;

[0174] R_{111} is chosen from:

[0175] -hydrogen;

[0176] —C_{1-20}alkyl or C_{2-20}alkenyl that is unsubstituted or substituted by one or more substituents chosen from:

[0177] -aryl;

[0178] -heteroaryl;

[0179] -heterocyclyl;

[0180] —O—C_{1-20}alkyl;

[0181] —O—(C_{1-20}alkyl)$_{0-1}$-aryl;

[0182] —O—(C_{1-20}alkyl)$_{0-1}$-heteroaryl;

[0183] —O—(C_{1-20}alkyl)$_{0-1}$-heterocyclyl;

[0184] —CO—O—C_{1-20}alkyl;

[0185] —$S(O)_{0-2}$—C_{1-20}alkyl;

[0186] —$S(O)_{0-2}$—(C_{1-20}alkyl)$_{0-1}$-aryl;

[0187] —$S(O)_{0-2}$—(C_{1-20}alkyl)$_{0-1}$-heteroaryl;

[0188] —$S(O)_{0-2}$—(C_{1-20}alkyl)$_{0-1}$-heterocyclyl;

[0189] —$N(R_{311})_2$;

[0190] —N_3;

[0191] oxo;

[0192] -halogen;

[0193] —NO_2;

[0194] —OH; and

[0195] —SH; and

[0196] —C_{1-20}alkyl-NR_{311}-Q-X—R_{411} or —C_{2-20}alkenyl-NR_{311}-Q-X—R_{411} wherein Q is —CO— or —SO_2—; X is a bond, —O— or —NR_{311}— and R_{411} is aryl; heteroaryl; heterocyclyl; or —C_{1-20}alkyl or C_{2-20}alkenyl that is unsubstituted or substituted by one or more substituents chosen from:

[0197] -aryl;

[0198] -heteroaryl;

[0199] -heterocycyl;

[0200] —O—C_{1-20}alkyl,

[0201] —O—(C_{1-20}alkyl)$_{0-1}$-aryl;

[0202] —O—(C_{1-20}alkyl)$_{0-1}$-heteroaryl;

[0203] —O—(C_{1-20}alkyl)$_{0-1}$-heterocyclyl;

[0204] —CO—O—C_{1-20}alkyl;

[0205] —$S(O)_{0-2}$—C_{1-20}alkyl;

[0206] —$S(O)_{0-2}$—(C_{1-20}alkyl)$_{0-1}$-aryl;

[0207] —$S(O)_{0-2}$—(C_{1-20}alkyl)$_{0-1}$-heteroaryl;

[0208] —$S(O)_{0-2}$—(C_{1-20}alkyl)$_{0-1}$-heterocyclyl;

[0209] —$N(R_{311})_2$;

[0210] —NR_{311}—CO—O—C_{1-20}alkyl;

[0211] —N_3;

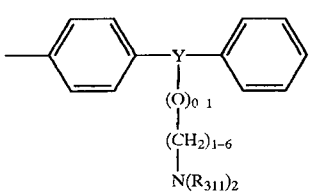
[0212] oxo;

[0213] -halogen;

[0214] —NO_2;

[0215] —OH; and

[0216] —SH; or R_{411} is



[0217] wherein Y is —N— or —CR—;

[0218] R_{211} is chosen from:

[0219] -hydrogen;

[0220] —C_{1-10}alkyl;

[0221] —C_{2-10}alkenyl;

[0222] -aryl

[0223] —C_{1-10}alkyl —O—C_{1-10}-alkyl;

[0224] —C_{1-10}alkyl-O—C_{2-10}alkenyl; and

[0225] —C_{1-10}alkyl or C_{2-10}alkenyl substituted by one or more substituents chosen from:

[0226] -OH;

[0227] -halogen;

[0228] —$N(R_{311})_2$;

[0229] —CO—$N(R_{311})_2$;

[0230] —CO—C_{1-10}alkyl;

[0231] —N_3;

[0232] -aryl;

[0233] -heteroaryl;

[0234] -heterocyclyl;

[0235] —CO-aryl; and

[0236] —CO-heteroaryl;

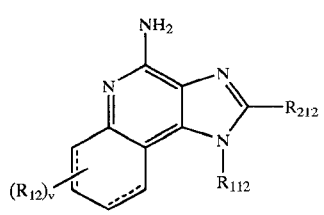
[0237] each R_{311} is independently chosen from hydrogen and C_{1-10}alkyl; and

[0238] each R is independently chosen from hydrogen, C_{1-10}alkyl, C_{1-10}alkoxy, halogen and trifluoromethyl,

[0239] and pharmaceutically acceptable salts thereof.

[0240] In a further embodiment, the IRM compound can be chosen from imidazoquinoline amines and imidazotetrahydroquinoline amines, for example, 1H-imidazo[4,5-c]quinolin-4-amines and tetrahydro-1H-imidazo[4,5-c]quinolin-4-amines defined by Formulas XII, XIII and XIV below:

XII



[0241] wherein

[0242] R_{112} is -alkyl-NR_{312}—CO—R_{412} or -alkenyl-NR_{312}—CO—R_{412} wherein R_{412} is aryl, heteroaryl, alkyl or alkenyl, each of which may be unsubstituted or substituted by one or more substituents chosen from:

[0243] -alkyl;

[0244] -alkenyl;

[0245] -alkynyl;

[0246] -$(alkyl)_{0-1}$-aryl;

[0247] -$(alkyl)_{0-1}$-(substituted aryl);

[0248] -$(alkyl)_{0-1}$-heteroaryl;

[0249] —$(alkyl)_{0-1}$-(substituted heteroaryl);

[0250] —O-alkyl;

[0251] —O-$(alkyl)_{0-1}$-aryl;

[0252] —O-$(alkyl)_{0-1}$-(substituted aryl);

[0253] —O-$(alkyl)_{0-1}$-heteroaryl;

[0254] —O-$(alkyl)_{0-1}$-(substituted heteroaryl);

[0255] —CO-aryl;

[0256] —CO-(substituted aryl);

[0257] —CO-heteroaryl;

[0258] —CO-(substituted heteroaryl);

[0259] —COOH;

[0260] —CO—O-alkyl;

[0261] —CO-alkyl;

[0262] —$S(O)_{0-2}$-alkyl;

[0263] —$S(O)_{0-2}$-$(alkyl)_{0-1}$-aryl;

[0264] —$S(O)_{0-2}$-$(alkyl)_{0-1}$-(substituted aryl);

[0265] —$S(O)_{0-2}$-$(alkyl)_{0-1}$-heteroaryl;

[0266] —$S(O)_{0-2}$-$(alkyl)_{0-1}$-(substituted heteroaryl);

[0267] —$P(O)(OR_{312})_2$;

[0268] —NR_{312}—CO—O-alkyl;

[0269] —N_3;

[0270] -halogen;

[0271] —NO_2;

[0272] —CN;

[0273] -haloalkyl;

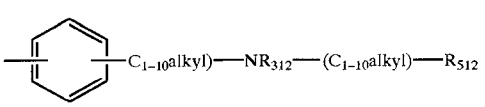
[0274] —O-haloalkyl;

[0275] —CO-haloalkyl;

[0276] —OH;

[0277] —SH; and in the case of alkyl, alkenyl, or heterocyclyl, oxo;

[0278] or R_{412} is



[0279] wherein R_{512} is an aryl, (substituted aryl), heteroaryl, (substituted heteroaryl), heterocyclyl or (substituted heterocyclyl) group;

[0280] R_{212} is chosen from:

[0281] -hydrogen;

[0282] -alkyl;

[0283] -alkenyl;

[0284] -aryl;

[0285] -(substituted aryl);

[0286] -heteroaryl;

[0287] -(substituted heteroaryl);

[0288] -heterocyclyl;

[0289] -(substituted heterocyclyl);

[0290] -alkyl-O-alkyl;

[0291] -alkyl-O-alkenyl; and

[0292] -alkyl or alkenyl substituted by one or more substituents chosen from:

[0293] —OH;

[0294] -halogen;

[0295] —$N(R_{312})_2$;

[0296] —CO—$N(R_{312})_2$;

[0297] —CO—C_{1-10}alkyl;

[0298] —CO—O—C_{1-10}alkyl;

[0299] —N_3;

[0300] -aryl;

[0301] -(substituted aryl);

[0302] -heteroaryl;

[0303] -(substituted heteroaryl);

[0304] -heterocyclyl;

[0305] -(substituted heterocyclyl);

[0306] —CO-aryl; and

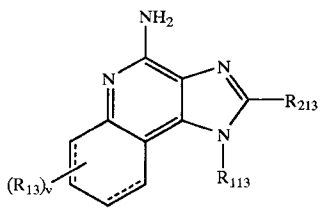
[0307] —CO-heteroaryl;

[0308] each R_{312} is independently chosen from hydrogen; C_{1-10}alkyl-heteroaryl; C_{1-10}alkyl-(substituted heteroaryl); C_{1-10}alkyl-aryl; C_{1-10}alkyl-(substituted aryl) and C_{1-10}alkyl;

[0309] v is 0 to 4;

[0310] and each R_{12} present is independently chosen from C_{1-10}alkyl, C_{1-10}alkoxy, halogen and trifluoromethyl;

XIII



[0311] wherein

[0312] R_{113} is -alkyl-NR_{313}—SO_2—X—R_{413} or -alkenyl-NR_{313}—SO_2—X—R_{413};

[0313] X is a bond or —NR_{513}—;

[0314] R_{413} is aryl, heteroaryl, heterocyclyl, alkyl or alkenyl, each of which may be unsubstituted or substituted by one or more substituents chosen from:

[0315] -alkyl;

[0316] -alkenyl;

[0317] -aryl;

[0318] -heteroaryl;

[0319] -heterocyclyl;

[0320] -substituted cycloalkyl;

[0321] -substituted aryl;

[0322] -substituted heteroaryl;

[0323] -substituted heterocyclyl;

[0324] —O-alkyl;

[0325] —O-$(alkyl)_{0-1}$-aryl;

[0326] —O-$(alkyl)_{0-1}$-substituted aryl;

[0327] —O-$(alkyl)_{0-1}$-heteroaryl;

[0328] —O-$(alkyl)_{0-1}$-substituted heteroaryl;

[0329] —O-$(alkyl)_{0-1}$-heterocyclyl;

[0330] —O-$(alkyl)_{0-1}$-substituted heterocyclyl;

[0331] —COOH;

[0332] —CO—O-alkyl;

[0333] —CO-alkyl;

[0334] —$S(O)_{0-2}$-alkyl;

[0335] —$S(O)_{0-2}$-$(alkyl)_{0-1}$-aryl;

[0336] —$S(O)_{0-2}$-$(alkyl)_{0-1}$-substituted aryl;

[0337] —$S(O)_{0-2}$-$(alkyl)_{0-1}$-heteroaryl;

[0338] —$S(O)_{0-2}$-$(alkyl)_{0-1}$-substituted heteroaryl;

[0339] —$S(O)_{0-2}$-$(alkyl)_{0-1}$-heterocyclyl;

[0340] —$S(O)_{0-2}$-$(alkyl)_{0-1}$-substituted heterocyclyl;

[0341] -$(alkyl)_{0-1}$-$NR_{313}R_{313}$;

[0342] -$(alkyl)_{0-1}$-NR_{313}—CO—O-alkyl;

[0343] -$(alkyl)_{0-1}$-NR_{313}—CO-alkyl;

[0344] -$(alkyl)_{0-1}$-NR_{313}—CO-aryl;

[0345] -$(alkyl)_{0-1}$-NR_{313}—CO-substituted aryl;

[0346] -$(alkyl)_{0-1}$-NR_{313}—CO-heteroaryl;

[0347] -$(alkyl)_{0-1}$-NR_{313}—CO-substituted heteroaryl;

[0348] —N_3;

[0349] -halogen;

[0350] -haloalkyl;

[0351] -haloalkoxy;

[0352] —CO-haloalkyl;

[0353] —CO-haloalkoxy;

[0354] —NO_2;

[0355] —CN;

[0356] —OH;

[0357] —SH; and in the case that R_{413} is alkyl, alkenyl, or heterocyclyl, oxo;

[0358] R_{213} is chosen from:

[0359] -hydrogen;

[0360] -alkyl;

[0361] -alkenyl;

[0362] -aryl;

[0363] -substituted aryl;

[0364] -heteroaryl;

[0365] -substituted heteroaryl;

[0366] -alkyl-O-alkyl;

[0367] -alkyl-O-alkenyl; and

[0368] -alkyl or alkenyl substituted by one or more substituents chosen from:

[0369] —OH;

[0370] -halogen;

[0371] —$N(R_{313})_2$;

[0372] —CO—$N(R_{313})_2$;

[0373] —CO—C_{1-10}alkyl;

[0374] —CO—O—C_{1-10}alkyl;

[0375] —N_3;

[0376] -aryl;

[0377] -substituted aryl;

[0378] -heteroaryl;

[0379] -substituted heteroaryl;

[0380] -heterocyclyl;

[0381] -substituted heterocyclyl;

[0382] —CO-aryl;

[0383] —CO-(substituted aryl);

[0384] -CO-heteroaryl; and

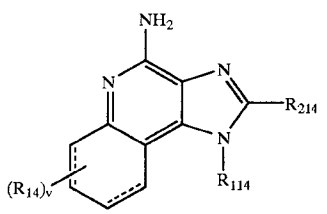
[0385] -CO-(substituted heteroaryl);

[0386] each R_{313} is independently chosen from hydrogen, C_{1-10}alkyl, and when X is a bond R_{313} and R_{413} can combine to form a 3 to 7 membered heterocyclic or substituted heterocyclic ring;

[0387] R_{513} is chosen from hydrogen, C_{1-10}alkyl, and R_{413} and R_{513} can combine to form a 3 to 7 membered heterocyclic or substituted heterocyclic ring;

[0388] v is 0 to 4 and each R_{13} present is independently chosen from C_{1-10}alkyl, C_{1-10}alkoxy, halogen and trifluoromethyl;

XIV



[0389] wherein

[0390] R_{114} is -alkyl-NR_{314}—CY—NR_{514}—X—R_{414} or -alkenyl-NR_{314}—CY—NR_{514}—X—R_{414}

[0391] wherein

[0392] Y is =O or =S;

[0393] X is a bond, —CO— or —SO_2—;

[0394] R_{414} is aryl, heteroaryl, heterocyclyl, alkyl or alkenyl, each of which may be unsubstituted or substituted by one or more substituents chosen from:

[0395] -alkyl;

[0396] -alkenyl;

[0397] -aryl;

[0398] -heteroaryl;

[0399] -heterocyclyl;

[0400] -substituted aryl;

[0401] -substituted heteroaryl;

[0402] -substituted heterocycyl;

[0403] —O-alkyl;

[0404] —O-(alkyl)$_{0-1}$-aryl;

[0405] —O-(alkyl)$_{0-1}$-substituted aryl;

[0406] —O-(alkyl)$_{0-1}$-heteroaryl;

[0407] —O-(alkyl)$_{0-1}$-substituted heteroaryl;

[0408] —O-(alkyl)$_{0-1}$-heterocyclyl;

[0409] —O-(alkyl)$_{0-1}$-substituted heterocyclyl;

[0410] —COOH;

[0411] —CO—O-alkyl;

[0412] —CO-alkyl;

[0413] —S(O)$_{0-2}$-alkyl;

[0414] —S(O)$_{0-2}$-(alkyl)$_{0-1}$-aryl;

[0415] —S(O)$_{0-2}$-(alkyl)$_{0-1}$-substituted aryl;

[0416] —S(O)$_{0-2}$-(alkyl)$_{0-1}$-heteroaryl;

[0417] —S(O)$_{0-2}$-(alkyl)$_{0-1}$-substituted heteroaryl;

[0418] —S(O)$_{0-2}$-(alkyl)$_{0-1}$-heterocyclyl;

[0419] —S(O)$_{0-2}$-(alkyl)$_{0-1}$-substituted heterocyclyl;

[0420] -(alkyl)$_{0-1}$-$NR_{314}R_{314}$;

[0421] -(alkyl)$_{0-1}$-NR_{314}—CO—O-alkyl;

[0422] -(alkyl)$_{0-1}$-NR_{314}—CO-alkyl;

[0423] -(alkyl)$_{0-1}$-NR_{314}—CO-aryl;

[0424] -(alkyl)$_{0-1}$-NR_{314}—CO-substituted aryl;

[0425] -(alkyl)$_{0-1}$-NR_{314}—CO-heteroaryl;

[0426] -(alkyl)$_{0-1}$-NR_{314}—CO-substituted heteroaryl;

[0427] —N_3;

[0428] -halogen;

[0429] -haloalkyl;

[0430] -haloalkoxy;

[0431] —CO-haloalkoxy;

[0432] —NO_2;

[0433] —CN;

[0434] —OH;

[0435] —SH; and, in the case that R_{414} is alkyl, alkenyl or heterocyclyl, oxo; with the proviso that when X is a bond R_{414} can additionally be hydrogen;

[0436] R_{214} is chosen from:

[0437] -hydrogen;

[0438] -alkyl;

[0439] -alkenyl;

[0440] -aryl;

[0441] -substituted aryl;

[0442] -heteroaryl;

[0443] -substituted heteroaryl;

[0444] -alkyl-O-alkyl;

[0445] -alkyl-O-alkenyl; and

[0446] -alkyl or alkenyl substituted by one or more substituents chosen from:

[0447] —OH;

[0448] -halogen;

[0449] —$N(R_{314})_2$;

[0450] —CO—$N(R_{314})_2$;

[0451] —CO—C_{1-10}alkyl;

[0452] —CO—O—C_{1-10}alkyl;

[0453] —N_3;

[0454] -aryl;

[0455] -substituted aryl;

[0456] -heteroaryl;

[0457] -substituted heteroaryl;

[0458] -heterocyclyl;

[0459] -substituted heterocyclyl;

[0460] —CO-aryl;

[0461] —CO-(substituted aryl);

[0462] —CO-heteroaryl; and

[0463] —CO-(substituted heteroaryl);

[0464] each R_{314} is independently chosen from hydrogen and C_{1-10}alkyl;

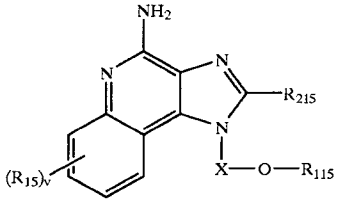
[0465] R_{514} is chosen from hydrogen, C_{1-10}alkyl, and R_{414} and R_{514} can combine to form a 3 to 7 membered heterocyclic or substituted heterocyclic ring;

[0466] v is 0 to 4 and each R_{14} present is independently chosen from C_{1-10}alkyl, C_{1-10}alkoxy, halogen and trifluoromethyl,

[0467] and pharmaceutically acceptable salts thereof.

[0468] In yet another embodiment, the IRM compound can be chosen from imidazoquinoline amines and imidazotetrahydroquinoline amines, for example, 1H-imidazo[4,5-c]quinolin-4-amines and tetrahydro-1H-imidazo[4,5-c]quinolin-4-amines defined by Formulas XV, XVI, XVII, XVIII, XIX, XX, XXI, XXII, XXIII, XXIV, XXV, and XXVI below

XV



[0469] wherein:

[0470] X is —CHR_{515}—, —CHR_{515}-alkyl-, or —CHR_{515}-alkenyl-;

[0471] R_{115} is chosen from:

[0472] —R_{415}—CR_{315}-Z-R_{615}-alkyl;

[0473] —R_{415}—CR_{315}-Z-R_{615}-alkenyl;

[0474] —R_{415}—CR_{315}-Z-R_{615}-aryl;

[0475] —R_{415}—CR_{315}-Z-R_{615}-heteroaryl;

[0476] —R_{415}—CR_{315}-Z-R_{615}-heterocyclyl;

[0477] —R_{415}—CR_{315}-Z-H;

[0478] —R_{415}—NR_{715}—CR_{315}—R_{615}-alkyl;

[0479] —R_{415}—NR_{715}—CR_{315}—R_{615}-alkenyl;

[0480] —R_{415}—NR_{715}—CR_{315}—R_{615}-aryl;

[0481] —R_{415}—NR_{715}—CR_{315}—R_{615}-heteroaryl;

[0482] —R_{415}—NR_{715}—CR_{315}—R_{615}-heterocyclyl; and

[0483] —R_{415}—NR_{715}—CR_{315}—R_{815};

[0484] Z is —NR_{515}—, —O—, or —S—;

[0485] R_{215} is chosen from:

[0486] -hydrogen;

[0487] -alkyl;

[0488] -alkenyl;

[0489] -aryl;

[0490] -heteroaryl;

[0491] -heterocyclyl;

[0492] -alkyl-Y-alkyl;

[0493] -alkyl-Y- alkenyl;

[0494] -alkyl-Y-aryl; and

[0495] -alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

[0496] —OH;

[0497] -halogen;

[0498] —$N(R_{515})_2$;

[0499] —CO—$N(R_{515})_2$;

[0500] —CO—C_{1-10}alkyl;

[0501] —CO—O—C_{1-10}alkyl;

[0502] —N_3;

[0503] -aryl;

[0504] -heteroaryl;

[0505] -heterocyclyl;

[0506] —CO-aryl; and

[0507] —CO-heteroaryl;

[0508] R_{315} is =O or =S;

[0509] R_{415} is alkyl or alkenyl, which may be interrupted by one or more —O— groups;

[0510] each R_{515} is independently H or C_{1-10}alkyl;

[0511] R_{615} is a bond, alkyl, or alkenyl, which may be interrupted by one or more —O— groups;

[0512] R_{715} is H, C_{1-10}alkyl, arylalkyl, or R_{415} and R_{715} can join together to form a 5 to 7 membered heterocyclcic ring;

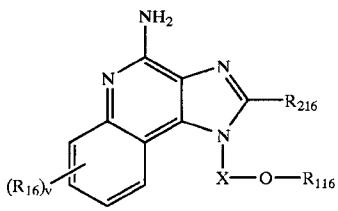
[0513] R_{815} is H, C_{1-10}alkyl, or R_{715} and R_{815} can join together to form a 5 to 7 membered heterocyclic ring;

[0514] Y is —O— or —$S(O)_{0-2}$—;

[0515] v is 0 to 4; and

[0516] each R_{15} present is independently chosen from C_{1-10}alkyl, C_{1-10}alkoxy, hydroxy, halogen and trifluoromethyl;

XVI



[0517] wherein:

[0518] X is —CHR_{516}—, —CHR_{516}-alkyl-, or —CHR_{516}-alkenyl-;

[0519] R_{116} is chosen from:

[0520] —R_{416}—CR_{316}-Z-R_{616}-alkyl;

[0521] —R_{416}—CR_{316}-Z-R_{616}-alkenyl;

[0522] —R_{416}—CR_{316}-Z-R_{616}-aryl;

[0523] —R_{416}—CR_{316}-Z-R_{616}-heteroaryl;

[0524] —R_{416}—CR_{316}-Z-R_{616}-heterocyclyl;

[0525] —R_{416}—CR_{316}-Z-H;

[0526] —R_{416}—NR_{716}—CR_{316}—R_{616}-alkyl;

[0527] —R_{416}—NR_{716}—CR_{316}—R_{616}-alkenyl;

[0528] —R_{416}—NR_{716}—CR_{316}—R_{616}-aryl;

[0529] —R_{416}—NR_{716}—CR_{316}—R_{616}-heteroaryl;

[0530] —R_{416}—NR_{716}—CR_{316}—R_{616}-heterocyclyl; and

[0531] —R_{416}—NR_{716}—CR_{316}—R_{816};

[0532] Z is —NR_{516}—, —O—, or —S—;

[0533] R_{216} is chosen from:

[0534] -hydrogen;

[0535] -alkyl;

[0536] -alkenyl;

[0537] -aryl;

[0538] -heteroaryl;

[0539] -heterocyclyl;

[0540] -alkyl-Y-alkyl;

[0541] -alkyl-Y-alkenyl;

[0542] -alkyl-Y-aryl; and

[0543] -alkyl or alkenyl substituted by one or more substituents chosen from:

[0544] —OH;

[0545] -halogen;

[0546] —$N(R_{516})_2$;

[0547] —CO—$N(R_{516})_2$;

[0548] —CO—C_{1-10}alkyl;

[0549] —CO—O—C_{1-10}alkyl;

[0550] —N_3;

[0551] -aryl;

[0552] -heteroaryl;

[0553] -heterocyclyl;

[0554] —CO-aryl; and

[0555] —CO-heteroaryl;

[0556] R_{316} is =O or =S;

[0557] R_{416} is alkyl or alkenyl, which may be interrupted by one or more —O— groups;

[0558] each R_{516} is independently H or C_{1-10}alkyl;

[0559] R_{616} is a bond, alkyl, or alkenyl, which may be interrupted by one or more —O— groups;

[0560] R_{716} is H, C_{1-10}alkyl, arylalkyl, or R_{416} and R_{716} can join together to form a 5 to 7 membered hetercyclic ring;

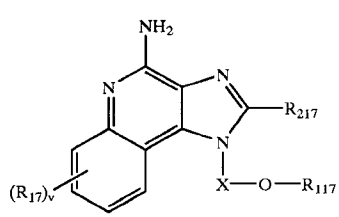
[0561] R_{816} is H or C_{1-10}alkyl; or R_{716} and R_{816} can join together to form a 5 to 7 membered heterocyclic ring;

[0562] Y is —O— or —$S(O)_{0-2}$—;

[0563] v is 0 to 4; and

[0564] each R_{16} present is independently chosen from C_{1-10}alkyl, C_{1-10}alkoxy, hydroxy, halogen, and trifluoromethyl;

XVII



[0565] wherein:

[0566] X is —CHR_{317}—, —CHR_{317}-alkyl-, or —CHR_{317}-alkenyl-;

[0567] R_{117} is chosen from:

[0568] -alkenyl;

[0569] -aryl; and

[0570] —R_{417}-aryl;

[0571] R_{217} is chosen from:

[0572] -hydrogen;

[0573] -alkyl;

[0574] -alkenyl;

[0575] -aryl;

[0576] -heteroaryl;

[0577] -heterocyclyl;

[0578] -alkyl-Y-alkyl;

[0579] -alkyl-Y-alkenyl;

[0580] -alkyl-Y-aryl; and

[0581] -alkyl or alkenyl substituted by one or more substituents chosen from:

[0582] —OH;

[0583] -halogen;

[0584] —$N(R_{317})_2$;

[0585] —CO—$N(R_{317})_2$;

[0586] —CO—C_{1-10}alkyl;

[0587] —CO—O—C_{1-10}alkyl;

[0588] —N_3;

[0589] -aryl;

[0590] -heteroaryl;

[0591] -heterocyclyl;

[0592] —CO-aryl; and

[0593] —CO-heteroaryl;

[0594] R_{417} is alkyl or alkenyl, which may be interrupted by one or more —O— groups;

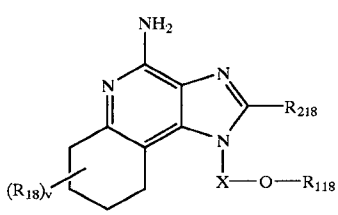
[0595] each R_{317} is independently H or C_{1-10}alkyl;

[0596] each Y is independently —O— or —$S(O)_{0-2}$—;

[0597] v is 0 to 4; and

[0598] each R_{17} present is independently chosen from C_{1-10}alkyl, C_{1-10}alkoxy, hydroxy, halogen and trifluoromethyl;

XVIII



[0599] wherein:

[0600] X is —CHR_{318}—, —CHR_{318}-alkyl-, or —CHR_{318}-alkenyl-;

[0601] R_{118} is chosen from:

[0602] -aryl;

[0603] -alkenyl; and

[0604] —R_{418}-aryl;

[0605] R_{218} is chosen from:

[0606] -hydrogen;

[0607] -alkyl;

[0608] -alkenyl;

[0609] -aryl;

[0610] -heteroaryl;

[0611] -heterocyclyl;

[0612] -alkyl-Y-alkyl;

[0613] -alkyl-Y-aryl;

[0614] -alkyl-Y-alkenyl; and

[0615] -alkyl or alkenyl substituted by one or more substituents chosen from:

[0616] —OH;

[0617] -halogen;

[0618] —$N(R_{318})_2$;

[0619] —CO—$N(R_{318})_2$;

[0620] —CO—C_{1-10}alkyl;

[0621] —CO—O—C_{1-10}alkyl;

[0622] —N_3;

[0623] -aryl;

[0624] -heteroaryl;

[0625] -heterocyclyl;

[0626] —CO-aryl; and

[0627] —CO-heteroaryl;

[0628] R_{418} is alkyl or alkenyl, which may be interrupted by one or more —O— groups;

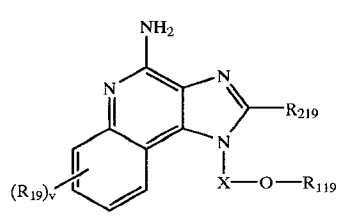
[0629] each R_{318} is independently H or C_{1-10}alkyl;

[0630] each Y is independently —O— or —$S(O)_{0-2}$—;

[0631] v is 0 to 4; and

[0632] each R_{18} present is independently chosen from C_{1-10}alkyl, C_{1-10}alkoxy, hydroxy, halogen and trifluoromethyl;

XIX



[0633] wherein:

[0634] X is —CHR_{319}—, —CHR_{319}-alkyl-, or —CHR_{319}-alkenyl-;

[0635] R_{119} is chosen from:

[0636] -heteroaryl;

[0637] -heterocyclyl;

[0638] —R_{419}-heteroaryl; and

[0639] —R_{419}-heterocyclyl;

[0640] R_{219} is chosen from:

[0641] -hydrogen;

[0642] -alkyl;

[0643] -alkenyl;

[0644] -aryl;

[0645] -heteroaryl;

[0646] -heterocyclyl;

[0647] -alkyl-Y-alkyl;

[0648] -alkyl-Y- alkenyl;

[0649] -alkyl-Y-aryl; and

[0650] -alkyl or alkenyl substituted by one or more substituents chosen from:

[0651] —OH;

[0652] -halogen;

[0653] —$N(R_{319})_2$;

[0654] —CO—$N(R_{319})_2$;

[0655] —CO—C_{1-10}alkyl;

[0656] —CO—O—C_{1-10}alkyl;

[0657] —N_3;

[0658] -aryl;

[0659] -heteroaryl;

[0660] -heterocyclyl;

[0661] —CO-aryl; and

[0662] —CO-heteroaryl;

[0663] R_{419} is alkyl or alkenyl, which may be interrupted by one or more —O— groups;

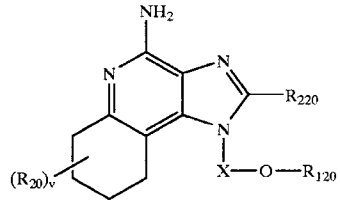
[0664] each R_{319} is independently H or C_{1-10}alkyl;

[0665] each Y is independently —O— or —$S(O)_{0-2}$—;

[0666] v is 0 to 4; and

[0667] each R_{19} present is independently chosen from C_{1-10}alkyl, C_{1-10}alkoxy, hydroxy, halogen and trifluoromethyl;

XX



[0668] wherein:

[0669] X is —CHR_{320}—, —CHR_{320}-alkyl-, or —CHR_{320}-alkenyl-;

[0670] R_{120} is chosen from:

[0671] -heteroaryl;

[0672] -heterocyclyl;

[0673] —R_{420}-heteroaryl; and

[0674] —R_{420}-heterocyclyl;

[0675] R_{220} is chosen from:

[0676] -hydrogen;

[0677] -alkyl;

[0678] -alkenyl;

[0679] -aryl;

[0680] -heteroaryl;

[0681] -heterocyclyl;

[0682] -alkyl-Y-alkyl;

[0683] -alkyl-Y- alkenyl;

[0684] -alkyl-Y-aryl; and

[0685] -alkyl or alkenyl substituted by one or more substituents chosen from:

[0686] —OH;

[0687] -halogen;

[0688] —$N(R_{320})_2$;

[0689] —CO—$N(R_{320})_2$;

[0690] —CO—C_{1-10}alkyl;

[0691] —CO—O—C_{1-10}alkyl;

[0692] —N_3;

[0693] -aryl;

[0694] -heteroaryl;

[0695] -heterocyclyl;

[0696] —CO-aryl; and

[0697] —CO-heteroaryl;

[0698] R_{420} is alkyl or alkenyl, which may be interrupted by one or more —O— groups;

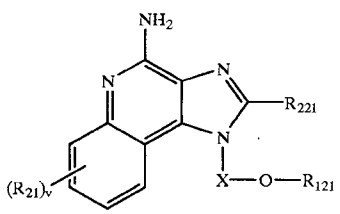
[0699] each R_{320} is independently H or C_{1-10}alkyl;

[0700] each Y is independently —O— or —S(O)$_{0-2}$—;

[0701] v is 0 to 4; and

[0702] each R_{20} present is independently chosen from C_{1-10}alkyl, C_{1-10}alkoxy, hydroxy, halogen and trifluoromethyl;

XXI



[0703] wherein:

[0704] X is —CHR_{521}—, —CHR_{521}-alkyl-, or —CHR_{521}-alkenyl-;

[0705] R_{121} is chosen from:

[0706] —R_{421}—NR_{321}—SO_2—R_{621}-alkyl;

[0707] —R_{421}—NR_{321}—SO_2—R_{621}-alkenyl;

[0708] —R_{421}—NR_{321}—SO_2—R_{621}-aryl;

[0709] —R_{421}—NR_{321}—SO_2—R_{621}-heteroaryl;

[0710] —R_{421}—NR_{321}—SO_2—R_{621}-heterocyclyl;

[0711] —R_{421}—NR_{321}—SO_2—R_{721};

[0712] —R_{421}—NR_{321}—SO_2—NR_{521}—R_{621}-alkyl;

[0713] —R_{421}—NR_{321}—SO_2—NR_{521}—R_{621}-alkenyl;

[0714] —R_{421}—NR_{321}—SO_2—NR_{521}—R_{621}-aryl;

[0715] —R_{421}—NR_{321}—SO_2—NR_{521}—R_{621}-heteroaryl;

[0716] —R_{421}—NR_{321}—SO_2—NR_{521}—R_{621}-heterocyclyl; and

[0717] —R_{421}—NR_{321}—SO_2—NH_2;

[0718] R_{221} is chosen from:

[0719] -hydrogen;

[0720] -alkyl;

[0721] -alkenyl;

[0722] -aryl;

[0723] -heteroaryl;

[0724] -heterocyclyl;

[0725] -alkyl-Y-alkyl;

[0726] -alkyl-Y-alkenyl;

[0727] -alkyl-Y-aryl; and

[0728] -alkyl or alkenyl substituted by one or more substituents chosen from:

[0729] —OH;

[0730] -halogen;

[0731] —$N(R_{521})_2$;

[0732] —CO—$N(R_{521})_2$;

[0733] —CO-C_{1-10}alkyl;

[0734] —CO—O—C_{1-10}alkyl;

[0735] —N_3;

[0736] -aryl;

[0737] -heteroaryl;

[0738] -heterocyclyl;

[0739] —CO-aryl; and

[0740] —CO-heteroaryl;

[0741] Y is —O— or —$S(O)_{0-2}$—;

[0742] R_{321} is H, C_{1-10}alkyl, or arylalkyl;

[0743] each R_{421} is independently alkyl or alkenyl, which may be interrupted by one or more —O— groups, or R_{321} and R_{421} can join together to form a 5 to 7 membered heterocyclic ring;

[0744] each R_{521} is independently H, C_{1-10}alkyl, or C_{2-10}alkenyl;

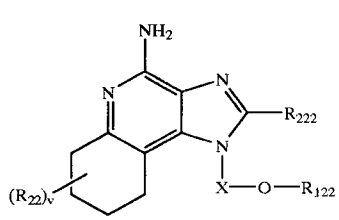
[0745] R_{621} is a bond, alkyl, or alkenyl, which may be interrupted by one or more —O— groups;

[0746] R_{721} is C_{1-10}alkyl, or R_{321} and R_{721} can join together to form a 5 to 7 membered heterocyclic ring;

[0747] v is 0 to 4; and

[0748] each R_{21} present is independently chosen from C_{1-10}alkyl, C_{1-10}alkoxy, hydroxy, halogen and trifluoromethyl;

XXII



[0749] wherein:

[0750] X is —CHR_{522}—, —CHR_{522}-alkyl-, or —CHR_{522}-alkenyl-;

[0751] R_{122} is chosen from:

[0752] —R_{422}—NR_{322}—SO_2—R_{622}-alkyl;

[0753] —R_{422}—NR_{322}—SO_2—R_{622}-alkenyl;

[0754] —R_{422}—NR_{322}—SO_2—R_{622}-aryl;

[0755] —R_{422}—NR_{322}—SO_2—R_{622}-heteroaryl;

[0756] —R_{422}—NR_{322}—SO_2—R_{622}-heterocyclyl;

[0757] —R_{422}—NR_{322}—SO_2—R_{722};

[0758] —R_{422}—NR_{322}—SO_2—NR_{522}—R_{622}-alkyl;

[0759] —R_{422}—NR_{322}—SO_2—NR_{522}—R_{622}-alkenyl;

[0760] —R_{422}—NR_{322}—SO_2—NR_{522}—R_{622}-aryl;

[0761] —R_{422}—NR_{322}—SO_2—NR_{522}—R_{622}-heteroaryl;

[0762] —R_{422}—NR_{322}—SO_2—NR_{522}—R_{622}-heterocyclyl; and

[0763] —R_{422}—NR_{322}—SO_2—NH_2;

[0764] R_{222} is chosen from:

[0765] -hydrogen;

[0766] -alkyl;

[0767] -alkenyl;

[0768] -aryl;

[0769] -heteroaryl;

[0770] -heterocyclyl;

[0771] -alkyl-Y-alkyl;

[0772] -alkyl-Y- alkenyl;

[0773] -alkyl-Y-aryl; and

[0774] -alkyl or alkenyl substituted by one or more substituents chosen from:

[0775] —OH;

[0776] -halogen;

[0777] —$N(R_{522})_2$;

[0778] —CO—$N(R_{522})_2$;

[0779] —CO—C_{1-10}alkyl;

[0780] —CO—O—C_{1-10}alkyl;

[0781] —N_3;

[0782] -aryl;

[0783] -heteroaryl;

[0784] -heterocyclyl;

[0785] —CO-aryl; and

[0786] —CO-heteroaryl;

[0787] Y is —O— or —$S(O)_{0-2}$—;

[0788] R_{322} is H, C_{1-10}alkyl, or arylalkyl;

[0789] each R_{422} is independently alkyl or alkenyl, which may be interrupted by one or more —O— groups, or R_{322} and R_{422} can join together to form a 5 to 7 membered heterocyclic ring;

[0790] each R_{522} is independently H, C_{1-10}alkyl, or C_{2-10}alkenyl;

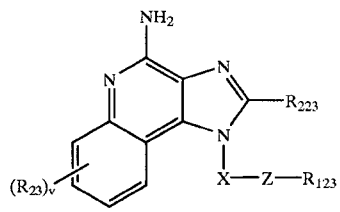
[0791] R_{622} is a bond, alkyl, or alkenyl, which may be interrupted by one or more —O— groups;

[0792] R_{722} is C_{1-10}alkyl, or R_{322} and R_{722} can join together to form a 5 to 7 membered heterocyclic ring;

[0793] v is 0 to 4; and

[0794] each R_{22} present is independently chosen from C_{1-10}alkyl, C_{1-10}alkoxy, hydroxy, halogen, and trifluoromethyl;

XXIII



[0795] wherein:

[0796] X is —CHR_{323}—, —CHR_{323}-alkyl-, or —CHR_{323}-alkenyl-;

[0797] Z is —S—, —SO—, or —SO_2—;

[0798] R_{123} is chosen from:

[0799] -alkyl;

[0800] -aryl;

[0801] -heteroaryl;

[0802] -heterocyclyl;

[0803] -alkenyl;

[0804] —R_{423}-aryl;

[0805] —R_{423}-heteroaryl;

[0806] —R_{423}-heterocyclyl;

[0807] R_{223} is chosen from:

[0808] -hydrogen;

[0809] -alkyl;

[0810] -alkenyl;

[0811] -aryl;

[0812] -heteroaryl;

[0813] -heterocyclyl;

[0814] -alkyl-Y-alkyl;

[0815] -alkyl-Y- alkenyl;

[0816] -alkyl-Y-aryl; and

[0817] -alkyl or alkenyl substituted by one or more substituents chosen from:

[0818] —OH;

[0819] -halogen;

[0820] —$N(R_{323})_2$;

[0821] —CO—$N(R_{323})_2$;

[0822] —CO—C_{1-10}alkyl;

[0823] —CO—O—C_{1-10}alkyl;

[0824] —N_3;

[0825] -aryl;

[0826] -heteroaryl;

[0827] -heterocyclyl;

[0828] —CO-aryl; and

[0829] —CO-heteroaryl;

[0830] each R_{323} is independently H or C_{1-10}alkyl;

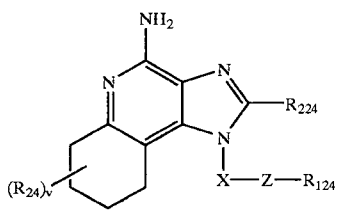
[0831] each R_{423} is independently alkyl or alkenyl;

[0832] each Y is independently —O— or —$S(O)_{0-2}$—;

[0833] v is 0 to 4; and

[0834] each R_{23} present is independently chosen from C_{1-10}alkyl, C_{1-10}alkoxy, hydroxy, halogen and trifluoromethyl;

XXIV



[0835] wherein:

[0836] X is —CHR_{324}—, —CHR_{324}-alkyl-, or —CHR_{324}-alkenyl-;

[0837] Z is —S—, —SO—, or —SO_2—;

[0838] R_{124} is chosen from:

[0839] -alkyl;

[0840] -aryl;

[0841] -heteroaryl;

[0842] -heterocyclyl;

[0843] -alkenyl;

[0844] —R_{424}-aryl;

[0845] —R_{424}-heteroaryl; and

[0846] —R_{424}-heterocyclyl;

[0847] R_{224} is chosen from:

[0848] -hydrogen;

[0849] -alkyl;

[0850] -alkenyl;

[0851] -aryl;

[0852] -heteroaryl;

[0853] -heterocyclyl;

[0854] -alkyl-Y-alkyl;

[0855] -alkyl-Y- alkenyl;

[0856] -alkyl-Y-aryl; and

[0857] -alkyl or alkenyl substituted by one or more substituent chosen from:

[0858] —OH;

[0859] -halogen;

[0860] —$N(R_{324})_2$;

[0861] —CO—$N(R_{324})_2$;

[0862] —CO—C_{1-10}alkyl;

[0863] —CO—O—C_{1-10}alkyl;

[0864] —N_3;

[0865] -aryl;

[0866] -heteroaryl;

[0867] -heterocyclyl;

[0868] —CO-aryl; and

[0869] —CO-heteroaryl;

[0870] each R_{324} is independently H or C_{1-10}alkyl;

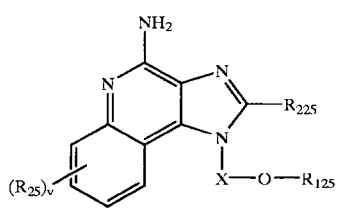
[0871] each R_{424} is independently alkyl or alkenyl;

[0872] each Y is independently —O— or —$S(O)_{0-2}$—;

[0873] v is 0 to 4; and

[0874] each R_{24} present is independently chosen from C_{1-10}alkyl, C_{1-10}alkoxy, hydroxy, halogen and trifluoromethyl;

XXV



[0875] wherein:

[0876] X is —CHR_{525}—, —CHR_{525}-alkyl-, or —CHR_{525}-alkenyl-;

[0877] R_{125} is chosen from:

[0878] —R_{425}—NR_{825}—CR_{325}—NR_{525}-Z-R_{625}-alkyl;

[0879] —R_{425}—NR_{825}—CR_{325}—NR_{525}-Z-R_{625}-alkenyl;

[0880] —R_{425}—NR_{825}—CR_{325}—NR_{525}-Z-R_{625}-aryl;

[0881] —R_{425}—NR_{825}—CR_{325}—NR_{525}-Z-R_{625}-heteroaryl;

[0882] —R_{425}—NR_{825}—CR_{325}—NR_{525}-Z-R_{625}-heterocyclyl;

[0883] —R_{425}—NR_{825}—CR_{325}—$NR_{525}R_{725}$;

[0884] —R_{425}—NR_{825}—CR_{325}—NR_{925}-Z-R_{625}-alkyl;

[0885] —R_{425}—NR_{825}—CR_{325}—NR_{925}-Z-R_{625}-alkenyl;

[0886] —R_{425}—NR_{825}—CR_{325}—NR_{925}-Z-R_{625}-aryl;

[0887] —R_{425}—NR_{825}—CR_{325}—NR_{925}-Z-R_{625}-heteroaryl; and

[0888] —R_{425}—NR_{825}—CR_{325}—NR_{925}-Z-R_{625}-heterocyclyl;

[0889] R_{225} is chosen from:

[0890] -hydrogen;

[0891] -alkyl;

[0892] -alkenyl;

[0893] -aryl;

[0894] -heteroaryl;

[0895] -heterocyclyl;

[0896] -alkyl-Y-alkyl;

[0897] -alkyl-Y-alkenyl;

[0898] -alkyl-Y-aryl; and

[0899] -alkyl or alkenyl substituted by one or more substituents chosen from:

[0900] —OH;

[0901] -halogen;

[0902] —$N(R_{525})_2$;

[0903] —CO—$N(R_{525})_2$;

[0904] —CO—$C_{1\text{-}10}$alkyl;

[0905] —CO—O—$C_{1\text{-}10}$alkyl;

[0906] —N_3;

[0907] -aryl;

[0908] -heteroaryl;

[0909] -heterocyclyl;

[0910] —CO-aryl; and

[0911] —CO-heteroaryl;

[0912] each R_{325} is =O or =S;

[0913] each R_{425} is independently alkyl or alkenyl, which may be interrupted by one or more —O— groups;

[0914] each R_{525} is independently H or $C_{1\text{-}10}$alkyl;

[0915] R_{625} is a bond, alkyl, or alkenyl, which may be interrupted by one or more —O— groups;

[0916] R_{725} is H, $C_{1\text{-}10}$alkyl which may be interrupted by a hetero atom, or R_{725} can join with R_{525} to form a 5 to 7 membered heterocyclic ring;

[0917] R_{825} is H, $C_{1\text{-}10}$alkyl, arylalkyl, or R_{425} and R_{825} can join together to form a 5 to 7 membered heterocyclic ring;

[0918] R_{925} is $C_{1\text{-}10}$alkyl which can join together with R_{825} to form a 5 to 7 membered heterocyclic ring;

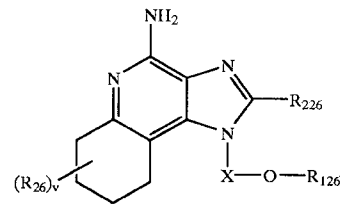
[0919] each Y is independently —O— or —$S(O)_{0\text{-}2}$—;

[0920] Z is a bond, —CO—, or —SO_2—;

[0921] v is 0 to 4; and

[0922] each R_{25} present is independently chosen from $C_{1\text{-}10}$alkyl, $C_{1\text{-}10}$alkoxy, hydroxy, halogen and trifluoromethyl;

XXVI



[0923] wherein:

[0924] X is —CHR_{526}—, —CHR_{526}-alkyl-, or —CHR_{526}-alkenyl-;

[0925] R_{126} is chosen from:

[0926] —R_{426}—NR_{826}—CR_{326}—NR_{526}-Z-R_{626}-alkyl;

[0927] —R_{426}—NR_{826}—CR_{326}—NR_{526}-Z-R_{626}-alkenyl;

[0928] —R_{426}—NR_{826}—CR_{326}—NR_{526}-Z-R_{626}-aryl;

[0929] —R_{426}—NR_{826}—CR_{326}—NR_{526}-Z-R_{626}-heteroaryl;

[0930] —R_{426}—NR_{826}—CR_{326}—NR_{526}-Z-R_{626}-heterocyclyl;

[0931] —R_{426}—NR_{826}—CR_{326}—$NR_{526}R_{726}$;

[0932] —R_{426}—NR_{826}—CR_{326}—NR_{926}-Z-R_{626}-alkyl;

[0933] —R_{426}—NR_{826}—CR_{326}—NR_{926}-Z-R_{626}-alkenyl;

[0934] —R_{426}—NR_{826}—CR_{326}—NR_{926}-Z-R_{626}-aryl;

[0935] —R_{426}—NR_{826}—CR_{326}—NR_{926}-Z-R_{626}-heteroaryl; and

[0936] —R_{426}—NR_{826}—CR_{326}—NR_{926}-Z-R_{626}-heterocyclyl;

[0937] R_{226} is chosen from:

[0938] -hydrogen;

[0939] -alkyl;

[0940] -alkenyl;

[0941] -aryl;

[0942] -heteroaryl;

[0943] -heterocyclyl;

[0944] -alkyl-Y-alkyl;

[0945] -alkyl-Y-alkenyl;

[0946] -alkyl-Y-aryl; and

[0947] -alkyl or alkenyl substituted by one or more substituents chosen from:

[0948] —OH;

[0949] -halogen;

[0950] —$N(R_{526})_2$;

[0951] —CO—$N(R_{526})_2$;

[0952] —CO—C_{1-10}alkyl;

[0953] —CO—O—C_{1-10}alkyl;

[0954] —N_3;

[0955] -aryl;

[0956] -heteroaryl;

[0957] -heterocyclyl;

[0958] —CO-aryl; and

[0959] —CO-heteroaryl;

[0960] each R_{326} is =O or =S;

[0961] each R_{426} is independently alkyl or alkenyl, which may be interrupted by one or more —O— groups;

[0962] each R_{526} is independently H or C_{1-10}alkyl;

[0963] R_{626} is a bond, alkyl, or alkenyl, which may be interrupted by one or more —O— groups;

[0964] R_{726} is H, C_{1-10}alkyl which may be interrupted by a hetero atom, or R_{726} can join with R_{526} to form a 5 to 7 membered heterocyclic ring;

[0965] R_{826} is H, C_{1-10}alkyl, arylalkyl, or R_{426} and R_{826} can join together to form a 5 to 7 membered heterocyclic ring;

[0966] R_{926} is C_{1-10}alkyl which can join together with R_{826} to form a 5 to 7 membered heterocyclic ring;

[0967] each Y is independently —O— or —$S(O)_{0-2}$—;

[0968] Z is a bond, —CO—, or —SO_2—;

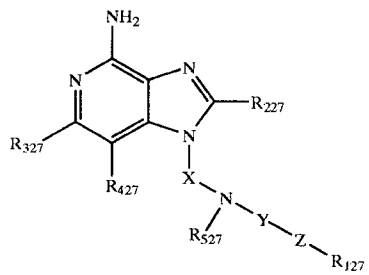
[0969] v is 0 to 4; and

[0970] each R_{26} present is independently chosen from C_{1-10}alkyl, C_{1-10}alkoxy, hydroxy, halogen, and trifluoromethyl;

[0971] and pharmaceutically acceptable salts of any of the foregoing.

[0972] In another embodiment, the IRM compound can be chosen from 1H-imidazo[4,5-c]pyridin-4-amines compounds defined by Formula XXVII

XXVII



[0973] wherein

[0974] X is alkylene or alkenylene;

[0975] Y is —CO—, —CS—, or —SO_2—;

[0976] Z is a bond, —O—, —S—, or —NR_{527}—;

[0977] R_{127} is aryl, heteroaryl, heterocyclyl, C_{1-20}alkyl or C_{2-20}alkenyl, each of which may be unsubstituted or substituted by one or more substituents independently chosen from:

[0978] -alkyl;

[0979] -alkenyl;

[0980] -aryl;

[0981] -heteroaryl;

[0982] -heterocyclyl;

[0983] -substituted cycloalkyl;

[0984] —O-alkyl;

[0985] —O-$(alkyl)_{0-1}$-aryl;

[0986] —O-$(alkyl)_{0-1}$-heteroaryl;

[0987] —O-$(alkyl)_{0-1}$-heterocyclyl;

[0988] —COOH;

[0989] —CO—O-alkyl;

[0990] —CO-alkyl;

[0991] —$S(O)_{0-2}$-alkyl;

[0992] —$S(O)_{0-2}$-$(alkyl)_{0-1}$-aryl;

[0993] —$S(O)_{0-2}$-$(alkyl)_{0-1}$-heteroaryl;

[0994] —$S(O)_{0-2}$-$(alkyl)_{0-1}$-heterocyclyl;

[0995] -$(alkyl)_{0-1}$-$N(R_{527})_2$;

[0996] -$(alkyl)_{0-1}$-NR_{527}—CO—O-alkyl;

[0997] -$(alkyl)_{0-1}$-NR_{527}—CO-alkyl;

[0998] -$(alkyl)_{0-1}$-NR_{527}—CO-aryl;

[0999] -$(alkyl)_{0-1}$-NR_{527}—CO-heteroaryl;

[1000] —N_3;

[1001] -halogen;

[1002] -haloalkyl;

[1003] -haloalkoxy;

[1004] —CO-haloalkyl;

[1005] —CO-haloalkoxy;

[1006] —NO_2;

[1007] —CN;

[1008] —OH;

[1009] —SH; and in the case of alkyl, alkenyl, and heterocyclyl, oxo;

[1010] R_{227} is chosen from:

[1011] -hydrogen;

[1012] -alkyl;

[1013] -alkenyl;

[1014] -alkyl-O-alkyl;

[1015] -alkyl-S-alkyl;

[1016] -alkyl-O-aryl;

[1017] -alkyl-S-aryl:

[1018] -alkyl-O-alkenyl;

[1019] -alkyl-S-alkenyl; and

[1020] -alkyl or alkenyl substituted by one or more substituents chosen from:

[1021] —OH;

[1022] -halogen;

[1023] —$N(R_{527})_2$;

[1024] —CO—$N(R_{527})_2$;

[1025] —CS—$N(R_{527})_2$;

[1026] —SO_2—$N(R_{527})_2$;

[1027] —NR_{527}—CO—C_{1-10}alkyl;

[1028] —NR_{527}—CS—C_{1-10}alkyl;

[1029] —NR_{527}—SO_2—C_{1-10}alkyl;

[1030] —CO—C_{1-10}alkyl;

[1031] —CO—O—C_{1-10}alkyl;

[1032] —N_3;

[1033] -aryl;

[1034] -heteroaryl;

[1035] -heterocyclyl;

[1036] —CO-aryl; and

[1037] —CO-heteroaryl;

[1038] R_{327} and R_{427} are independently chosen from hydrogen, alkyl, alkenyl, halogen, alkoxy, amino, alkylamino, dialkylamino and alkylthio;

[1039] each R_{527} is independently H or C_{1-10}alkyl;

[1040] and pharmaceutically acceptable salts thereof.

[1041] As used herein, the terms "alkyl", "alkenyl" and the prefix "alk-" are inclusive of both straight chain and branched chain groups and of cyclic groups, i.e. cycloalkyl and cycloalkenyl. Unless otherwise specified, these groups contain from 1 to 20 carbon atoms, with alkenyl groups containing from 2 to 20 carbon atoms. Preferred groups have a total of up to 10 carbon atoms. Cyclic groups can be monocyclic or polycyclic and preferably have from 3 to 10 ring carbon atoms. Exemplary cyclic groups include cyclopropyl, cyclopropylmethyl, cyclopentyl, cyclohexyl and adamantyl.

[1042] The term "haloalkyl" is inclusive of groups that are substituted by one or more halogen atoms, including perfluorinated groups. This is also true of groups that include the prefix "halo-". Examples of suitable haloalkyl groups are chloromethyl, trifluoromethyl, and the like.

[1043] The term "aryl" as used herein includes carbocyclic aromatic rings or ring systems. Examples of aryl groups include phenyl, naphthyl, biphenyl, fluorenyl and indenyl. The term "heteroaryl" includes aromatic rings or ring systems that contain at least one ring hetero atom (e.g., O, S, N). Suitable heteroaryl groups include furyl, thienyl, pyridyl, quinolinyl, isoquinolinyl, indolyl, isoindolyl, triazolyl, pyrrolyl, tetrazolyl, imidazolyl, pyrazolyl, oxazolyl, thiazolyl, benzofuranyl, benzothiophenyl, carbazolyl, benzoxazolyl, pyrimidinyl, benzimidazolyl, quinoxalinyl, benzothiazolyl, naphthyridinyl, isoxazolyl, isothiazolyl, purinyl, quinazolinyl, and so on.

[1044] "Heterocyclyl" includes non-aromatic rings or ring systems that contain at least one ring hetero atom (e.g., O, S, N) and includes all of the fully saturated and partially unsaturated derivatives of the above mentioned heteroaryl groups. Exemplary heterocyclic groups include pyrrolidinyl, tetrahydrofuranyl, morpholinyl, thiomorpholinyl, piperidinyl, piperazinyl, thiazolidinyl, imidazolidinyl, isothiazolidinyl, and the like.

[1045] In some embodiments, the topical formulations of the present invention are prepared using the free base form of the IRM compound.

[1046] The amount of an IRM compound that will be therapeutically effective in a specific situation will depend on such things as the activity of the particular compound, the dosing regimen, the application site, the particular formulation and the condition being treated. As such, it is generally not practical to identify specific administration amounts herein; however, those skilled in the art will be able to determine appropriate therapeutically effective amounts based on the guidance provided herein, information available in the art pertaining to these compounds, and routine testing. The term "a therapeutically effective amount" means an amount of the compound sufficient to induce a therapeutic effect, such as cytokine induction, inhibition of TH2 immune response, antiviral or antitumor activity, reduction or elimination of postsurgical scarring, or reduction or resolution of actinic keratosis or pre-actinic keratosis lesions.

[1047] In general, the amount of the IRM compound present in a topical formulation of the invention will be an amount effective to treat a targeted condition, to prevent recurrence of the condition, or to promote immunity against the condition. The amount or concentration of the IRM compound can range from 0.001% to 10% by weight based on the total formulation weight, such as, for example, from

0.03% to 5.0% by weight, or from 0.1 to 1.0% by weight. In certain embodiments, the amount of the IRM compound is at least 0.003% by weight, such as, for example, at least 0.005%, at least 0.01%, at least 0.03%, at least 0.10%, at least 0.30% and at least 1.0%. In other embodiments, the amount of the IRM compound is at most 5.0% by weight, such as, for example, at most 3.0%, and at most 1.0%.

[1048] The topical formulations of the invention additionally comprise a fatty acid. As used herein, the term "fatty acid" means a carboxylic acid, either saturated or unsaturated, comprising 6 to 28 carbon atoms, such as, for example, from 10 to 22 carbon atoms. Non-limiting examples of such fatty acids include isostearic acid, oleic acid, and linear- or-branched chained carboxylic acids of 6 to 18 carbon atoms. The fatty acid may be present in the formulation in an amount sufficient to solubilize the IRM compound. In one embodiment, the amount of the fatty acid can range from 0.05% to 40% by weight based on the total weight of the formulation, such as, for example, from 1% to 30%, from 3% to 15% and from 5% to 10%. In certain embodiments, the amount of the fatty acid is at least 3.0% by weight, such as, for example, at least 5.0%, at least 10.0%, and at least 25%. The fatty acid component of the formulation can comprise one or more fatty acids.

[1049] The topical formulations of the invention additionally comprise at least one hydrophobic, aprotic component miscible with the fatty acid and comprising a hydrocarbyl group of 7 or more carbon atoms. By "hydrophobic" is meant that the component is essentially insoluble in water, i.e. immiscible with water and unable to form a micelle in water, and does not contain polyoxyethylene or acid salt groups. Preferably the hydrophobic, aprotic component has a hydrophilic lipophilic balance (HLB) of less than 2. The HLB of a component may be determined as described, for example, in Attwood, D., Florence, A. T. *Surfactant Systems: Their Chemistry Pharmacy, and Biology.* New York: Chapman & Hall, 471-473, 1983. By "aprotic" is meant that the component cannot donate a proton to the IRM and does not contain groups such as carboxyl, hydroxy, primary and secondary amino, primary and secondary amido, or quaternary ammonium groups. Preferably this component has a pKa of at least 14.2 and does not substantially solubilize or form a complex such as an acid-base pair or complex or a hydrogen bond complex with the IRM compound. By "not substantially" is meant that the ratio of the IRM compound's solubility in the hydrophilic, aprotic component to that in isostearic acid is less than 1:40.

[1050] Formulations intended for dermal or topical use desirably have a certain minimum amount of an oil phase to provide qualities such as spreadability, feel on the skin, texture, and so on. However, if all the components of the oil phase solubilize the IRM, then the degree of saturation of the IRM in the formulation will decrease, making it more difficult to deliver the IRM from the formulation to the skin. Addition of the hydrophobic, aprotic component can increase the oil phase volume of the topical formulation to provide desirable qualitites such as spreadability and feel, while at the same time not appreciably altering the degree of saturation or thermodynamic activity of the IRM. For example, the amount of fatty acid, which solubilizes the IRM, can be reduced to increase the degree of IRM saturation while maintaining a sufficient oil phase volume by virtue of the addition of the hydrophobic, aprotic component, which does not offset the increased IRM saturation. Thus, the topical formulation of the present invention can facilitate both physical property and drug delivery requirements. Degree of saturation and thermodynamic activity of the IRM in these formulations is equal to the IRM concentration in the oil phase divided by the saturation concentration of the IRM in the oil phase. When the topical formulations of the present invention contain saturated IRM the thermodynamic activity or degree of saturation is unity, and when partially saturated the thermodynamic activity or degree of saturation is less than unity.

[1051] The amount of the hydrophobic, aprotic component present in a formulation of the invention can range from 1% to 30% by weight based on the total formulation weight, for example, from 3% to 15% by weight, and from 5 to 10% by weight. In certain embodiments, the amount of the hydrophobic, aprotic component is at least 3.0% by weight, for example, at least 5.0%, and at least 10.0%. The weight ratio of the hydrophobic, aprotic component to the fatty acid can be 0.025:1 to 600:1, for example, 0.5:1 to 50:1, and 2:1 to 30:1. The combined amount (weight percent of the total topical formulation weight) of the hydrophobic, aprotic component and the fatty acid can be 2% to 50% by weight, for example 2% to 30%, 5% to 30%, 5% to 20%, and 10% to 20%.

[1052] Examples of useful hydrophobic, aprotic components include but are not limited to fatty acid esters, for example, isopropyl mysristate, isopropyl palmitate, diisopropyl dimer dilinoleate; triglycerides, for example, caprylic/capric triglyceride; cetyl esters wax; hydrocarbons of 8 or more carbon atoms, for example, light mineral oil, white petrolatum; and waxes, for example, beeswax. In some embodiments, the hydrophobic, aprotic component is chosen from one or more of isopropyl mysristate, isopropyl palmitate, caprylic/capric triglyceride, and diisopropyl dimer dilinoleate.

[1053] The formulations of the present invention can also comprise a hydrophilic viscosity enhancing agent. Examples of suitable hydrophilic viscosity enhancing agents include cellulose ethers such as hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, and carboxymethylcellulose; polysaccharide gums such as xanthan gum; and homopolymers and copolymers of acrylic acid crosslinked with allyl sucrose or allyl pentaerythriol such as those polymers designated as carbomers in the United States Pharmacopoeia. Suitable carbomers include, for example, those available as Carbopol™ 934P, Carbopol 971P, Carbopol 940, Carbopol 974P, Carbopol 980, and Pemulen™ TR-1 (USP/NF Monograph; Carbomer 1342), all available from Noveon, Cleveland, Ohio. In one embodiment of the present invention, the viscosity enhancing agent is chosen from Carbopol 974P and 980. When included, the viscosity enhancing agent is generally present in an amount ranging from 0.1% to 10% by weight of total formulation weight, such as, for example, from 0.5% to 5% by weight, from 0.5% to 1.5% by weight, and from 0.7% to 3% by weight. In certain embodiments, the amount of the viscosity enhancing agent is at least 0.5% by weight, for example, at least 0.6% by weight, at least 0.7% by weight, at least 0.9% by weight, and at least 1.0% by weight.

[1054] The formulations of the invention can additionally comprise an emulsifier. Suitable emulsifiers include non-

ionic surfactants such as, for example, polysorbate 60, sorbitan monostearate, polyglyceryl-4 oleate, polyoxyethylene(4) lauryl ether, etc. In certain embodiments, the emulsifier is chosen from poloxamers (e.g., Pluronic™ F68, also known as Poloxamer 188, a poly(ethylene glycol)-block-poly(propylene glycol)-block-poly(ethylene glycol), available from BASF, Ludwigshafen, Germany) and sorbitan trioleate (e.g., Span 85 available from Uniqema, New Castle, Del.). If included, the emulsifier is generally present in an amount of 0.1% to 10% by weight of total formulation weight, for example, from 0.5% to 5% by weight, and from 0.75% to 3.5% by weight. In certain embodiments, the amount of the emulsifier is at least 1.0% by weight, for example, at least 2.5%, at least 3.5%, and at least 5.0%.

[1055] In certain embodiments of the present invention, the formulation can also include at least one chelating agent. The chelating agent functions to chelate metal ions that may be present in the formulation. Suitable chelating agents include salts of ethylenediaminetetraacetate (EDTA), such as the disodium salt. If included, the chelating agent is generally present in an amount ranging from 0.001% to 0.1% by weight, and preferably from 0.01% to 0.05% by weight. In certain embodiments, the amount of the chelating agent is at least 0.005% by weight, such as, for example, at least 0.01%, and at least 0.05%.

[1056] The formulation can also include a preservative system. The preservative system is generally comprised of at least one preservative compound chosen from methylparaben, ethylparaben, propylparaben, phenoxyethanol, iodopropynyl butylcarbamate, sorbic acid, a fatty acid monoester of glycerin such as glycerol monolaurate, and a fatty acid monoester of propylene glycol such as propylene glycol monocaprylate. The preservative system may also include a preservative enhancing solubilizer which enhances the solubility of the preservative in the aqueous phase, examples of which include diethylene glycol monoethyl ether and propylene glycol. In one embodiment, the preservative system can be comprised of methylparaben, propylparaben, and propylene glycol. In another embodiment, the preservative system can be comprised of methylparaben, ethylparaben, and diethylene glycol monoethyl ether. In one embodiment, the preservative system can be comprised of phenoxyethanol, methylparaben or methyl- and ethylparaben, and diethylene glycol monoethyl ether. In another embodiment, the preservative system can be comprised of iodopropynyl butylcarbamate. In another embodiment, the preservative system can be comprised of iodopropynyl butylcarbamate, diethylene glycol monoethyl ether, and poly(ethylene glycol)(4) monolaurate. In another embodiment, the preservative system can be comprised of iodopropynyl butylcarbamate, one or more of methylparaben, ethylparaben, propylparaben, or phenoxyethanol, and diethylene glycol monoethyl ether. In the above embodiments, the methylparaben, ethylparaben, and propylparaben can each be present in the formulations in an amount ranging from 0.01% to 0.5% by weight of the formulation weight, for example, from 0.05% to 0.25% by weight, and from 0.1% to 0.2% by weight. The iodopropynyl butylcarbamate can be present in the formulations in an amount ranging from 0.01% to 0.1%. The phenoxyethanol can be present in the formulations in an amount ranging from 0.1% to 1%. The propylene glycol and diethylene glycol monoethyl ether can each be present in the formulations in an amount ranging from 1% to 30% by weight of the formulation weight, such as, for example, from 5% to 25% by weight, and from 10% to 15% by weight. The preservative system can be present in the formulations in an amount ranging from 0.01% to 30% by weight of the formulation weight, for example, from 0.05% to 30%, from 0.1% to 25% by weight, and from 0.2% to 15% by weight. In a further embodiment, the methylparaben, ethylparaben, propylparaben, iodopropynyl butylcarbamate, and phenoxyethanol can be solubilized in propylene glycol, poly(ethylene glycol)(4) monolaurate, or diethylene glycol monoethyl ether prior to addition to the formulation. The preservative system can be selected such that it meets the criteria for antimicrobial effectiveness set forth in the United States Pharmacopeia <51>.

[1057] The formulations of the present invention may additionally comprise at least one pH adjuster. Suitable pH adjusters include organic bases and inorganic bases such as, for example, KOH, NaOH. The pH of the topical formulations of the present invention generally ranges from 3.5 to 7.0. In one embodiment, the pH of the topical formulations of the present invention can range from 4.0 to 6.0, preferably 5.0. In another embodiment of the invention, the pH of the topical formulations of the present invention can range from 5.5 to 6.5, preferably 6.0.

[1058] Any of the foregoing formulations can be in the form of an oil-in-water emulsion such as a cream or a lotion. Such an emulsion can comprise an oil phase comprising the IRM compounds, a fatty acid in an amount sufficient to solubilize the IRM compounds, a hydrophobic, aprotic component; and an aqueous phase comprising a hydrophilic viscosity enhancing agent, for example, a carbomer. In certain embodiments, the amount or concentration of the IRM in the oil phase can be at least 0.01%, for example, at least 0.02%, at least 0.1%, and at least 1% with respect to oil phase weight. In other embodiments, the amount or concentration of the IRM in the oil phase can be at most 20%, for example, at most 10%, and at most 5% with respect to oil phase weight. The emulsion can be preserved so that when challenged by an antimicrobial effectiveness test, it meets regulatory requirements for topical creams packaged in multiple-use containers.

[1059] Any of the foregoing formulations according to the present invention can be applied to the dermal surfaces of a mammal. Depending on the IRM compound concentration, formulation composition, and dermal surface, the therapeutic effect of the IRM compound may extend only to the superficial layers of the dermal surface or to tissues below the dermal surface. Thus, another aspect of the present invention is directed to a method for the treatment of a dermal associated condition comprising applying to skin one of the foregoing formulations. As used herein, a "dermal associated condition" means an inflammatory, infectious, neoplastic or other condition that involves a dermal surface or that is in sufficient proximity to a dermal surface to be affected by a therapeutic agent topically applied to the dermal surface. Examples of a dermal associated condition include warts, atopic dermatitis, basal cell carcinoma, post-surgical scars, and actinic keratosis.

[1060] In one embodiment, the formulations can be applied to the surface of skin for treatment of actinic keratosis (AK). Actinic keratoses are premalignant lesions considered biologically to be either carcinoma in-situ or squamous intraepidermal neoplasia. AK is the most frequent

epidermal tumor and is induced by ultraviolet (UV) radiation, typically from sunlight. Because of its precancerous nature, AK may be considered the most important manifestation of sun-induced skin damage.

[1061] In some embodiments, the above described formulations are particularly advantageous for dermal application for a period of time sufficient to obtain a desired therapeutic effect without undesired systemic absorption of the IRM.

EXAMPLES

[1062] The following Examples are provided to further describe various IRM formulations and methods according to the invention. The examples, however, are not intended to limit the formulations and methods within the spirit and scope of the invention.

Examples 1-7 and Comparative Example C1

[1063] Table 1 summarizes topical formulations made in accordance with the present invention in a percentage weight-by-weight basis.

TABLE 1

	Topical Cream (percentage weight-by-weight)							
Ingredient (Compendial Status)	Comparative Example C1 (Placebo)	Example 1	Example 2	Example 3	Example 4	Example 5	Example 6	Example 7
IRM Compound 1	0.00	0.001	0.003	0.010	0.03	0.10	0.30	1.00
Isostearic Acid	5.00	5.00	5.00	5.00	5.00	5.00	7.00	10.00
Isopropyl Myristate (NF)	10.00	10.00	10.00	10.00	10.00	10.00	8.00	5.00
Carbomer 974P (NF)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Poloxamer 188 (NF)	2.50	2.50	2.50	2.50	2.50	2.50	2.50	2.50
Propylene Glycol (USP)	15.00	15.00	15.00	15.00	15.00	15.00	15.00	15.00
Methylparaben (NF)	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20
Propylparaben (NF)	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10
Edetate Disodium (USP)	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Sodium Hydroxide (NF) Solution, 20% w/w	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50
Purified Water (USP)	65.65	65.649	65.647	65.64	65.62	65.55	65.35	64.60
Total	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00

[1064] The formulations set forth in Table 1 were prepared in the following manner:

[1065] Oil phase preparation: 2-methyl-1-(2-methylpropyl)-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine (IRM compound 1) was dissolved in isostearic acid and isopropyl myristate, with heat if necessary. Carbomer 974P was then dispersed in the oil phase.

[1066] Water phase preparation: Edetate disodium was dissolved in the water. Methylparaben and propylparaben were dissolved in propylene glycol and the solution was subsequently added to the water phase. Poloxamer 188 was then added to the water phase and mixed until dissolved.

[1067] Phase combination: The oil phase was added to the water phase at ambient conditions. The emulsion was then homogenized. After homogenization, sodium hydroxide solution (20% w/w) was added and the resulting cream was mixed until smooth and uniform. The pH of the cream was measured and a pH adjustment was made with additional sodium hydroxide solution, if necessary, to meet the in-process target pH of 5.

[1068] Formulations containing 2-methyl-1-(2-methylpropyl)-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine (IRM Compound 1) were tested for their ability to induce increases in cytokine concentrations in rats following topical application. This study was undertaken to evaluate cytokine induction following a single dosing of various strengths and timepoints or a multiple vs. single dosing of IRM Compound 1. The formulations described above were tested by examining tissue and serum concentrations of TNF-α, MCP-1 (monocyte chemoattractant protein-1) and IFN-α cytokines following drug treatment.

[1069] Female CD hairless rats (Charles River Laboratories, Wilmington, Mass.) weighing 200-250 grams were used in all studies. Animals were randomized to treatment groups and dosed five per treatment group.

[1070] The rats were acclimated to collars around the neck on two consecutive days prior to actual dosing. The rats were collared before dosing to prevent ingestion of the drug, and were then dosed topically with 50 μL of active cream or the appropriate placebo on right flank and then housed individually following dosing. At various times following dosing, the rats were anesthetized and blood was collected by cardiac puncture. Blood was allowed to clot at room temperature and serum was separated from the clot via centrifugation and stored at −20° C. until it was analyzed for cytokine concentrations.

[1071] Following blood collection, the rats were euthanized and their skins removed. Tissue from both treated site (at) and contralateral site (away) were obtained using an 8 mm punch biopsy, weighed, placed in a sealed 1.8 ml cryovial and flash frozen in liquid nitrogen. The frozen tissue sample was then suspended in 1.0 mL RPMI medium (Celox, Hopkins, Minn.) containing 10% fetal bovine serum (Sigma, St. Louis, Mo.), 2 mM L-glutamine, penicillin/streptomycin, and 2-mercaptoethanol (RPMI complete) combined with a protease inhibitor cocktail set III (Calbiochem, San Diego, Calif.). The tissue was homogenized using a Tissue Tearor™ (Biospec Products, Bartlesville, Okla.) for

approximately 1 minute. The tissue suspension was then centrifuged at 2000 rpm for 10 minutes under refrigeration to pellet debris, and the supernatant collected and stored at −20° C. until analyzed for cytokine concentrations.

[1072] ELISAs for rat MCP-1 were purchased from BioSource Intl. (Camarillo, Calif.) and rat TNF-α were purchased from BD Pharmingen (San Diego, Calif.) and performed according to manufacturer's specifications. Results for both TNF-α, and MCP-1 were expressed in pg/200 mg tissue or pg/ml serum. The sensitivity of the TNF-α ELISA was 31.2 pg/ml and of the MCP-1 ELISA was 11.7 pg/ml. IFN-α concentrations in both serum and skin tissue were determined using a bioassay that measured inhibition of the viral cytopathic effect of vesicular stomatitis virus on rat LMS-C2 fibroblast cells as previously described (Reiter, M. J., Testerman, T. L., Miller, R. L., Weeks, C. E., and Tomai, M. A. (1994) "Cytokine Induction in Mice by the Immunomodulator Imiquimod." J. Leukocyte Biol. 55, 234-240). IIT Research Institute, Chicago Ill., performed these assays. Results for IFN-α concentrations were normalized to a standard reference rat IFN-α, preparation with results being reported in U/mL and are normalized per mg of tissue.

[1073] The data shown below in Tables 2-4 are from three separate experiments and analyzed to 1) measure pharmacokinetics by full time course, 2) measure dose response and 3) measure multiple vs. single dosing.

[1074] In order to determine the kinetics of local and systemic cytokine production following local administration of IRM Compound 1, the full time course study (Study 1 with results in Table 2) was done by topically dosing rats with the topical cream formulation of Example 7. Serum and tissue samples were taken at 1, 2, 4, 8, 16, 24 and 48 hours post dose. Multiple cytokines (MCP-1, TNF-α and IFN-α) were analyzed separately.

[1075] With the tissue data, for each hour measured, a paired t-test (used to eliminate within subject variability) analyzed the difference between treated tissue and control tissue from the same animal. A p-value less than alpha=0.05 indicated a statistically significant difference between the treated and control tissue at that hour. The data are presented in Table 2.

TABLE 2

Cytokine Concentrations in Rat Serum and Dermal Tissue Following Application of the Topical Formulation of Example 7 Full Time Course[a]

Time (hours)		Cytokine Concentration[b] TNF-α		
Post Dose	Dose	Serum	Treated Site	Control site
0	untreated	0	NA	96 ± 5
16	placebo	0	103 ± 8	71 ± 6
1	1%	6 ± 6	318 ± 33[c]	96 ± 13
2	1%	0	1125 ± 74[c]	124 ± 18
4	1%	0	1120 ± 51[c]	129 ± 11
8	1%	24 ± 16	429 ± 56[c]	91 ± 12
16	1%	6 ± 4	231 ± 22[c]	87 ± 27
24	1%	32 ± 32	198 ± 28[c]	103 ± 13
48	1%	49 ± 49	74 ± 10	69 ± 15
		MCP-1		
0	untreated	81 ± 30	NA	44 ± 2
16	placebo	144 ± 9	144 ± 41	42 ± 3
1	1%	86 ± 29	40 ± 8	42 ± 3

TABLE 2-continued

Cytokine Concentrations in Rat Serum and Dermal Tissue Following Application of the Topical Formulation of Example 7 Full Time Course[a]

2	1%	123 ± 31	234 ± 29[c]	50 ± 4
4	1%	101 ± 28	723 ± 89[c]	41 ± 5
8	1%	438 ± 91[c]	1474 ± 202[c]	38 ± 3
16	1%	424 ± 96[c]	1209 ± 325[c]	31 ± 5
24	1%	187 ± 39	813 ± 151[c]	39 ± 1
48	1%	141 ± 24	145 ± 48[c]	36 ± 6
			IFN-α	
0	untreated	<200	NA	<650
16	placebo	<200	<650	<650
1	1%	<200	<650	<650
2	1%	<200	<650	<650
4	1%	<200	<650	<650
8	1%	<200	3/5≧650	<650
16	1%	<200	<650	<650
24	1%	<200	<650	<650
48	1%	<200	<650	<650

[a]Female hairless CD rats were dosed topically with cream formulated Compound 1.
[b]TNF-α and MCP-1 were measured by ELISA. IFN-α was measured by bioassay. Results are presented in pg/ml for serum samples and pg/200 mg tissue for tissue samples and represent the mean of five animals ± SEM.
[c]Indicates $p < 0.05$ when compared to either placebo for serum samples or the difference between treated tissue and control tissue from the same animal.

[1076] A multiple dose study was done to monitor effects of a multiple dose regimen (Study 2 with results shown in Table 3). Rats were dosed two times a week for six hours for three weeks with topical cream formulation of Example 5. Placebo (Comparative Example C1) and single dosed rats were done for comparison and done simultaneously with the last dosing of the multiple dose set. Serum and tissue samples were taken at 8 and 24 hours post dose and analyzed for MCP-1.

[1077] An analysis identical to that of Study 1 was performed for Study 2. This data set was broken up by treatment (multiple- or single-use) and time point prior to analysis. Again, placebo data were recorded only at the 8-hour time point for single use, but were used to compare placebo to every treatment and time point combination separately. The results are set forth in Table 3 below.

TABLE 3

Cytokine Concentrations in Rat Serum and Dermal Tissue Following Topical Application of the Topical Cream Formulation of Example 5 Multiple vs. Single Dose[a]

Time (hours)		Cytokine Concentration[b] MCP-1		
Post Dose	Dose	Serum	Treated Site	Control Site
0	None (untreated)	89 ± 11	NA	20 ± 10
24	Placebo	41 ± 14	42 ± 15	28 ± 6
8	Multiple 0.1%	71 ± 13	784 ± 48[c]	42 ± 5

TABLE 3-continued

Cytokine Concentrations in Rat Serum and Dermal Tissue Following Topical Application of the Topical Cream Formulation of Example 5 Multiple vs. Single Dose[a]

Time (hours)		Cytokine Concentration[b] MCP-1		
Post Dose	Dose	Serum	Treated Site	Control Site
24	Multiple 0.1%	105 ± 36	145 ± 23[c]	32 ± 6
8	Single 0.1%	73 ± 9	519 ± 99[c]	33 ± 6
24	Single 0.1%	82 ± 3[c]	412 ± 130[c]	35 ± 7

[a]Female hairless CD rats were dosed topically with cream formulated Compound 1.
[b]MCP-1 was measured by ELISA. Results are presented in pg/ml for serum samples and pg/200 mg tissue for tissue samples and represent the mean of five animals ± SEM.
[c]Indicates $p < 0.05$ when compared to either placebo for serum samples or the difference between treated tissue and control tissue from the same animal.

[1078] A dose response study (Study 3 with results shown in Table 4) was performed by dosing with the topical cream formulations of Examples 3-5 and 7, containing various concentrations of IRM Compound 1. Serum and tissue samples were taken at 8 and 24 hours post dose and analyzed for MCP-1. The studies tested topical delivery of creams comprising IRM Compound 1 for its ability to affect a local MCP-1 induction at four concentrations.

[1079] Serum data compared active treatment to placebo (Comparative Example C1) separately at each specified time point. Note that the placebo group was only measured at 24 hours post dose and these observations were compared to each time point for the active group.

TABLE 4

Cytokine Concentrations in Rat Serum and Dermal Tissue Following Topical Application of the Formulations of Examples 3–5 and 7[a]

Time (hours)		Cytokine Concentration[b] MCP-1		
Post Dose	Dose	Serum	Treated Site	Control Site
0	controls	207 ± 96	NA	38 ± 12
24	placebo (Comparative Example C1)	367 ± 178	61 ± 14	20 ± 5
8	0.01% (Example 3)	81 ± 23	61 ± 12	36 ± 7
8	0.03% (Example 4)	81 ± 20	271 ± 29	48 ± 5
8	0.1% (Example 5)	153 ± 14	1119 ± 122[c]	51 ± 8
8	1.0% (Example 7)	136 ± 23	1370 ± 99[c]	50 ± 15
24	0.01% (Example 3)	71 ± 18	183 ± 49[c]	33 ± 13
24	0.03% (Example 4)	71 ± 20	212 ± 49[c]	40 ± 7
24	0.1% (Example 5)	226 ± 73	628 ± 127[c]	40 ± 11
24	1.0% (Example 7)	149 ± 45	756 ± 38[c]	30 ± 9

[a]Female hairless CD rats were dosed topically with cream formulated Compound 1.
[b]MCP-1 was measured by ELISA. Results are presented in pg/ml for serum samples and pg/200 mg tissue for tissue samples and represent the mean of five animals ± SEM.
[c]Indicates $p < 0.05$ when compared to either placebo for serum samples or the difference between treated tissue and control tissue from the same animal.

Examples 8-13

[1080] Table 5 summarizes topical formulations made in accordance with the present invention in a percentage weight-by-weight basis.

TABLE 5

Ingredient	Topical Cream (percentage weight-by weight)					
(Compendial Status)	Example 8	Example 9	Example 10	Example 11	Example 12	Example 13
IRM Compound 2	0.01	0.03	0.10	1.00	0.003	0.30
Isostearic Acid	5.00	5.00	5.00	10.00	5.00	5.00
Isopropyl Myristate (NF)	10.00	10.00	10.00	5.00	10.00	10.00
Carbomer 974P (NF)	1.00	1.00	1.00	0.75	1.00	1.00
Poloxamer 188 (NF)	2.50	2.50	2.50	2.50	2.50	2.50
Propylene Glycol (USP)	15.00	15.00	15.00	15.00	15.00	15.00
Methylparaben (NF)	0.20	0.20	0.20	0.20	0.20	0.20
Propylparaben (NF)	0.10	0.10	0.10	0.10	0.10	0.10
Edetate Disodium (USP)	0.05	0.05	0.05	0.05	0.05	0.05
Sodium Hydroxide (NF) Solution, 20% w/w	0.50	0.50	0.50	0.35	0.50	0.50
Purified Water (USP)	65.64	65.62	65.55	65.05	65.647	65.35
Total	100.00	100.00	100.00	100.00	100.00	100.00

[1081] The formulations set forth in Table 5 were prepared in the following manner:

[1082] Oil phase preparation: N-[4-(4-Amino-2-butyl-1H-imidazo[4,5-c][1,5]naphthyridin-1-yl)butyl]-N'-cyclohexylurea (IRM Compound 2) was dissolved in isostearic acid and isopropyl myristate, with heat if necessary. Carbomer 974P was then dispersed in the oil phase.

[1083] Water phase preparation: Edetate disodium was dissolved in the water. Methylparaben and propylparaben were dissolved in propylene glycol, and the solution was subsequently added to the water phase. Poloxamer 188 was then added to the water phase and mixed until dissolved.

[1084] Phase combination: The oil phase was added to the water phase at ambient conditions. The emulsion was then homogenized. After homogenization, sodium hydroxide solution (20% w/w) was added and the resulting cream was mixed until smooth and uniform. The pH of the cream was measured, and a pH adjustment was made with additional sodium hydroxide solution, if necessary, to meet the in-process target pH of 5.

[1085] Formulations containing N-[4-(4-Amino-2-butyl-1H-imidazo[4,5-c][1,5]naphthyridin-1-yl)butyl]-N'-cyclohexylurea (IRM Compound 2) were tested for their ability to induce increases in cytokine concentrations in rats following topical application. This study was undertaken to evaluate cytokine induction following a single dosing of various strengths and timepoints or a multiple vs. single dosing of IRM Compound 2. The formulations described above were tested by examining tissue and serum concentrations of TNF-α, MCP-1 and IFN-α following drug treatment as described in Examples 1-7.

[1086] The data shown below in Tables 6-8 are from three separate experiments and analyzed to 1) measure pharmacokinetics by full time course, 2) measure dose response and 3) measure multiple vs. single dosing.

[1087] In order to determine the kinetics of local and systemic, cytokine production following local administration of IRM Compound 2, the full time course study (Study 1 with results in Table 6) was done by topically dosing rats with the topical cream formulation of Example 11 as described in Examples 1-7. The data are presented in Table 6.

TABLE 6

Cytokine Concentrations in Rat Serum and Dermal Tissue Following Application of the Topical Formulation of Example 11 Full Time Course[a]

Time (hours)		Cytokine Concentration[b] TNF-α		
Post Dose	Dose	Serum	Treated Site	Control site
0	untreated	29 ± 15	NA	70 ± 11
16	placebo	42 ± 9	131 ± 32	69 ± 11
1	1%	38 ± 38	44 ± 14	35 ± 19
2	1%	2 ± 2	75 ± 20[c]	33 ± 13
4	1%	3 ± 3	321 ± 18[c]	62 ± 20
8	1%	0	894 ± 180[c]	21 ± 9
16	1%	12 ± 12	377 ± 45[c]	22 ± 12
24	1%	16 ± 8	285 ± 15[c]	52 ± 14
48	1%	24 ± 7	74 ± 9	65 ± 13
			MCP-1	
0	untreated	100 ± 20	NA	33 ± 7
16	placebo	144 ± 9	225 ± 106	22 ± 4
1	1%	117 ± 17	56 ± 9	55 ± 9
2	1%	126 ± 29	50 ± 13	54 ± 8
4	1%	136 ± 29	161 ± 18[c]	71 ± 9
8	1%	189 ± 28	1020 ± 319	45 ± 15
16	1%	297 ± 35	1294 ± 122[c]	40 ± 9
24	1%	217 ± 12	1044 ± 185[c]	41 ± 11
48	1%	120 ± 22	134 ± 14[c]	34 ± 7
			IFN-α	
0	untreated	<65	NA	<650
16	placebo	<65	<650	<650
1	1%	<65	<650	<650
2	1%	<65	<650	<650
4	1%	<65	<650	<650
8	1%	<65	901 ± 571	<650
16	1%	<65	1330 ± 386[c]	<650
24	1%	<65	<650	<650
48	1%	<65	<650	<650

[a]Female hairless CD rats were dosed topically with cream formulated Compound 2.
[b]TNF-α and MCP-1 were measured by ELISA. IFN-α was measured by bioassay. Results are presented in pg/ml for serum samples and pg/200 mg tissue for tissue samples and represent the mean of five animals ± SEM.
[c]Indicates $p < 0.05$ when compared to either placebo for serum samples or the difference between treated tissue and control tissue from the same animal.

[1088] A multiple dose study was done to monitor effects of a multiple dose regimen (Study 2 with results shown in Table 7). Rats were dosed two times a week for six hours for three weeks with topical cream formulation of Example 10. Placebo (Comparative Example C1) and single dosed rats were done for comparison and done simultaneously with the last dosing of the multiple dose set. Serum and tissue samples were taken at 16 and 24 hours post dose and analyzed for MCP-1.

[1089] An analysis identical to that of Study 1 was performed for Study 2. This data set was broken up by treatment (multi or single use) and time point prior to analysis. Again, placebo data were recorded only at the 16-hour time point for single use, but were used to compare placebo to every treatment and time point combination separately. The results are set forth in Table 7 below.

TABLE 7

Cytokine Concentrations in Rat Serum and Dermal Tissue Following Topical Application of the Topical Cream Formulation of Example 10 Multiple vs. Single Dose[a]

Time (hours)		Cytokine Concentration[b] MCP-1		
Post Dose	Dose	Serum	Treated Site	Control Site
0	None (untreated	161 ± 58	NA	80 ± 22

TABLE 7-continued

Cytokine Concentrations in Rat Serum and Dermal Tissue Following Topical Application of the Topical Cream Formulation of Example 10 Multiple vs. Single Dose[a]

Time (hours)		Cytokine Concentration[b] MCP-1		
Post Dose	Dose	Serum	Treated Site	Control Site
16	Placebo	214 ± 35	71 ± 16	47 ± 11
16	Multiple 0.1%	321 ± 62	1173 ± 117[c]	86 ± 14
24	Multiple 0.1%	217 ± 43	388 ± 80[c]	58 ± 5
16	Single 0.1%	205 ± 32	1448 ± 241[c]	77 ± 15
24	Single 0.1%	279 ± 45	1172 ± 288[c]	90 ± 15

[a]Female hairless CD rats were dosed topically with cream formulated Compound 2.
[b]MCP-1 was measured by ELISA. Results are presented in pg/ml for serum samples and pg/200 mg tissue for tissue samples and represent the mean of five animals ± SEM.
[c]Indicates $p < 0.05$ when compared to either placebo for serum samples or the difference between treated tissue and control tissue from the same animal.

[1090] A dose response study (Study 3 with results shown in Table 8) was performed by dosing with the topical cream formulations of Examples 8-11, containing various concentrations of IRM Compound 2. Serum and tissue samples were taken at 16 and 24 hours post dose and analyzed for MCP-1. The studies tested topical delivery of creams comprising IRM Compound 2 for its ability to affect a local MCP-1 induction at four concentrations.

[1091] Serum data compared active treatment to placebo (Comparative Example C1) separately at each specified time point. Note that the placebo group was only measured at 16 hours post dose and these observations were compared to each time point for the active group.

TABLE 8

Cytokine Concentrations in Rat Serum and Dermal Tissue Following Topical Application of the Formulations of Examples 8–11[a]

Time (hours)		Cytokine Concentration[b] MCP-1		
Post Dose	Dose	Serum	Treated Site	Control Site
0	controls	293 ± 23	NA	41 ± 11
16	placebo (Comparative Example C1)	293 ± 76	44 ± 10	36 ± 12
16	0.01% (Example 8)	276 ± 50	257 ± 85	57 ± 20
16	0.03% (Example 9)	318 ± 86	210 ± 10	45 ± 9
16	0.10% (Example 10)	529 ± 141	2622 ± 616[c]	73 ± 9
16	1.0% (Example 11)	345 ± 51	3166 ± 470[c]	71 ± 11
24	0.01% (Example 8)	298 ± 65	276 ± 87	94 ± 32
24	0.03% (Example 9)	253 ± 34	427 ± 238	28 ± 14
24	0.10% (Example 10)	331 ± 93	1461 ± 264[c]	19 ± 7

TABLE 8-continued

Cytokine Concentrations in Rat Serum and Dermal Tissue Following Topical Application of the Formulations of Examples 8–11[a]

Time (hours)		Cytokine Concentration[b] MCP-1		
Post Dose	Dose	Serum	Treated Site	Control Site
24	1.0% (Example 11)	358 ± 52	1952 ± 185[c]	17 ± 6

[a]Female hairless CD rats were dosed topically with cream formulated Compound 2.
[b]MCP-1 was measured by ELISA. Results are presented in pg/ml for serum samples and pg/200 mg tissue for tissue samples and represent the mean of five animals ± SEM.
[c]Indicates $p < 0.05$ when compared to either placebo for serum samples or the difference between treated tissue and control tissue from the same animal.

Examples 14-18

[1092] Table 9 summarizes topical formulations made in accordance with the present invention on a percentage weight-by-weight basis.

TABLE 9

	Topical Creams (percentage weight-by-weight)				
Ingredients	Ex. 14	Ex. 15	Ex. 16	Ex. 17	Ex. 18
IRM Compound 1	0.01	0.10	1.00	3.00	1.00
Isostearic Acid (874)	5.00	5.00	10.00	25.00	10.00
*Diisopropyl dimer dilinoleate	10.00	10.00	5.00	5.00	—
**Caprylic/capric triglycerides	—	—	—	—	5.00
Carbomer 980, NF	0.70	0.70	0.70	0.90	0.70
Diethylene glycol monoethyl ether USA - NF	10.00	10.00	10.00	10.00	10.00
Disodium EDTA, USP	0.05	0.05	0.05	0.05	0.05
Poloxamer 188, NF	2.50	2.50	2.50	2.50	2.50
Purified Water	70.94	70.85	69.95	52.55	69.95
Methylparaben, NF	0.20	0.20	0.20	0.20	0.20
Ethylparaben	0.20	0.20	0.20	0.20	0.20
20% (w/w) NaOH	0.40	0.40	0.40	0.60	0.40
Total % w/w	100.00	100.00	100.00	100.00	100.00

*Available under the trade name PRIPURE 3786 from Uniquema, New Castle, DE
**Available under the trade name Crodamol GTCC-PN from Croda, Inc, Parsippany, NJ

Examples 19-24

[1093] Table 10 summarizes topical formulations made in accordance with the present invention on a percentage weight-by-weight basis.

TABLE 10

	Topical Creams (percentage weight-by-weight)					
Ingredients	Ex. 19	Ex. 20	Ex. 21	Ex. 22	Ex. 23	Ex. 24
IRM Compound 2	0.003	0.03	0.10	1.00	3.00	1.00

TABLE 10-continued

Ingredients	Topical Creams (percentage weight-by-weight) Ex. 19	Ex. 20	Ex. 21	Ex. 22	Ex. 23	Ex. 24
Isostearic Acid (874)	5.00	5.00	5.00	10.00	25.00	10.00
Diisopropyl dimer dilinoleate	10.00	10.00	10.00	5.00	5.00	—
Caprylic/capric triglycerides	—	—	—	—	—	5.00
Carbomer 980, NF	0.70	0.70	0.70	0.70	0.60	0.70
Diethylene glycol monoethyl ether USA - NF	10.00	10.00	10.00	10.00	10.00	10.00
Disodium EDTA, USP	0.05	0.05	0.05	0.05	0.05	0.05
Poloxamer 188, NF	2.50	2.50	2.50	2.50	2.50	2.50
Purified Water	70.95	70.92	70.85	69.95	53.19	69.95
Methylparaben, NF	0.20	0.20	0.20	0.20	0.20	0.20
Ethylparaben	0.20	0.20	0.20	0.20	0.20	0.20
20% (w/w) NaOH	0.40	0.40	0.40	0.40	0.26	0.40
Total % w/w	100.00	100.00	100.00	100.00	100.00	100.00

[1094] The formulations described in Tables 9 and 10 were prepared using the following general method:

[1095] Oil Phase Preparation:

[1096] The IRM compound was dissolved in isostearic acid and diisopropyl dimer dilinoleate (or caprylic/capric acid triglyceride) with heat if necessary.

[1097] Water Phase Preparation:

[1098] Edetate disodium was dissolved in the water. Poloxamer 188 was then added to the water phase and mixed until dissolved. Carbomer 980 was then added to the water phase and mixed until the carbomer was fully dispersed and hydrated. Methylparaben and propylparaben were dissolved in diethylene glycol monoethyl ether and the solution was subsequently added to the water phase.

[1099] Phase Combination:

[1100] The water phase was added to the oil phase at ambient conditions. The emulsion was then mixed at high speed or homogenized. After homogenization, sodium hydroxide solution (20% w/w) was added and the resulting cream was mixed until smooth and uniform. The pH of the cream was measured and a pH adjustment was made with additional sodium hydroxide solution, if necessary, to meet the in-process target pH of 5.

Examples 25-28

[1101] Table 11 summarizes topical formulations made in accordance with the present invention on a percentage weight-by-weight basis.

TABLE 11

Ingredient	Topical Cream (percentage weight-by-weight) Ex. 25	Ex. 26	Ex. 27	Ex. 28
IRM Compound 1	1	1	1	1
Isostearic Acid (874)	10	10	10	8
Diisopropyl dimer dilinoleate	5	5	5	1
Carbomer 980, NF	0.7	0.7	0.7	0.7
Diethylene glycol monoethyl ether USA —NF	10	10	10	10
Disodium EDTA, USP	0.05	0.05	0.05	0.05
Poloxamer 188, NF	2.5	2.5	2.5	2.5
Purified Water	Qs to 100	Qs to 100	Qs to 100	Qs to 100
Methylparaben, NF	0.2	0.2	0.2	0.2
Ethylparaben	0.2	0.2	0.2	0.2
20% (w/w) NaOH	0.4	0.4	0.4	0.4
10% iodopropynyl butylcarbamate in PEG-4 laurate	—	1	—	—
Phenoxyethanol	—	—	0.5	—

Examples 29-135

[1102] Topical creams containing the IRM compounds listed in Table 12 were prepared using the general methods described above for Examples 1-24. Each IRM was formulated into one or more of the model formulations shown in Tables 13 and 14. Table 15 summarizes the topical creams that were prepared.

TABLE 12

IRM Compound	Chemical Name
3	1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine
4	1-(2-methylpropyl)-1H-imidazo[4,5-c][1,8]naphthyridin-4-amine
5	2-butyl-1-(2-methylpropyl)-1H-imidazo[4,5-c][1,8]naphthyridin-4-amine
6	1-(2-methylpropyl)-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine
7	2-methylthiazolo[4,5-c]quinolin-4-amine
8	2-ethoxymethyl-1-phenylmethyl-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine
9	2-ethylthiazolo[4,5-c]quinolin-4-amine
10	4-amino-2-butyl-α,α-dimethyl-1H-imidazo[4,5-c][1,5]naphthyridine-1-ethanol
11	N^1-[2-(4-amino-1H-imidazo[4,5-c]quinolin-1-yl)ethyl]benzamide
12	1-{2-[3-(3-pyridyl)propoxy]ethyl}-1H-imidazo[4,5-c]quinolin-4-amine
13	1-(2-phenoxyethyl)-1H-imidazo[4,5-c]quinolin-4-amine
14	1-[(R)-1-phenylethyl]-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine
15	N^4-[4-(4-amino-1H-imidazo[4,5-c]quinolin-1-yl)butyl]-4-morpholinecarboxamide
16	N^3-[4-(4-amino-1H-imidazo[4,5-c]quinolin-1-yl)butyl]nicotinamide
17	1-{2-[3-(1,3-thiazol-2-yl)propoxy]ethyl}-1H-imidazo[4,5-c]quinolin-4-amine
18	1-[2-(pyridin-4-ylmethoxy)ethyl]-1H-imidazo[4,5-c]quinolin-4-amine
19	2-methyl-1-[5-(methylsulfonyl)pentyl]-1H-imidazo[4,5-c]quinolin-4-amine
20	N-[3-(4-amino-2-methyl-1H-imidazo[4,5-c]quinolin-1-yl)propyl]cyclohexanecarboxamide
21	N-[3-(4-amino-2-methyl-1H-imidazo[4,5-c]quinolin-1-yl)propyl]-2-methylpropanamide

TABLE 12-continued

IRM Compound	Chemical Name
22	N-[3-(4-amino-2-methyl-1H-imidazo[4,5-c]quinolin-1-yl)propyl]butanamide
23	2-butyl-1-{2-[(1-methylethyl)sulfonyl]ethyl}-1H-imidazo[4,5-c]quinolin-4-amine
24	N-{2-[4-amino-2-(ethoxymethyl)-1H-imidazo[4,5-c]quinolin-1-yl]ethyl}ethanesulfonamide
25	N-{2-[4-amino-2-(ethoxymethyl)-1H-imidazo[4,5-c]quinolin-1-yl]ethyl}propanamide
26	1-[2-(methylsulfonyl)ethyl]-2-propyl-1H-imidazo[4,5-c]quinolin-4-amine
27	N-{2-[4-amino-2-(ethoxymethyl)-1H-imidazo[4,5-c]quinolin-1-yl]ethyl}-N'-ethylthiourea
28	2-ethyl-1-{4-[(1-methylethyl)sulfonyl]butyl}-1H-imidazo[4,5-c]quinolin-4-amine
29	2-ethyl-1-[4-(ethylsulfonyl)butyl]-1H-imidazo[4,5-c]quinolin-4-amine
30	N-{3-[4-amino-2-(ethoxymethyl)-1H-imidazo[4,5-c]quinolin-1-yl]propyl}cyclopentanecarboxamide
31	N-{3-[4-amino-2-(ethoxymethyl)-6,7-dimethyl-1H-imidazo[4,5-c]pyridin-1-yl]propyl}morpholine-4-carboxamide
32	1-(2-methylpropyl)-6,7,8,9-tetrahydro-1H-imidazo[4,5-c]quinolin-4-amine
33	8,9,10,11-tetrahydropyrido[1',2':1,2]imidazo[4,5-c]quinolin-6-amine
34	4-amino-α,α,2-trimethyl-6,7,8,9-tetrahydro-1H-imidazo[4,5-c]quinoline-1-ethanol
35	2-hydroxymethyl-1-(2-methylpropyl)-6,7,8,9-tetrahydro-1H-imidazo[4,5-c]quinolin-4-amine
36	2-butyl-1-(2-phenoxyethyl)-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine
37	N-[3-(4-amino-2-methyl-1H-imidazo[4,5-c]quinolin-1-yl)propyl]methanesulfonamide

[1103]

TABLE 13

	Model Formulation (percentage weight-by-weight)						
Ingredient	A	B	C	D	E	F	G
IRM	0.01	0.1	1	1	1	1	1
Isostearic acid	5	5	5	20	42	13	6
Isopropyl myristate	10	10	10	10	2	10	10
Carbomer 974P	1	1	1	1	1	1.5	1
Purified water	*	*	*	*	*	*	*
Poloxamer 188	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Propylene glycol	15	15	15	15	13	15	15
Xanthan gum	—	—	—	—	0.4	—	—
Methylparaben	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Disodium EDTA	0.05	0.05	0.05	0.05	0.05	0.05	0.05
20% NaOH	0.7	0.7	0.7	0.7	0.7	0.7	0.7

* Qs to 100

[1104]

TABLE 14

	Model Formulation (percentage weight-by-weight)					
Ingredient	H	I	J	K	L	M
IRM	0.01	0.1	1	1	3	5
Isostearic acid	5	5	5	10	10	10

TABLE 14-continued

	Model Formulation (percentage weight-by-weight)					
Ingredient	H	I	J	K	L	M
Diisopropyl dimer dilinoleate	10	10	10	5	5	5
Carbomer 980	0.7	0.7	0.7	1.0	1.0	1.0
Purified water	*	*	*	*	*	*
Poloxamer 188	2.5	2.5	2.5	2.6	2.6	2.6
Diethylene glycol monoethyl ether	10	10	10	10	10	10
Xanthan gum	—	—	—	0.1	0.1	0.1
Methylparaben	0.2	0.2	0.2	0.2	0.2	0.2
Ethylparaben	0.2	0.2	0.2	0.2	0.2	0.2
Disodium EDTA	0.05	0.05	0.05	0.05	0.05	0.05
20% NaOH	0.4	0.4	0.4	0.4	0.4	0.4

* Qs to 100

[1105]

TABLE 15

Example	IRM Compound	Model Formulation
29	3	A
30	3	B
31	3	C
32	4	A
33	4	B
34	4	C
35	5	A
36	5	B
37	5	D
38	6	A
39	6	B
40	6	C
41	7	A
42	7	B
43	7	C
44	8	A
45	8	B
46	8	C
47	9	A
48	9	B
49	9	C
50	10	A
51	10	B
52	10	C
53	11	A
54	11	B
55	11	E
56	12	A
57	12	B
58	12	C
59	13	A
60	13	B
61	13	F
62	14	A
63	14	B
64	14	G
65	15	H
66	15	I
67	15	K
68	16	H
69	16	I
70	16	K
71	17	A
72	17	B
73	17	C
74	18	H
75	18	I
76	18	K

TABLE 15-continued

Example	IRM Compound	Model Formulation
77	19	H
78	19	I
79	19	K
80	20	H
81	20	I
82	20	K
83	20	L
84	20	M
85	21	H
86	21	I
87	21	K
88	22	H
89	22	I
90	22	J
91	23	H
92	23	I
93	23	J
94	24	H
95	24	I
96	24	K
97	25	H
98	25	I
99	25	K
100	26	H
101	26	I
102	26	K
103	27	H
104	27	I
105	27	K
106	28	H
107	28	I
108	28	K
109	29	H
110	29	I
111	29	K
112	30	H
113	30	I
114	30	K
115	31	H
116	31	I
117	31	K
118	32	A
119	32	B
120	32	C
121	33	A
122	33	B
123	33	C
124	34	A
125	34	B
126	34	C
127	35	A
128	35	B
129	35	C
130	36	A
131	36	B
132	36	C
133	37	H

TABLE 15-continued

Example	IRM Compound	Model Formulation
134	37	I
135	37	K

[1106] The topical creams of Examples 29-135 were tested using the test method described below. The results are shown in Table 16 below where each value is the mean of the values from the 3rats in the treatment group.

Single Dose MCP-1 Induction Test Method

[1107] Female CD hairless rats (Charles River Laboratories, Wilmington, Mass.) weighing 200-250 grams are used. Animals are randomized to treatment groups and dosed three per treatment group.

[1108] The rats are acclimated to collars around the neck on two consecutive days prior to actual dosing. A 50 μL dose of active cream or the appropriate placebo is applied to the right flank and gently rubbed into the skin of the rat. The rats are then collared and housed individually to prevent ingestion of the drug. At selected post treatment time points, the rats are anesthetized, and blood (3 mls) is collected by cardiac puncture. Blood is allowed to clot at room temperature. Serum is separated from the clot via centrifugation, and stored at −20° C. until it is analyzed for MCP-1 concentration.

[1109] Following blood collection, the rats are euthanized, and their skins removed. Tissue samples (4 from each site) from both the treated site and contralateral site (untreated) are obtained using an 8 mm punch biopsy, weighed, placed in a sealed 1.8 ml cryovial, and flash frozen in liquid nitrogen. The frozen tissue sample is then suspended in 1.0 mL RPMI medium (Celox, Hopkins, Minn.) containing 10% fetal bovine serum (Sigma, St. Louis, Mo.), 2 mM L-glutamine, penicillin/streptomycin, and 2-mercaptoethanol (RPMI complete) combined with a protease inhibitor cocktail set III (Calbiochem, San Diego, Calif.). The tissue is homogenized using a Tissue Tearor™ (Biospec Products, Bartlesville, Okla.) for approximately 1 minute. The tissue suspension is then centrifuged at 2000 rpm for 10 minutes under refrigeration to pellet debris, and the supernatant is collected and stored at −20° C. until analyzed for MCP-1 concentration.

[1110] ELISAs for rat MCP-1 are purchased from BioSource Intl. (Camarillo, Calif.) and performed according to manufacturer's specifications. Results are expressed in pg/ml, the values for the tissue samples are normalized per 200 mg of tissue. The sensitivity of the MCP-1 ELISA is 12 pg/ml.

TABLE 16

MCP-1 (pg/ml)

	IRM Cream							
Cream of	6 hours			24 hours			Placebo Cream	
Example	Serum	Treated	Untreated	Serum	Treated	Untreated	Serum	Untreated
29	123	202	46	291	55	34	142	59
30	119	92	31	177	201	43	142	59

TABLE 16-continued

	MCP-1 (pg/ml)							
	IRM Cream							
Cream of	6 hours			24 hours			Placebo Cream	
Example	Serum	Treated	Untreated	Serum	Treated	Untreated	Serum	Untreated
31	212	1235	54	267	606	125	142	59
32	26	54	59	79	82	69	54	56
33	54	70	71	56	74	58	54	56
34	72	88	58	59	319	69	54	56
35	170	110	55	162	142	62	80	58
36	94	674	46	86	1216	96	80	58
37	153	1826	38	136	2036	77	80	58
38	178	65	120	211	121	86	142	59
39	193	220	61	259	263	59	142	59
40	226	1204	58	284	1086	95	142	59
41	54	82	96	45	88	71	73	96
42	65	129	78	54	126	88	73	96
43	77	824	68	89	1016	93	73	96
44	86	256	*	177	488	*	128	**28
45	172	1444	*	157	1041	*	128	**28
46	177	1720	*	406	1023	*	128	**28
47	58	53	59	81	95	73	37	73
48	71	200	61	63	112	61	37	73
49	92	1254	62	83	1436	75	37	73
50	170	1033	56	*	655	56	88	*
51	625	551	787	*	149	787	88	*
52	811	348	314	*	86	314	88	*
53	70	63	46	76	47	45	7	31
54	68	35	27	71	26	24	7	31
55	75	35	21	44	33	32	7	31
56	115	44	*	115	425	*	201	**42
57	119	411	*	267	1252	*	201	**42
58	190	1560	*	476	1508	*	201	**42
59	155	46	36	271	41	53	107	54
60	123	53	58	175	80	69	107	54
61	133	172	52	151	1131	46	107	54
62	143	211	55	174	428	61	96	26
63	320	1614	51	230	1217	74	96	26
64	970	1094	529	425	390	99	96	26
65	43	34	57	46	81	61	83	59
66	29	73	28	32	42	74	83	59
67	19	54	61	25	34	72	83	59
68	60	77	82	91	72	35	68	72
69	143	74	52	99	73	59	68	72
70	59	77	34	91	134	60	68	72
71	259	79	62	134	84	57	177	53
72	138	255	65	122	990	63	177	53
73	251	999	63	293	1411	108	177	53
74	99	66	71	73	99	89	61	91
75	76	101	78	3	170	73	61	91
76	66	6779	64	188	4949	104	61	91
77	28	47	35	21	43	40	30	38
78	27	35	37	33	49	59	30	38
79	24	41	40	27	50	38	30	38
80	51	59	23	50	163	0	97	15
81	9	0	15	83	34	10	97	15
82***	61	32	0	121	303	45	97	15
82***	50	149	36	79	225	76	93	120
83	110	164	124	61	275	172	93	120
84	59	177	92	98	629	40	93	120
85	81	0	0	0	0	0	177	0
86	116	0	0	0	0	0	177	0
87	69	0	0	0	0	0	177	0
88	114	56	41	87	43	42	141	33
89	74	47	49	132	49	40	141	33
90	91	96	47	111	109	41	141	33
91	42	91	53	86	874	57	34	46
92	83	1238	74	92	1087	67	34	46
93	98	2037	64	114	1124	74	34	46
94	102	98	107	48	136	133	110	100
95	49	130	90	95	158	112	110	100
96	68	255	79	132	528	81	110	100
97	34	88	106	54	95	92	36	102

TABLE 16-continued

Cream of Example	MCP-1 (pg/ml) IRM Cream 6 hours Serum	Treated	Untreated	24 hours Serum	Treated	Untreated	Placebo Cream Serum	Untreated
98	17	116	108	83	123	91	36	102
99	51	150	89	43	945	76	36	102
100	111	81	83	55	115	72	82	58
101	33	72	55	75	209	64	82	58
102	79	489	54	112	3199	103	82	58
103	82	88	69	31	107	94	7	61
104	13	66	55	61	72	63	7	61
105	75	83	87	54	60	69	7	61
106	72	96	103	64	168	158	8	137
107	21	129	98	48	168	75	8	137
108	95	314	72	135	3267	128	8	137
109	72	60	71	71	78	62	12	31
110	44	76	57	92	72	75	12	31
111	70	143	83	32	2397	68	12	31
112	66	67	120	28	84	70	30	102
113	46	107	106	70	1034	93	30	102
114	14	627	65	196	2880	111	30	102
115	39	38	41	84	77	90	84	157
116	73	81	90	64	57	223	84	157
117	66	113	52	79	91	61	84	157
118	132	59	59	135	46	52	*	*
119	123	184	31	144	104	42	*	*
120	124	1261	45	171	892	56	*	*
121	90	74	51	88	96	75	78	57
122	72	415	50	91	613	82	78	57
123	156	1502	52	226	1043	48	78	57
124	92	94	27	96	95	110	97	652
125	123	198	128	107	72	120	97	652
126	136	1828	97	73	1348	349	97	652
127	67	66	46	81	90	22	51	81
128	63	80	58	55	53	35	51	81
129	49	382	58	35	809	59	51	81
130	132	55	41	135	162	43	74	32
131	124	279	59	144	822	60	74	32
132	124	1901	13	171	1212	11	74	32
133	64	106	0	52	199	32	26	8
134	9	76	0	70	59	0	26	8
135	59	89	0	76	47	0	26	8

* MCP-1 concentration was not measured
** MCP-1 concentration is for the treated site.
*** The cream of Example 82 was used in 2 seperate experiments

Examples 136-140

[1111] Table 17 summarizes topical formulations made in accordance with the present invention on a percentage weight-by-weight basis.

TABLE 17

Ingredients	Topical Creams (percentage weight-by-weight) Ex. 136	Ex. 137	Ex. 138	Ex. 139	Ex. 140
IRM Compound 1	1	1	1	1	1
Isostearic Acid	10	10	8	10	10
Diisopropyl dimer dilinoleate	—	5	1	5	5
Caprylic/ capric triglycerides	5	—	—	—	—

TABLE 17-continued

Ingredients	Topical Creams (percentage weight-by-weight) Ex. 136	Ex. 137	Ex. 138	Ex. 139	Ex. 140
Carbomer 980	0.7	0.7	0.7	0.7	0.7
Diethylene glycol monoethyl ether	10	10	10	10	10
Disodium EDTA	0.05	0.05	0.05	0.05	0.05
Poloxamer 188	2.5	2.5	2.5	2.5	2.5
Purified Water	Qs to 100	Qs to 100	Qs to 100	Qs to 100	Qs to 100
Methylparaben	0.2	0.1	0.2	0.2	0.2

TABLE 17-continued

Ingredients	Topical Creams (percentage weight-by-weight) Ex. 136	Ex. 137	Ex. 138	Ex. 139	Ex. 140
Ethylparaben 20% (w/w)	0.2 Qs to pH	0.1 Qs to pH	0.2 Qs to pH	0.2 Qs to pH	0.2 Qs to pH
NaOH	5–5.5	5–5.5	5–5.5	6.5	5–5.5
Iodopropynyl butylcarbamate	—	0.1	—	—	—
PEG-4 Laurate	—	0.9	—	—	—
Phenoxyethanol	—	1	—	—	—
Sorbic acid	—	0.15	—	—	—

[1112] The topical creams of Examples 136-140 were tested using the test method described below. The results are shown in Table 18 below where each value is the mean of the values from the 3 rats in the treatment group. "Normal animals" did not receive any treatment.

Single Dose Cytokine Induction Test Method

[1113] Female CD hairless rats (Charles River Laboratories, Wilmington, Mass.) weighing 200-250 grams are used. Animals are randomized to treatment groups and dosed three per treatment group.

[1114] The rats are acclimated to collars around the neck on two consecutive days prior to actual dosing. A 50 μL dose of active cream is applied to the right flank and gently rubbed into the skin of the rat. The rats are then collared and housed individually to prevent ingestion of the drug. At 6 hours post treatment, the rats are anesthetized, and blood (3 mls) is collected by cardiac puncture. Blood is allowed to clot at room temperature, serum is separated from the clot via centrifugation, and stored at −20° C. until it is analyzed for cytokine concentrations.

[1115] Following blood collection, the rats are euthanized, and their skins removed. Tissue samples (4 from each site) from both the treated site and contralateral site (untreated) are obtained using an 8 mm punch biopsy, weighed, placed in a sealed 1.8 ml cryovial, and flash frozen in liquid nitrogen. The frozen tissue sample is then suspended in 1.0 mL RPMI medium (Celox, Hopkins, Minn.) containing 10% fetal bovine serum (Sigma, St. Louis, Mo.), 2 mM L-glutamine, penicillin/streptomycin, and 2-mercaptoethanol (RPMI complete) combined with a protease inhibitor cocktail set III (Calbiochem, San Diego, Calif.). The tissue is homogenized using a Tissue Tearor™ (Biospec Products, Bartlesville, Okla.) for approximately 1 minute. The tissue suspension is then centrifuged at 2000 rpm for 10 minutes under refrigeration to pellet debris. The supernatant is collected and stored at −20° C. until analyzed for cytokine concentrations.

[1116] ELISAs for rat MCP-1 are purchased from Bio-Source Intl. (Camarillo, Calif.) and rat TNF-α are purchased from BD Pharmingen (San Diego, Calif.) and performed according to manufacturer's specifications. Results are expressed in pg/ml, the values for the tissue samples are normalized per 200 mg of tissue. The sensitivity of the MCP-1 ELISA is 12 pg/ml and the sensitivity of the TNF-α ELISA is 31 pg/ml.

TABLE 18

	Cytokine Induction									
	IRM Cream Treated Animals						Normal Animals			
Cream of	MCP-1 (pg/ml)			TNF-α (pg/ml)			MCP-1 (pg/ml)		TNF-α (pg/ml)	
Example	Serum	Treated	Untreated	Serum	Treated	Untreated	Serum	Tissue	Serum	Tissue
136	119	1208	51	64	808	85	73	39	64	67
137	90	1815	78	78	597	78	73	39	64	67
138	5	1351	27	66	636	69	73	39	64	67
139	62	1509	85	50	443	75	73	39	64	67
140	24	2373	28	80	948	95	73	39	64	67

What is claimed is:

1. A pharmaceutical formulation comprising:

an immune response modifier (IRM) compound selected from imidazoquinoline amines, imidazotetrahydroquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, 1,2-bridged imidazoquinoline amines, thiazoloquinoline amines, oxazoloquinoline amines, thiazolopyridine amines, oxazolopyridine amines, imidazonaphthyridine amines, imidazotetrahydronaphthyridine amines, and thiazolonaphthyridine amines;

a fatty acid;

a hydrophobic, aprotic component miscible with the fatty acid and comprising a hydrocarbyl group of 7 or more carbon atoms; and

a hydrophilic viscosity enhancing agent selected from cellulose ethers and carbomers.

2. The formulation according to claim 1 wherein the formulation further comprises a preservative system and an emulsifier.

3. The formulation according to claim 1 wherein the hydrophobic, aprotic component has a hydrophilic lipophilic balance of less than 2.

4. The formulation according to claim 1 wherein the hydrophobic, aprotic component has a pKa greater than 14.2.

5. The formulation according to claim 1 wherein the ratio of the hydrophobic, aprotic component to the fatty acid is 0.025:1 to 600:1.

6. The formulation according to claim I wherein the combined weight percent of the hydrophobic, aprotic component and the fatty acid is 2 to 50.

7. The formulation according to claim 1 wherein the fatty acid is isostearic acid.

8. The formulation according to claim 1 wherein the hydrophobic, aprotic component is selected from aprotic fatty acid esters, hydrocarbons of 8 or more carbon atoms, and waxes.

9. The formulation according to claim 8 wherein the aprotic fatty acid ester is isopropyl myristate, isopropyl palmitate, diisopropyl dimer dilinoleate, caprylic/capric triglyceride, cetyl esters wax, or a combination thereof.

10. The formulation according to claim 8 wherein the hydrocarbon of 8 or more carbon atoms is mineral oil or petrolatum.

11. The formulation according to claim 1 wherein the hydrophilic viscosity enhancing agent comprises a carbomer.

12. The formulation according to claim 2 wherein the preservative system comprises methylparaben at 0.01 to 0.5% w/w of the formulation and propylparaben at 0.01 to 0.5% w/w of the formulation.

13. The formulation according to claim 2 wherein the preservative system comprises methylparaben at 0.01 to 0.5% w/w of the formulation and ethylparaben at 0.01 to 0.5% w/w of the formulation.

14. The formulation according to claim 2 wherein the preservative system comprises iodopropynyl butylcarbamate.

15. The formulation according to claim 2 wherein the preservative system comprises iodopropynyl butylcarbamate and one or more of methylparaben, ethylparaben, propylparaben, or phenoxyethanol.

16. The formulation according to claim 2 wherein the preservative system comprises iodopropynyl butylcarbamate, methylparaben, and ethylparaben.

17. The formulation according to claim 2 wherein the preservative system comprises phenoxyethanol and one or both of methylparaben and ethylparaben.

18. The formulation according to claim 2 wherein the preservative system comprises a preservative enhancing solubilizer.

19. The formulation according to claim 18 wherein the preservative enhancing solubilizer comprises diethylene glycol monoethyl ether, propylene glycol or a combination thereof.

20. The formulation of claim 2 comprising:

(a) 0.001 to 5% w/w

2-methyl-1-(2-methylpropyl)-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine,

N-[4-(4-amino-2-butyl-1H-imidazo[4,5-c][1,5]naphthyridin-1-yl)butyl]-N'-cyclohexylurea,

1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine,

2-butyl-1-(2-methylpropyl)-1H-imidazo[4,5-c][1,8]naphthyridin-4-amine,

1-(2-methylpropyl)-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine,

2-methylthiazolo[4,5-c]quinolin-4-amine,

2-ethoxymethyl-1-phenylmethyl-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine,

2-ethylthiazolo[4,5-c]quinolin-4-amine,

4-amino-2-butyl-α,α-dimethyl-1H-imidazo[4,5-c][1,5]naphthyridine-1-ethanol,

1-{2-[3-(3-pyridyl)propoxy]ethyl}-1H-imidazo[4,5-c]quinolin-4-amine,

1-(2-phenoxyethyl)-1H-imidazo[4,5-c]quinolin-4-amine,

1-[(R)-1-phenylethyl]-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine,

1-{2-[3-(1,3-thiazol-2-yl)propoxy]ethyl}-1H-imidazo[4,5-c]quinolin-4-amine,

1-[2-(pyridin-4-ylmethoxy)ethyl]-1H-imidazo[4,5-c]quinolin-4-amine,

N-[3-(4-amino-2-methyl-1H-imidazo[4,5-c]quinolin-1-yl)propyl]cyclohexanecarboxamide,

2-butyl-1-{2-[(1-methylethyl)sulfonyl]ethyl}-1H-imidazo[4,5-c]quinolin-4-amine,

N-{2-[4-amino-2-(ethoxymethyl)-1H-imidazo[4,5-c]quinolin-1-yl]ethyl}ethanesulfonamide,

N-{2-[4-amino-2-(ethoxymethyl)-1H-imidazo[4,5-c]quinolin-1-yl]ethyl}propanamide,

1-[2-(methylsulfonyl)ethyl]-2-propyl-1H-imidazo[4,5-c]quinolin-4-amine,

2-ethyl-1-{4-[(1-methylethyl)sulfonyl]butyl}-1H-imidazo[4,5-c]quinolin-4-amine,

2-ethyl-1-[4-(ethylsulfonyl)butyl]-1H-imidazo[4,5-c]quinolin-4-amine,

N-{3-[4-amino-2-(ethoxymethyl)-1H-imidazo[4,5-c]quinolin-1-yl]propyl}cyclopentanecarboxamide,

1-(2-methylpropyl)-6,7,8,9-tetrahydro-1H-imidazo[4,5-c]quinolin-4-amine,

8,9,10,11-tetrahydropyrido[1',2':1,2]imidazo[4,5-c]quinolin-6-amine,

4-amino-α,α,2-trimethyl-6,7,8,9-tetrahydro-1H-imidazo[4,5-c]quinoline-1-ethanol,

2-hydroxymethyl-1-(2-methylpropyl)-6,7,8,9-tetrahydro-1H-imidazo[4,5-c]quinolin-4-amine,

2-butyl-1-(2-phenoxyethyl)-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine,

or a combination thereof;

(b) 0.05 to 40% w/w isostearic acid;

(c) 1 to 30% w/w hydrophobic, aprotic component;

(d) 0.5 to 10% w/w emulsifier;

(e) 0.01 to 30% w/w preservative system; and

(f) 0.1 to 10% carbomer.

21. The formulation of claim 20 comprising:

(a) 0.03 to 3% w/w 2-methyl-1-(2-methylpropyl)-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine, N-[4-(4-amino-2-butyl-1H-imidazo[4,5-c][1,5]naphthyridin-yl-)butyl]-N'-cyclohexylurea, 2-butyl-1-{2-[(1-

methylethyl)sulfonyl]ethyl}-1H-imidazo[4,5-c] quinolin-4-amine, or a combination thereof;

(b) 3 to 25% w/w isostearic acid;

(c) 3 to 15% w/w hydrophobic, aprotic component;

(d) 0.75 to 3.5% w/w emulsifier;

(e) 0.1 to 25% w/w preservative system; and

(f) 0.5 to 5% w/w carbomer.

22. A method of treating a dermal associated condition, the method comprising a step of:

applying to skin a formulation comprising an immune response modifier (IRM) selected from imidazoquinoline amines, imidazotetrahydroquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, 1,2-bridged imidazoquinoline amines, thiazoloquinoline amines, oxazoloquinoline amines, thiazolopyridine amines, oxazolopyridine amines, imidazonaphthyridine amines, imidazotetrahydronaphthyridine amines, and thiazolonaphthyridine amines; a fatty acid; a hydrophobic, aprotic component miscible with the fatty acid and comprising a hydrocarbyl group of 7 or more carbon atoms; and a hydrophilic viscosity enhancing agent selected from cellulose ethers and carbomers.

23. The method according to claim 22 wherein the ratio of the hydrophobic, aprotic component to the fatty acid is 0.025:1 to 600:1.

24. The method according to claim 22 wherein the combined weight percent of the hydrophobic, aprotic component and the fatty acid is 2 to 50.

25. The method according to claim 22 wherein the hydrophobic, aprotic component is selected from the group consisting of aprotic fatty acid esters, hydrocarbons of 8 or more carbon atoms, and waxes.

26. The method according to claim 25 wherein the aprotic fatty acid ester is isopropyl myristate, isopropyl palmitate, diisopropyl dimer dilinoleate, caprylic/capric triglyceride, cetyl esters wax, or combinations thereof.

27. The method according to claim 22 wherein the hydrophilic viscosity enhancing agent comprises a carbomer.

28. The method according to claim 22 wherein the topical formulation further comprises:

a preservative system; and

an emulsifier.

29. The method according to claim 22 wherein the IRM is 2-methyl-1-(2-methylpropyl)-1H-imidazo[4,5-c][1,5] naphthyridin-4-amine, N-[4-(4-amino-2-butyl-1H-imidazo [4,5-c][1,5]naphthyridin-1-yl)butyl]-N'-cyclohexylurea, 1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine,

2-butyl-1-(2-methylpropyl)-1H-imidazo[4,5-c][1,8]naphthyridin-4-amine,

1-(2-methylpropyl)-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine,

2-methylthiazolo[4,5-c]quinolin-4-amine,

2-ethoxymethyl-1-phenylmethyl-1H-imidazo[4,5-c][1,5] naphthyridin-4-amine,

2-ethylthiazolo[4,5-c]quinolin-4-amine,

4-amino-2-butyl-α,α-dimethyl-1H-imidazo[4,5-c][1,5] naphthyridine-1-ethanol,

1-{2-[3-(3-pyridyl)propoxy]ethyl}-1H-imidazo[4,5-c] quinolin-4-amine,

1-(2-phenoxyethyl)-1H-imidazo[4,5-c]quinolin-4-amine,

1-[(R)-1-phenylethyl]-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine,

1-{2-[3-(1,3-thiazol-2-yl)propoxy]ethyl}-1H-imidazo[4,5-c]quinolin-4-amine,

1-[2-(pyridin-4-ylmethoxy)ethyl]-1H-imidazo[4,5-c] quinolin-4-amine,

N-[3-(4-amino-2-methyl-1H-imidazo[4,5-c]quinolin-1-yl)propyl]cyclohexanecarboxamide,

2-butyl-1-{2-[(1-methylethyl)sulfonyl]ethyl}-1 H-imidazo[4,5-c]quinolin-4-amine,

N-{2-[4-amino-2-(ethoxymethyl)-1H-imidazo[4,5-c] quinolin-1-yl]ethyl}ethanesulfonamide,

N-{2-[4-amino-2-(ethoxymethyl)-1H-imidazo[4,5-c] quinolin-1-yl]ethyl}propanamide,

1-[2-(methylsulfonyl)ethyl]-2-propyl-1H-imidazo[4,5-c] quinolin-4-amine,

2-ethyl-1-{4-[(1-methylethyl)sulfonyl]butyl}-1H-imidazo[4,5-c]quinolin-4-amine,

2-ethyl-1-[4-(ethylsulfonyl)butyl]-1H-imidazo[4,5-c] quinolin-4-amine,

N-{3-[4-amino-2-(ethoxymethyl)-1H-imidazo[4,5-c] quinolin-1-yl]propyl}cyclopentanecarboxamide,

1-(2-methylpropyl)-6,7,8,9-tetrahydro-1H-imidazo[4,5-c]quinolin-4-amine,

8,9,10,11-tetrahydropyrido[1',2': 1,2]imidazo[4,5-c] quinolin-6-amine,

4-amino-α,α,2-trimethyl-6,7,8,9-tetrahydro-1H-imidazo [4,5-c]quinoline-1-ethanol,

2-hydroxymethyl-1-(2-methylpropyl)-6,7,8,9-tetrahydro-1H-imidazo[4,5-c]quinolin-4-amine,

2-butyl-1-(2-phenoxyethyl)-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine, or a combination thereof.

30. The method according to claim 22 wherein the dermal associated condition is selected from actinic keratosis, post-surgical scars, basal cell carcinoma, atopic dermatitis, and warts.

31. The method according to claim 30 wherein the IRM is 2-methyl-1-(2-methylpropyl)-1H-imidazo[4,5-c][1,5] naphthyridin-4-amine,

N-[4-(4-amino-2-butyl-1H-imidazo[4,5-c][1,5]naphthyridin-1-yl)butyl]-N'-cyclohexylurea,

1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine,

2-butyl-1-(2-methylpropyl)-1H-imidazo[4,5-c][1,8]naphthyridin-4-amine,

1-(2-methylpropyl)-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine,

2-methylthiazolo[4,5-c]quinolin-4-amine,

2-ethoxymethyl-1-phenylmethyl-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine,

2-ethylthiazolo[4,5-c]quinolin-4-amine,

4-amino-2-butyl-α,α-dimethyl-1H-imidazo[4,5-c][1,5]naphthyridine-1-ethanol,

1-{2-[3-(3-pyridyl)propoxy]ethyl}-1H-imidazo[4,5-c]quinolin-4-amine,

1-(2-phenoxyethyl)-1H-imidazo[4,5-c]quinolin-4-amine,

1-[(R)-1-phenylethyl]-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine,

1-{2-[3-(1,3-thiazol-2-yl)propoxy]ethyl}-1H-imidazo[4,5-c]quinolin-4-amine,

1-[2-(pyridin-4-ylmethoxy)ethyl]-1H-imidazo[4,5-c]quinolin-4-amine,

N-[3-(4-amino-2-methyl-1H-imidazo[4,5-c]quinolin-1-yl)propyl]cyclohexanecarboxamide,

2-butyl-1-{2-[(1-methylethyl)sulfonyl]ethyl} -1H-imidazo[4,5-c]quinolin-4-amine,

N-{2-[4-amino-2-(ethoxymethyl)-1H-imidazo[4,5-c]quinolin-1-yl]ethyl}ethanesulfonamide,

N-{2-[4-amino-2-(ethoxymethyl)-1H-imidazo[4,5-c]quinolin-1-yl]ethyl}propanamide,

1-[2-(methylsulfonyl)ethyl]-2-propyl-1H-imidazo[4,5-c]quinolin-4-amine,

2-ethyl-1-{4-[(1-methylethyl)sulfonyl]butyl}-1H-imidazo[4,5-c]quinolin-4-amine,

2-ethyl-1-[4-(ethylsulfonyl)butyl]-1H-imidazo[4,5-c]quinolin-4-amine,

N-{3-[4-amino-2-(ethoxymethyl)-1H-imidazo[4,5-c]quinolin-1-yl]propyl}cyclopentanecarboxamide,

1-(2-methylpropyl)-6,7,8,9-tetrahydro-1H-imidazo[4,5-c]quinolin-4-amine,

8,9,10,11-tetrahydropyrido[1',2':1,2]imidazo[4,5-c]quinolin-6-amine,

4-amino-α,α,2-trimethyl-6,7,8,9-tetrahydro-1H-imidazo[4,5-c]quinoline-1-ethanol,

2-hydroxymethyl-1-(2-methylpropyl)-6,7,8,9-tetrahydro-1H-imidazo[4,5-c]quinolin-4-amine,

2-butyl-1-(2-phenoxyethyl)-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine, or a combination thereof.

32. The method according to claim 30 wherein the formulation further comprises a preservative system and an emulsifier.

33. The method according to claim 32 wherein the preservative system comprises methylparaben at 0.01 to 0.5% w/w of the formulation and propylparaben at 0.01 to 0.5% w/w of the formulation.

34. The method according to claim 32 wherein the preservative system comprises methylparaben at 0.01 to 0.5% w/w of the formulation and ethylparaben at 0.01 to 0.5% w/w of the formulation.

35. The method according to claim 32 wherein the preservative system comprises iodopropynyl butylcarbamate.

36. The method according to claim 32 wherein the preservative system comprises iodopropynyl butylcarbamate and one or more of methylparaben, ethylparaben, propylparaben, or phenoxyethanol.

37. The method according to claim 32 wherein the preservative system comprises iodopropynyl butylcarbamate, methylparaben, and ethylparaben.

38. The method according to claim 32 wherein the preservative system comprises phenoxyethanol and one or both of methylparaben and ethylparaben.

39. The method according to claim 32 wherein the preservative system comprises a preservative enhancing solubilizer.

40. The method according to claim 39 wherein the preservative enhancing solubilizer comprises diethylene glycol monoethyl ether, propylene glycol or a combination thereof.

41. A method for delivering an immune response modifier (IRM) to a dermal surface, the method comprising the steps of:

selecting a formulation comprising:

(a) an immune response modifier selected from imidazoquinoline amines, imidazotetrahydroquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, 1,2-bridged imidazoquinoline amines, thiazoloquinoline amines, oxazoloquinoline amines, thiazolopyridine amines, oxazolopyridine amines, imidazonaphthyridine amines, imidazotetrahydronaphthyridine amines, and thiazolonaphthyridine amines;

(b) a fatty acid;

(c) a hydrophobic, aprotic component miscible with the fatty acid and comprising a hydrocarbyl group of 7 or more carbon atoms; and

(d) a hydrophilic viscosity enhancing agent selected from cellulose ethers and carbomers; and

applying the selected topical formulation to the dermal surface.

42. A pharmaceutical formulation comprising:

an immune response modifier (IRM) compound selected from the group consisting of imidazonaphthyridine amines, tetrahydroimidazonaphthyridine amines, and thiazolonaphthyridine amines;

a fatty acid; and

a hydrophobic, aprotic component miscible with the fatty acid and comprising a hydrocarbyl group of 7 or more carbon atoms.

43. The formulation according to claim 42 wherein the formulation further comprises a preservative system.

44. The formulation according to claim 42 wherein the hydrophobic, aprotic component has a hydrophilic lipophilic balance of less than 2.

45. The formulation according to claim 42 wherein the hydrophobic, aprotic component has a pKa greater than 14.2.

46. The formulation according to claim 42 wherein the ratio of the hydrophobic, aprotic component to the fatty acid is 0.025:1 to 600:1.

47. The formulation according to claim 42 wherein the combined weight percent of the hydrophobic, aprotic component and the fatty acid is 2 to 50.

48. The formulation according to claim 42 wherein the fatty acid is isostearic acid.

49. The formulation according to claim 42 wherein the hydrophobic, aprotic component is selected from aprotic fatty acid esters, hydrocarbons of 8 or more carbon atoms, and waxes.

50. The formulation according to claim 49 wherein the aprotic fatty acid ester is isopropyl myristate, isopropyl palmitate, diisopropyl dimer dilinoleate, caprylic/capric triglyceride, cetyl esters wax, or combinations thereof.

51. The formulation of claim 49 wherein the hydrocarbon of 8 or more carbon atoms is mineral oil or petrolatum.

52. The formulation according to claim 43 wherein the preservative system comprises methylparaben at 0.01 to 0.5% w/w of the formulation and propylparaben at 0.01 to 0.5% w/w of the formulation.

53. The formulation according to claim 43 wherein the preservative system comprises methylparaben at 0.01 to 0.5% w/w of the formulation and ethylparaben at 0.01 to 0.5% w/w of the formulation.

54. The formulation according to claim 43 wherein the preservative system comprises iodopropynyl butylcarbamate.

55. The formulation according to claim 43 wherein the preservative system comprises iodopropynyl butylcarbamate and one or more of methylparaben, ethylparaben, propylparaben, or phenoxyethanol.

56. The formulation according to claim 43 wherein the preservative system comprises iodopropynyl butylcarbamate, methylparaben, and ethylparaben.

57. The formulation according to claim 43 wherein the preservative system comprises phenoxyethanol and one or both of methylparaben and ethylparaben.

58. The formulation according to claim 43 wherein the preservative system comprises a preservative enhancing solubilizer.

59. The formulation according to claim 58 wherein the preservative enhancing solubilizer comprises diethylene glycol monoethyl ether, propylene glycol or a combination thereof.

60. The formulation of claim 43 comprising:

(a) 0.001 to 5% w/w imidazonaphthyridine amine, imidazotetrahydronaphthyridine amine, thiazolonaphthyridine amine, or a combination thereof;

(b) 0.05 to 40% w/w isostearic acid;

(c) 1 to 30% w/w hydrophobic, aprotic component; and

(d) 0.01 to 30% w/w preservative system.

61. The formulation of claim 43 further comprising an emulsifier and a hydrophilic viscosity enhancing agent.

62. The formulation of claim 60 further comprising an emulsifier and a hydrophilic viscosity enhancing agent.

63. The formulation of claim 62 wherein the viscosity enhancing agent comprises a carbomer.

64. The formulation of claim 63 comprising:

(a) 0.03 to 3% w/w

2-methyl-1-(2-methylpropyl)-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine,

N-[4-(4-amino-2-butyl-1H-imidazo[4,5-c][1,5]naphthyridin-1-yl)butyl]-N'-cyclohexylurea,

2-butyl-1-(2-methylpropyl)-1H-imidazo[4,5-c][1,8]naphthyridin-4-amine,

1-(2-methylpropyl)-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine,

2-ethoxymethyl-1-phenylmethyl-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine,

4-amino-2-butyl-α,α-dimethyl-1H-imidazo[4,5-c][1,5]naphthyridine-1-ethanol,

1-[(R)-1-phenylethyl]-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine,

2-butyl-1-(2-phenoxyethyl)-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine,

or a combination thereof;

(b) 3 to 25% w/w isostearic acid;

(c) 3 to 15% w/w hydrophobic, aprotic component;

(d) 0.1 to 25% w/w preservative system;

(e) 0.75 to 3.5% w/w emulsifier; and

(f) 0.5 to 5% w/w carbomer.

65. A method of treating a dermal associated condition, the method comprising a step of:

applying to skin a formulation comprising an immune response modifier (IRM) chosen from imidazonaphthyridine amines, imidazotetrahydronaphthyridine amines, and thiazolonaphthyridine amines; a fatty acid; and a hydrophobic, aprotic component miscible with the fatty acid and comprising a hydrocarbyl group of 7 or more carbon atoms.

66. The method according to claim 65 wherein the ratio of the hydrophobic, aprotic component to the fatty acid is 0.025:1 to 600:1.

67. The method according to claim 65 wherein the combined weight percent of the hydrophobic, aprotic component and the fatty acid is 2 to 50.

68. The method according to claim 65 wherein the hydrophobic, aprotic component is selected from the group consisting of aprotic fatty acid esters, hydrocarbons of 8 or more carbon atoms, and waxes.

69. The method according to claim 68 wherein the aprotic fatty acid ester is isopropyl myristate, isopropyl palmitate, diisopropyl dimer dilinoleate, caprylic/capric triglyceride, cetyl esters wax, or combinations thereof.

70. The method according to claim 65 wherein the formulation further comprises:

a preservative system; and

an emulsifier.

71. The method according to claim 65 wherein the IRM is 2-methyl-1-(2-methylpropyl)-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine, N-[4-(4-amino-2-butyl-1H-imidazo[4,5-c][1,5]naphthyridin-1-yl)butyl]-N'-cyclohexylurea,

2-butyl-1-(2-methylpropyl)-1H-imidazo[4,5-c][1,8]naphthyridin-4-amine,

1-(2-methylpropyl)-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine,

2-ethoxymethyl-1-phenylmethyl-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine,

4-amino-2-butyl-α,α-dimethyl-1H-imidazo[4,5-c][1,5] naphthyridine-1-ethanol,

1-[(R)-1-phenylethyl]-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine,

2-butyl-1-(2-phenoxyethyl)-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine, or a combination thereof.

72. The method according to claim 65 wherein the dermal associated condition is actinic keratosis, postsurgical scars, basal cell carcinoma, atopic dermatitis, and warts.

73. The method according to claim 72 wherein the IRM is 2-methyl-1-(2-methylpropyl)-1H-imidazo[4,5-c][1,5] naphthyridin-4-amine, N-[4-(4-amino-2-butyl-1H-imidazo [4,5-c][1,5]naphthyridin-1-yl)butyl]-N'-cyclohexylurea,

2-butyl-1-(2-methylpropyl)-1H-imidazo[4,5-c][1,8]naphthyridin-4-amine,

1-(2-methylpropyl)-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine,

2-ethoxymethyl-1-phenylmethyl-1H-imidazo[4,5-c][1,5] naphthyridin-4-amine,

4-amino-2-butyl-α,α-dimethyl-1H-imidazo[4,5-c][1,5] naphthyridine-1-ethanol,

1-[(R)-1-phenylethyl]-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine,

2-butyl-1-(2-phenoxyethyl)-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine, or a combination thereof.

74. The method according to claim 72 wherein the formulation further comprises: a preservative system; and

an emulsifier.

75. The method according to claim 74 wherein the preservative system comprises methylparaben at 0.01 to 0.5% w/w of the formulation and propylparaben at 0.01 to 0.5% w/w of the formulation.

76. The method according to claim 74 wherein the preservative system comprises methylparaben at 0.01 to 0.5% w/w of the formulation and ethylparaben at 0.01 to 0.5% w/w of the formulation.

77. The method according to claim 74 wherein the preservative system comprises iodopropynyl butylcarbamate.

78. The method according to claim 74 wherein the preservative system comprises iodopropynyl butylcarbamate and one or more of methylparaben, ethylparaben, propylparaben, or phenoxyethanol.

79. The method according to claim 74 wherein the preservative system comprises iodopropynyl butylcarbamate, methylparaben, and ethylparaben.

80. The method according to claim 74 wherein the preservative system comprises phenoxyethanol and one or both of methylparaben and ethylparaben.

81. The method according to claim 74 wherein the preservative system comprises a preservative enhancing solubilizer.

82. The method according to claim 81 wherein the preservative enhancing solubilizer comprises diethylene glycol monoethyl ether, propylene glycol or a combination thereof.

83. A method for delivering an immune response modifier (IRM) to a dermal surface, the method comprising the steps of:

selecting a formulation comprising:

(a) an immune response modifier selected from imidazonaphthyridine amines, imidazotetrahydronaphthyridine amines, and thiazolonaphthyridine amines;

(b) at fatty acid;

(c) a hydrophobic, aprotic component miscible with the fatty acid and comprising a hydrocarbyl group of 7 or more carbon atoms; and

applying the selected formulation to the dermal surface.

* * * * *

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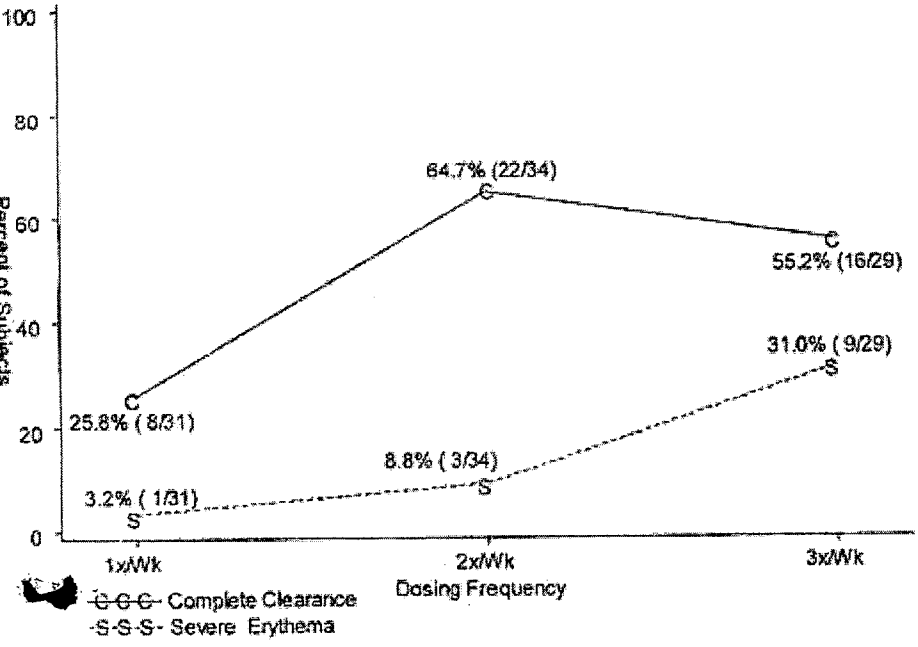
100
80
60
40
20
0
Percent of Subjects
64.7% (22/34)
55.2% (16/29)
31.0% (9/29)
25.8% (8/31)
8.8% (3/34)
3.2% (1/31)
1x/Wk
2x/Wk
3x/Wk
Dosing Frequency
C C C Complete Clearance
S S S Severe Erythema

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762

2020
Bogotá, D.C.,

Doctor:
Juan Pablo Cadena Sarmiento
Apoderado

Oficio N°: 11296

ASUNTO:

Radicación PCT Nº	07-94650
Trámite	011
Evento	379
Actuación	440
Folios	009

Con fundamento en lo previsto por el artículo 43 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que la oposición presentada por la doctora Eliana Isaura Moreno Bohórquez, en su calidad de apoderada de Gynopharm S.A., reúne los requisitos formales exigidos por la ley al momento de su presentación.

En cumplimiento de lo dispuesto en la citada norma, se le concede el término de sesenta (60) días hábiles siguientes a la fecha de notificación del presente oficio, para que haga valer sus argumentaciones y presente pruebas.

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.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior oficio fue notificado por fijación en lista de fecha, 05 SET 2008.

202021

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