



No. 08-088449-00004-0000

Fecha: 2010-04-27 11:10:35 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYI Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 68

FORMULARIO ÚNICO DE OPOSICIÓN

①

OPOSICIÓN A:

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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

Numero del expediente: 08.088.449

Solicitante: GRACEWAY PHARMACEUTICALS, LLC

Apoderado: JUAN PABLO CADENA SARMIENTO

Título de la nueva creación o denominación del signo: FORMULACIONES DEL
MODIFICADOR DE INMUNORESPUESTA QUE CONTIENEN ACIDO OLEICO Y METODOS

Gaceta: 612

③

OPOSICIÓN PRESENTADA POR:

SOLICITANTE

Nombre: PROCAPS S.A.

Dirección: CALLE 80 No. 78b-201

Nacionalidad o Domicilio: COLOMBIA
Lugar de Constitución: BARRANQUILLA

Teléfono: 371 99 00 Fax: 373 08 18
E-mail:

IDENTIFICACION

C.C. ☐ NIT ☒

C.E. ☐ Otro ☐

Cual

Numero 890.106.527-5

REPRESENTANTE
O APODERADO

Nombre: CIELO ANGELA PEÑA
RODRIGUEZ

Dirección: CARRERA 13 No. 119-95

Teléfono: (571)213 12 13 Fax: (571)612 19 79
E-mail: negocios@optimum-co.com

IDENTIFICACION

C.C. ☒ NIT ☐

C.E. ☐ Otro ☐

Cual

Numero 51.940.252 TP 82701

④

FUNDAMENTOS DE LA OPOSICIÓN:

Art.14, 16, 18, 20 y 30 de la Decisión 486 de la CAN

Causal: 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

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

⑦

NOMBRE: CIELO ANGELA PEÑA RODRIGUEZ

FIRMA: 

C.C. 51.940.252

TP. 82701

Señora Jefe,

DIVISIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Referencia : Expediente N° 08 88449 ✓

Asunto : Oposición a la solicitud de patente de Invención titulada
"FORMULACIONES DEL MODIFICADOR DE
INMUNORESPUESTA QUE CONTIENEN ÁCIDO
OLEICO Y MÉTODOS"

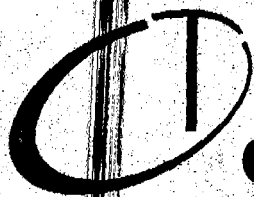
Solicitante : 3M INNOVATIVE PROPERTIES COMPANY

Opositora : PROCAPS S.A.

Publicada en la Gaceta de la Propiedad Industrial

N° 612 del 29 de enero de 2010

Yo, *CIELO ANGELA PEÑA RODRIGUEZ*, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. *82701* del Consejo Superior de la Judicatura, en mi condición de apoderada de la sociedad **PROCAPS 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 "FORMULACIONES DEL MODIFICADOR DE INMUNORESPUESTA QUE CONTIENEN ÁCIDO OLEICO Y MÉTODOS", cuyo titular es **3M INNOVATIVE PROPERTIES COMPANY**, y pido a Usted



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declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

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 legítimo 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 ACIDO OLEICO. 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 25 de agosto de 2008 reivindicando prioridad bajo la solicitud WO2006US49517 del 2006-12-29; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 612 del 29 de enero de 2010, cuya publicación internacional corresponde a la WO2008/082381 del 10/07/2008.

2.2. La solicitud colombiana 08 88449 objeto de la presente oposición, se refiere a una formulación farmacéutica que comprende:



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una cantidad terapéuticamente eficaz de un compuesto modificador de la inmunorespuesta (IRM) seleccionado del grupo que consiste en aminas de imidazoquinolina, aminas de tetrahydroimidazoquinolina, aminas de imidazopiridina, aminas de cicloalquilimidazopiridina 6,7-fundidas, aminas de imidazoquinolina 1,2-en. puente, aminas de imidazonaftiridina, aminas de tetrahydroimidazonaftiridina, aminas de oxazoloquinolina, aminas de tiazoloquinolina, aminas de oxazolopiridina, aminas de tiazolopiridina, aminas de oxazolonaftiridina, aminas de tiazolonaftiridina, 1H-imidazo dimeros fundido a las aminas de piridina, aminas de quinolina, aminas de tetrahydroquinolina, aminas de naftiridina, o aminas de tetrahidronaftiridina, y combinaciones de las mismas; y un vehículo farmacéuticamente aceptable incluyendo un componente de ácido oleico, en donde la formulación está substancialmente libre de impurezas polares introducido por el componente de ácido oleico.

2.3. Con base en el artículo 14 de la Decisión 486 de la CAN que 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 afectan la patentabilidad de la presente solicitud:

- D1: US2003199538 publicada el 23 de octubre de 2003.
- D2: US2004089855 publicada el 13 de mayo de 1999.



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2.4. Ahora bien, el documento D1, particularmente en la en su descripción se refiere a una formulación farmacéutica que comprende: un modificador de la respuesta inmune (IRM) compuesto seleccionado de entre aminos de imidazoquinolina, aminos de imidazotetrahidroquinolina, aminos de imidazopiridina, aminos 6,7-fusionados de cicloalquilimidazopiridina, aminos puenteadas de 1 , 2-imidazoquinolina, aminos de tiazoloquinolinamina, aminos de oxazoloquinolina, aminos de tiazolopiridina, aminos de oxazolopiridina, aminos de imidazonaftiridina, aminos de imidazotetrahidronaftiridin, y aminos de tiazolonaftiridina; un ácido graso; y un componente hidrofóbico aprótico mezclable con el ácido graso comprendiendo un grupo hidrocarbilo de 7 o más átomos de carbono incluyendo ácido oleico, cómo es posible ver en la reivindicación 1 de dicho documento D1. Según el mismo documento D1, en cuanto a la formulación, esta es prácticamente libre de impurezas polares gracias a la presencia del ácido oleico y dicho documento D1 revela además que el componente hidrofóbico aprótico puede aumentar el volumen de la fase oleosa de la formulación tópica para proporcionar cualidades deseables, como la extensibilidad y la sensación, mientras que no altera de forma sensible la saturación de la actividad termodinámica del IRM.

2.5. Adicionalmente el documento D2, particularmente en la página 3, párrafo 0037, revela la eliminación de impurezas polares del aceite en una alta composición de aceite de ácido oleico.

2.6. Tomando los documentos D1 y D2, como el estado más cercano de la técnica, no es posible reconocer altura inventiva, ya que sería obvio para un experto en la



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materia a partir del documento D1, apoyado en el librarse de las impurezas polares para proporcionar estabilidad a una fórmula mejorada para compensar el componente de ácido oleico como lo revela el documento D2, concebir una formulación farmacéutica que comprende una cantidad terapéuticamente eficaz de un compuesto modificador de la inmunorespuesta (IRM) seleccionado del grupo que consiste en aminas de imidazoquinolina, aminas de tetrahydroimidazoquinolina, aminas de imidazopiridina, aminas de cicloalquilimidazopiridina 6,7-fundidas, aminas de imidazoquinolina 1,2-en puente, aminas de imidazonaftiridina, aminas de tetrahydroimidazonaftiridina, aminas de oxazoloquinolina, aminas de tiazoloquinolina, aminas de oxazolopiridina, aminas de tiazolopiridina, aminas de oxazonaftiridina, aminas de tiazolonaftiridina, 1H-imidazo dimeros fundido a las aminas de piridina, aminas de quinolina, aminas de tetrahydroquinolina, aminas de naftiridina, o aminas de tetrahydronaftiridina, y combinaciones de las mismas; y un vehículo farmacéuticamente aceptable incluyendo un componente de ácido oleico, en donde la formulación está substancialmente libre de impurezas polares gracias al componente de ácido oleico. Así entonces las reivindicaciones 1 a 28 de la solicitud objeto de la presente oposición, carecen de altura inventiva.

2.7. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 08 88449 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con uno de los tres requisitos necesarios para su protección.

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

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2.8.1. CARENCA DE ALTURA INVENTIVA. Según la Decisión 486 de la Comunidad Andina de Naciones, Artículo 18.- *"Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica."* A la fecha de prioridad, 29 de diciembre de 2006, a partir del documento D1 por sí solo, o por la combinación de los documentos D1 y D2, puede llegar de manera evidente a una formulación farmacéutica que comprende una cantidad terapéuticamente eficaz de un compuesto modificador de la inmunorepuesta (IRM) seleccionado del grupo que consiste en aminos de imidazoquinolina, aminos de tetrahidroimidazoquinolina, aminos de imidazopiridina, aminos de cicloalquilimidazopiridina 6,7-fundidos, aminos de imidazoquinolina 1,2-en puente, aminos de imidazonaftiridina, aminos de tetrahidroimidazonaftiridina, aminos de oxazoloquinolina, aminos de tiazoloquinolina, aminos de oxazolopiridina, aminos de tiazolopiridina, aminos de oxazonaftiridina, aminos de tiazolonaftiridina, 1H-imidazo dímeros fundido a las aminos de piridina, aminos de quinolina, aminos de tetrahidroquinolina, aminos de naftiridina, o aminos de tetrahidronaftiridina, y combinaciones de las mismas; y un vehículo farmacéuticamente aceptable incluyendo un componente de ácido oleico, en donde la formulación está substancialmente libre de impurezas polares por el componente de ácido oleico, sobre las cuales busca protección en el capítulo reivindicatorio.

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*



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Industrial y Comercio Exterior

la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial". La solicitud pretendida no cumple con uno 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 en consecuencia negar el registro a la solicitud de patente titulada "FORMULACIONES DEL MODIFICADOR DE INMUNORESPUESTA QUE CONTIENEN ÁCIDO OLEICO Y MÉTODOS", cuyo titular es 3M INNOVATIVE PROPERTIES COMPANY, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 612 del 29 de enero de 2010.

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.
- D2: US2004089855 publicada el 13 de mayo de 1999.

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 PROCAPS S.A.
3. Recibo de caja del respectivo pago de tasa.
4. Copias de los documentos:
 - DI: US2003199538 publicada el 23 de octubre de 2003.
 - DE: US2004089855 publicada el 13 de mayo de 1999.

6. NOTIFICACIONES

Para efectos de notificaciones que por disposición del artículo 50 del Decreto 01 de 1993 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 N° 11995, Of. 104 de esta ciudad de Bogotá.

Señor Superintendente,



CIELO ANGELLA PEÑA RODRIGUEZ
C.C. 51'222.252 de Bogotá
T.P.A. 8'221 del C.S. de la J.

467 167

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 08-088449-00004-0000

Fecha: 2010-04-27 11:10:35 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYI Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 68

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 10 - 32,635
FECHA : ABRIL 27 DE 2010

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
LAB. PROCAPS	CONSIGNACION	BANCO DE BOGOTA	062754387	174684996	07/04/2010	590,000.00
LAB. PROCAPS	CONSIGNACION	BANCO DE BOGOTA	062754387	174685000	07/04/2010	1,475,000.00

***** CONCEPTO *****

CANT. RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-04 PRESENTACION DE OBSERVACIONES	12 MARCAS Y LENAS COMERCIALES	295,000.00
	TOTAL :	\$ 295,000.00

SOM: DOSCIENTOS NOVENTA Y CINCO MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

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PODER ESPECIAL

Yo, **WALTER TANAKA TATEKAWA**, 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 **PROCAPS S.A.** sociedad legalmente constituida y domiciliada en la ciudad de Barranquilla (Colombia), por el presente documento otorgo a la doctora **CIELO ANGELA PEÑA RODRIGUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 82701 del C.S. de la J., poder especial, amplio y suficiente, para formular oposiciones u observaciones a la solicitud de patente No. ~~08 088.449~~, titulada **"FORMULACIONES DEL MODIFICADOR DE INMUNORÉSPUESTA QUE CONTIENEN ÁCIDO OLEICO Y MÉTODOS"**, cuyo titular es **3M INNOVATIVE PROPERTIES COMPANY**, publicada en la gaceta No. gaceta No. 612 del 29 de enero de 2010.

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 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 12 días del mes de abril de 2010.

PROCAPS S.A.

C.C. N° 16'251.923
NIT: 890.106.527-5
Representante Legal

Acepto:

CIELO ANGELA PEÑA RODRIGUEZ
C.C. 51'940.252 de Bogotá
T.P.A. 82701 del C.S. de la J.

NOTARIA
NOTARIA TERCERA DEL CÍRCULO DE BARRANQUILLA
DILIGENCIA DE RECONOCIMIENTO
Ante el Notario Tercero de Barranquilla se presentó:
WALTER TANAKA TATEKAWA
Identificado con: C16.751.913 PALMIRA
Y declaro que el contenido del anterior Documento es cierto
y cuya la firma fue lo referida
Barranquilla: 14 ABR. 2010





***** Pag. 1
CAMARA DE COMERCIO
DE BARRANQUILLA
07*****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----
NIT: 890.106.527-5.

EN JUNIO DE ESTE AÑO SE ELEGIRÁ JUNTA DIRECTIVA DE LA CÁMARA DE COMERCIO. LAS INSCRIPCIONES DE CANDIDATOS DEBEN HACERSE EN LA PRIMERA QUINCENA DE MAYO. PARA INFORMACIÓN DETALLADA DIRIGIRSE A LA SEDE PRINCIPAL O COMUNICARSE AL SIGUIENTE TELEFONO: 3303718-3303716.

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 Pública No. 1,190 del 22 de Julio de 1976, otorgada en la Notaria Tercera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 28 de Julio de 1976 bajo el No. 6,070 del libro respectivo, fue constituida la sociedad-----
limitada denominada "PRODUCTORA DE CAPSULAS DE GELATINAS LIMITADA
"PROCAPS LIMITADA".-----

C E R T I F I C A

Que por Escritura Pública No. 1,307 del 28 de Junio de 1979, otorgada en la Notaria Tercera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 23 de Julio de 1979 bajo el No. 10,039 del libro respectivo, la sociedad antes mencionada-----
se transformo en sociedad anonima bajo la denominacion social de
"PRODUCTORA DE CAPSULAS DE GELATINA S.A." PROCAPS S.A.".-----

C E R T I F I C A

Que por Escritura Pública No. 3,810 del 31 de Dic/bre de 1980, otorgada en la Notaria Primera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 30 de Enero de 1981 bajo el No. 12,705 del libro respectivo, la sociedad antes mencionada-----
se transformo en sociedad de responsabilidad limitada bajo al razon
social de "PRODUCTORA DE CAPSULAS DE GELATINA LIMITADA "PROCAPS LI -
MITADA".-----

C E R T I F I C A

Que por Escritura Pública No. 3,755 del 10 de Nov/bre de 1983, otorgada en la Notaria Unica de Soledad, inscrito(as) en esta Cámara de Comercio, el 22 de Nov/bre de 1983 bajo el No. 17,922 del libro respectivo, la sociedad antes mencionada-----
se transformo en sociedad anonima bajo la denominacion social de
"PRODUCTORA DE CAPSULAS DE GELATINA S.A. "PROCAPS S.A.".-----

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.
NIT: 890.106.527-5.

C E R T I F I C A

Que por Escritura Pública No. 3,615 del 06 de Dic/bre de 1996, otorgada en la Notaria 2a. de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 20 de Dic/bre de 1996 bajo el No. 67,218 del libro respectivo, la sociedad antes mencionada-----
cambio de razon social, por la denominacion LABORATORIOS PROCAPS S.A.-----

C E R T I F I C A

Que por Escritura Pública No. 3,775 del 18 de Dic/bre de 1996, otorgada en la Notaria 2a. de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 23 de Enero de 1997 bajo el No. 67,704 del libro respectivo, la sociedad antes mencionada-----
cambio de razon social, por la denominacion PROCAPS 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
39	1979/01/18	Notaria 3a. de Barranquilla.	9,452	1979/01/24
992	1981/04/30	Notaria 1a. de Barranquilla.	13,112	1981/05/06
1,464	1982/08/27	Notaria Unica de Soledad	15,533	1982/09/08
2,744	1983/08/18	Notaria Unica de Soledad	17,416	1983/08/26
3,826	1984/07/16	Notaria Unica de Soledad	19,554	1984/07/27
3,835	1985/08/26	Notaria Unica de Soledad	22,230	1985/09/04
2,260	1986/09/10	Notaria Unica de Soledad.	24,995	1986/09/15
1,849	1989/07/11	Notaria 2a. de Barranquilla.	33,909	1989/07/13
444	1990/02/21	Notaria 2a. de Barranquilla.	36,101	1990/03/16
3,090	1991/12/17	Notaria 2a. de Barranquilla	43,993	1992/01/28
269	1993/02/01	Notaria 2a. de Barranquilla	48,428	1993/02/16
2,342	1993/07/28	Notaria 2a. de Barranquilla	50,582	1993/08/10
3,652	1993/11/09	Notaria 2a. de Barranquilla	51,798	1993/11/22
3,615	1996/12/06	Notaria 2a. de Barranquilla	67,218	1996/12/20
89	1997/01/16	Notaria 2a. de Barranquilla	67,704	1997/01/23
2,070	1997/07/17	Notaria 2a. de Barranquilla	70,627	1997/07/31
2,281	1997/08/04	Notaria 2a. de Barranquilla	70,813	1997/08/14
765	1999/04/22	Notaria 3a. de Barranquilla	80,628	1999/04/23
459	2001/02/21	Notaria 2a. de Barranquilla	91,502	2001/02/23
2,608	2001/10/05	Notaria 2a. de Barranquilla	95,771	2001/11/08
1,730	2004/07/29	Notaria 2. de Barranquilla	112,999	2004/08/26
416	2005/03/03	Notaria 2. de Barranquilla	116,364	2005/03/10
1,613	2005/07/28	Notaria 2. de Barranquilla	119,322	2005/08/18
710	2009/05/05	Notaria 3 a. de Barranquilla	150,130	2009/06/30
1,054	2009/06/25	Notaria 3 a. de Barranquilla	150,130	2009/06/30

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:



***** Pag. 2

CAMARA DE COMERCIO
DE BARRANQUILLA

07*****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5.

PROCAPS S.A.-----

SIGLA: PROCAPS.

DOMICILIO PRINCIPAL: Barranquilla.

NIT No: 890.106.527-5.

MATRICULA MERCANTIL: 24,802.

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 término de duración de la sociedad se fijó hasta el 18 de Agosto de 2073.

C E R T I F I C A

OBJETO SOCIAL: El objeto principal de la sociedad sera: a) La fabricacion, importacion y comercializacion de alimentos procesados y suplementos dietarios. b) La fabricacion de capsulas y otros 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, alimenticias y cosmeticas, para uso y consumo humano y veterinario. c) La investigacion, desarrollo y fabricacion de toda clase de productos y sustancias quimicas, farmaceuticas, alimenticias y cosmeticas para uso y consumo humano, animal y vegetal. d) La compra y venta de materias primas, insumos y productos intermedios necesarios para los procesos de fabricacion de sustancias quimicas, farmaceuticas, alimenticias y cosmeticas, asi como la comercializacion interna y externa de los productos terminados. e) 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. f) La compra, venta, exportacion, fabricacion, importacion, distribucion de dulces, confites, galletas y todo tipo de golosinas o alimentos para el consumo humano. g) 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 cualquiera de las actividades descritas en los literales a), b), c), d) y e) antes descritos. h) Prestar los servicios de asesorias y consultoria en las areas administrativas,

***** C O N T I N U A *****

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NIT: 890.106.527-5.

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 PROCAPS S.A., asi como los de publicidad y promocion de productos quimicos, alimenticios, cosmeticos y farmaceuticos para uso humano, animal o industrial. i) Adquirir, operar, administrar y explotar, a cualquier titulo, empresa o establecimientos dedicados a la investigacion, desarrollo, fabricacion o comercializacion de productos quimicos, farmaceuticos, alimenticios, 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 operaciones; girar, aceptar, otorgar y protestar todo tipo de titulos valores e instrumentos negociables, comprar, vender y constituir gravámenes sobre bienes muebles e inmuebles, designar representantes 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 la de sus socios. La sociedad podra garantizar el cumplimiento de sus obligaciones adquiridas por terceros o por sus socios, para lo cual podra inclusive constituir gravámenes reales sobre sus bienes de cualquier naturaleza.-----

C E R T I F I C A

CAPITAL	Nro Acciones	Valor Acción
Autorizado		
\$*****2,000,000,000	*****2,000,000	*****1,000
Suscrito		
\$*****1,229,071,000	*****1,229,071	*****1,000
Pagado		
\$*****1,229,071,000	*****1,229,071	*****1,000

C E R T I F I C A

ADMINISTRACION: La direccion y administracion de la sociedad corresponde a la Asamblea General de Accionistas, a la Junta Directiva, al Presidente, al Vicepresidente y a un Gerente General. Corresponde a la Junta Directiva las siguientes funciones y atribuciones entre otras: Autorizar cualquier acto o contrato cuya cuantia sea superior al equivalente en pesos Colombianos a doscientos cincuenta mil dolares de los Estados Unidos de America (US\$250.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la transacion. Cuando se trate de operaciones en virtud de las cuales la sociedad garantice obligaciones de terceros o de los socios, se requiera que la operacion sea aprobada con el voto de por lo menos 2/3 partes de los integrantes de la Junta Directiva.

***** C O N T I N U A *****



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CAMARA DE COMERCIO
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07*****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

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NIT: 890.106.527-5.

La sociedad tendra un Presidente , quien ejercera la representacion legal de la sociedad y tendra las siguientes atribuciones entre otras: Ejecutar las decisiones de la Asamblea General de Accionistas y de la Junta Directiva. 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. Constituir apoderados judiciales y extrajudiciales, recibir notificaciones, absolver interrogatorios de parte, confesar obligaciones de la sociedad, transigir, disistir y allanar a la sociedad en cualquier asunto judicial. Aprobar y celebrar en nombre de la socieda todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos colombianos a doscientos cincuenta mil dolares de los Estados Unidos de America (US\$250.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la transacion o celebracion del acto. Las demas funciones que le correspondan como Representante Legal por disposicion de la ley, de estos estatutos o de la Junta Directiva. El Presidente tendra un suplente, designado por la Junta Directiva, quien reemplazara al Presidente en sus faltas temporales, absolutas o meramente accidentales, con entidades facultades y sin que sea necesario para ello acreditar la ausencia del principal. La sociedad tendra un Vicepresidente designado por la Junta Directiva, quien tambien ejercera la representacion legal de la sociedad, pudiendo ejercerla conjunta o separadamente con el Presidente. El vicepresidente tendra las siguientes facultades entre otras. Ejecutar dentro de su competencia las decisiones de la Asamblea General de Accionistas, de la Junta Directiva y del Presidente. 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. Constituir apoderados judiciales y extrajudiciales, recibir notificaciones, absolver interrogatorios de parte, confesar obligaciones de la sociedad, transigir, desistir y allanar a la sociedad en cualquier asunto judicial. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos colombianos a ciento cincuenta mil dolares de los Estados Unidos de America (US\$150.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto, siempre que no se trate de enajenar bienes inmuebles o cualquier otro activo fijo de la sociedad, inclusive de naturaleza muebles, acciones, cuotas o partes de interes inversiones y todo tipo de derechos de la sociedad, o de constituir gravámenes sobre cualquiera de los anteriores, facultades que radican exclusiva y privativamente en cabeza del Presidente. Las demas funciones que le corresponda como

***** C O N T I N U A *****

100150505-C
REGISTRAR EIA NIT. 890.321.151-8

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS

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Representante legal por disposicion de la ley, de estos estatutos o de la Junta Directiva. El Vicepresidente tendra (1) suplente, designado por la Junta Directiva, quien lo reemplazara conjunta o separadamente en sus faltas temporales, absolutas o meramente accidentales, con identicas facultades y sin que sea necesario para ello acreditar la ausencia del principal. La sociedad tendra un (1) Gerente General, con su respectivo Suplente, designados por la Junta Directiva. El Suplente reemplazara al Gerente General, en sus faltas temporales, absolutas o meramente accidentales, quien junto con el gerente general, llevaran la representacion legal de la sociedad, con identicas facultades, pudiendolas ejercer conjunta o separadamente con el Presidente y Vicepresidente, con identicas facultades que el Gerente General y sin que sea necesario para ello acreditar la ausencia del titular. El Gerente General tendra las siguientes facultades 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), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto, siempre que no se trate de enajenar a cualquier titulo bienes inmuebles o cualquier otro activo fijo de la sociedad, inclusive de naturaleza mueble, acciones, cuotas o partes de interes, inversiones y todo tipo de derechos de la sociedad o de constituir gravámenes sobre cualquiera de las anteriores facultades que radican exclusiva y privativamente en cabeza del Presidente.

C E R T I F I C A

Que según Acta No. 116 del 27 de Junio de 1997 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad:

PROCAPS S.A.-----
cuya parte pertinente se inscribió en esta Cámara de Comercio, el 15 de Agosto de 1997 bajo el No. 70,838 del libro respectivo, y según Acta No. 127 del 22 de Marzo de 2000 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad:

PROCAPS S.A.-----
cuya parte pertinente se inscribió en esta Cámara de Comercio, el 29 de Mayo de 2000 bajo el No. 87,250 del libro respectivo, fueron hechos los siguientes nombramientos:

CLASE: JUNTA DIRECTIVA

Principales

1. Minski Gontovnik Ruben	CC.*****7,463,982
2. Minski Gontovnik Meyer	CC.*****7,461,324
3. Minski Gontovnik Jose	CC.*****8,671,834

Suplentes

1. Minski Zirberblum Elliot	CC.*****72,219,541
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***** C O N T I N U A *****



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C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A
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PROCAPS S.A.-----

NIT: 890.106.527-5.

2. Minski Deitel Daniel
3. Minski Sharon

PA.*990,212,082,805

C E R T I F I C A

Que según Acta No. 116 del 27 de Junio de 1997 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 15 de Agosto de 1997 bajo el No. 70,838 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Presidente.	
Minski Gontovnik Ruben	CC.*****7,463,982
Suplente del Presidente	
Minski Minski Abraham	CC.*****802,575
Vicepresidente	
Minski Gontovnik Meyer	CC.*****7,461,324
Suplente del vicepresidente	
Minski Gontovnik Jose	CC.*****8,671,834

C E R T I F I C A

Que según Acta No. 11 del 01 de Febrero de 2001 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 12 de Febrero de 2001 bajo el No. 91,273 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Gerente General.	
Uribe Ochoa Guillermo Luis	CC.*****70,073,754

C E R T I F I C A

Que según Acta No. 406 del 02 de Sep/bre de 2004 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 09 de Sep/bre de 2004 bajo el No. 113,263 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Suplente del Gerente.	
Tanaka Tatekawa Walter	CC.*****16,251,923

C E R T I F I C A

Que según Acta No. 124 del 29 de Marzo de 1999 correspondiente a

***** C O N T I N U A *****

PROCAPS S.A. NIT. 890.106.527-5

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----
NIT: 890.106.527-5.

la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 04 de Agosto de 1999 bajo el No. 82,226 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Revisor Fiscal Ppal. Vargas Pertuz Ana Isabel	CC.*****32,696,645

C E R T I F I C A

Que según Acta No. 151 del 31 de Marzo de 2009 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 30 de Julio de 2009 bajo el No. 151,129 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Suplente del Revisor Fiscal. Duarte Diaz David	CC.*****73,115,965

C E R T I F I C A

Que por Escritura Pública No. 2,784 del 07 de Dic/bre de 2007, otorgada en la Notaria 2 a. de Barranquilla cuya parte pertinente se inscribió en esta Cámara de Comercio, el 20 de Dic/bre de 2007 bajo el No. 3,492 del libro respectivo,-----
y las inscripciones 3.492-1, 3.493, 3.494, 3.495, 3.496, 3.497, ---
3.498, 3.499, 3.500, 3.501, 3.502, 3.503, 3.504, 3.505, 3.506, ----
3.507, Consta que RUBEN MINSKI GONTOVNIK, C.C. No. 7.463.982, -----
obrando como Presidente y Representante Legal de la sociedad C.I. NATURMEGA S.A., que obrando en su condicion de Presidente y -----
Representante Legaql de la sociedad PROCAPS S.A., el presidente ----
debidamente facultado por los Estatutos Sociales y por el Maximo Organo Social, otorga los siguientes poderes: Otorgar poder -----
general, amplio y suficiente a los doctores JOSEFINA DEL CARMEN ----
MIELES BUELVAS CC.No.33.138.497; a MARCELA CARVAJALINO PAGANO -----
CC.No.22.579.748; CRISTINA VIOLI FRANCESCHINI CC.No.22.463.716, con las facultades que se transcriben a continuacion: a.- Para que ----
representen a la sociedad PROCAPS S.A, ante todo tipo de -----
autoridades administrativas y jurisdiccionales, en asuntos de -----
naturaleza civil, laboral, comercial, penal, aduanera, cambiaria, tributaria, policiva, administrativa y fiscal. b.- Contestar y ----
presentar demandas, requerimientos, recursos, pedir y aportar -----
pruebas, recibir, notificarse, ejercer la accion de tutela, -----
tramitar incidente de desacato, comparecer en los procesos que ----
cursen contra la sociedad, allanarse en nombre de la sociedad en los asuntos que sean necesarios, transigir, desistir, sustituir, renunciar y reasumir el poder. c.- La facultad expresa de -----
conciliar, por tanto pueden llegar a acuerdos conciliatorios, -----
transaccionales, judiciales o extrajudiciales o extrajudiciales, cualquiera que sea su cuantia, para lo cual las apoderadas deben aportar la autorizacion simple y escrita del Representante legal de la sociedad d.- Podran presentar solicitudes de devolucion y/o compensacion de impuestos, ventas y rentas, recibir los pagos por

***** C O N T I N U A *****



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CAMARA DE COMERCIO
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07*****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----
NIT: 890.106.527-5.

las devoluciones y adelantar todo tramite o proceso administrativo ante la DIAN, de tal forma que en ningun momento quede sin ----- representacion legal de la sociedad. PODERES ESPECIALES: a.- Se ---- confiere poder especial amplio y suficiente a las personas que se determinan seguidamente, que conforman el grupo A y B, para, para que conjuntamente suscriban contratos de suministros de mercancías y servicios con entidades oficiales, hasta la suma de OCHOCIENTOS MIL DOLARES DE LOS ESTADOS UNIDOS DE AMERICA (US800.000.00), ----- liquidados a la tasa representativa del mercado vigente en el día que se realice la respectiva transaccion. Grupo A. WALTER NANAKA TATEKAWA CC.No.16.251.923, CLAUDIA TANGARIFE CASTILLO ----- CC.No.41.660.293, CARMEN ALICIA FLOREZ CC.No.22.434.044, IVAN ----- VILLAREAL CAMACHO CC.No.91.201.749, CARMEN ALICIA HERRERA ----- DIAZGRANADOS CC.No.22.377.540, DAVID ANTONIO CHARRIS GIRALDO ----- CC.No.19.341.274, RICARDO DORADO HURTADO CC.No.79.715.772, JAIME FORERO LLINAS CC.No.19.300.593. b.- Se confiere poder especial ---- amplio y suficiente al señor WILLIAM ALBERTO BARROS CERRA ----- CC.No.8.715.941, para que en nombre y representacion de PROCAPS ---- S.A., suscriban declaraciones cambiarias, aduaneras y tributarias a que este obligada la sociedad, en el giro normal de sus negocios y operaciones sociales, por tanto quedan facultados para firmarlas, como tambien los demas documentos relacionados con ellas, ----- notificarse, aportar y solicitar las pruebas que sean necesarias. c.-Otorgar poder especial amplio y suficiente al señor MARLON ----- TATIS PAREDES CC.No.72.176.874 y al señor WILLIAM ALBERTO BARROS CERRA CC.No.8.715.941, para que en nombre y representacion de ----- PROCANPS S.A., suscriban las declaraciones, reportes y cualquier documento relacionado con los tramites o registros de Comercio ---- Exterior y o cualquier entidad del Estado que haga sus veces: d) Otorgar poder especial amplio y suficiente a la doctora CARMEN ---- ALICIA HERRERA DIAZGRANADOS, CC.No.22.377.540 y al doctor WALTER TANAKA TATEKAWA, CC.No.16.251.923, para que en nombre y ----- representacion de PROCAPS S.A.; endosen los titulos valores de la sociedad hasta por la suma de UN MIL MILLONES DE PESOS ----- (1.000.000.000.00) M.L. CUARTO: El representante legal de la ---- sociedad PROCAPS S.A.; doctor RUBEN MINSKI GONTOVNIK, manifiesta que la presente reforma fue aprobada por la Asamblea General ---- Extraordinaria de Accionista de PROCAPS S.A., con observancia de las disposiciones legales y estatutarias.-----

C E R T I F I C A

Que por Escritura Pública No. 1,933 del 16 de Sep/bre de 2008, otorgada en la Notaria 2 a. de Barranquilla cuya parte pertinente se inscribió en esta Cámara de Comercio, el 06 de Octubre de 2008

***** C O N T I N U A *****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS

PROCAPS S.A.

NIT: 890.106.527-5.

bajo el No. 3,748 del libro respectivo,-----
Consta que el señor RUBEN MINSKI GONTOVNIK, C.C. No. 7.463.982, que
comparece en su condicion de Presidente y Representante Legal de la
Sociedad PROCAPS S.A., confiere por medio de este instrumento -----
publico Poder especial Amplio y Suficiente a la doctora MILENA -----
ESCAFFI PARDO, C.C. No. 32.758.420, para que en nombre y -----
representacion de PROCAPS S.A., suscriba declaraciones cambiarias,
aduaneras y tributarias a que este obligada la sociedad en el giro
normal de sus negocios y operaciones sociales, por tanto queda -----
facultada para firmar, como tambien los demas documentos -----
relacionados con ellas, notificarse, aportar y solicitar las -----
pruebas que sean necesarias.-----

C E R T I F I C A

Que en esta Cámara de Comercio no aparecen inscripciones posteriores
de documentos referentes a reforma, disolución, liquidación o
nombramientos de representantes legales de la expresada sociedad.

C E R T I F I C A

Que su última Renovación fue el: 30 de Marzo de 2010.

La información sobre embargos de establecimiento se suministra en
Certificados de Matrícula, la de contratos sujetos a registro, en
Certificados Especiales.

C E R T I F I C A

Que los actos de registro aquí certificados quedan en firme cinco
días hábiles despues de la correspondiente inscripción, siempre
que, dentro de dicho término, no sean objeto de los recursos de
reposición ante esta entidad, y/o de apelación para ante la
Superintendencia de Industria y Comercio.

m. l. g. o. n.



US 20030199538A1

(19) **United States**(12) **Patent Application Publication**
Skwierczynski et al.(10) **Pub. No.: US 2003/0199538 A1**(43) **Pub. Date: Oct. 23, 2003**(54) **PHARMACEUTICAL FORMULATION
COMPRISING AN IMMUNE RESPONSE
MODIFIER**(75) **Inventors: Raymond D. Skwierczynski, Oakdale,
MN (US); Terri F. Busch, St. Paul,
MN (US); Amy L. Gust-Helting,
Hudson, WI (US); Mary Fretland,
Eagan, MN (US); Matthew T. Scholz,
Woodbury, MN (US)**

Correspondence Address:
**Attention: Dean A. Ersfeld
Office of Intellectual Property Counsel
3M Innovative Properties Company
P.O. Box 33427
St. Paul, MN 55133-3427 (US)**

(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-quinolinamines, 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/agglomeration 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, 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; 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.

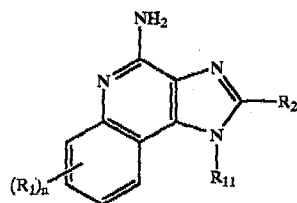
DETAILED DESCRIPTION

[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:



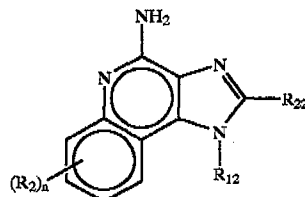
[0021] wherein

[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;



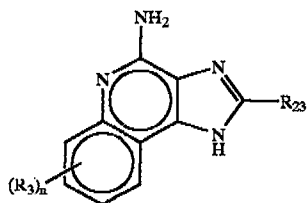
II

[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;



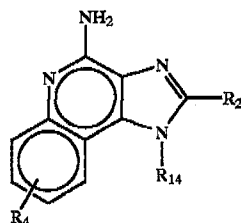
III

[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;



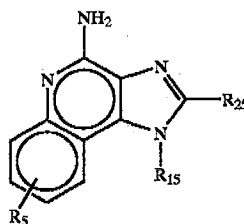
IV

[0032] wherein

[0033] R_{14} is $-\text{CHR}_x\text{R}_y$, 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 tetrahydrofuran 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

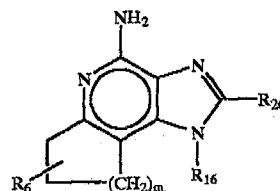
[0040] R_S and R_T are independently chosen from hydrogen, alkyl of one to four carbon atoms, phenyl, and substituted phenyl wherein the substituent is chosen from alkyl of one to four carbon atoms, alkoxy of one to four carbon atoms, and halogen;

[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 $-\text{CHR}_x\text{R}_y$,

[0048] wherein

[0049] R_x is hydrogen or a carbon-carbon bond, with the proviso that when R_x is hydrogen R_y 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 tetrahydrofuran group optionally substituted with one or more substituents independently chosen from hydroxy and hydroxyalkyl of one to four carbon atoms,

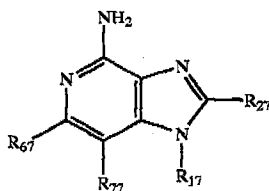
[0050] R_{26} is chosen from hydrogen, straight chain or branched chain alkyl containing one to eight carbon atoms, straight chain or branched chain hydroxyalkyl containing one to six carbon atoms, morpholinoalkyl, benzyl, (phenyl)ethyl and phenyl, the benzyl, (phenyl)ethyl or phenyl substituent being 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:



[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;

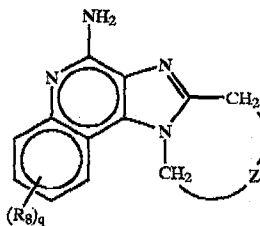
[0057] R_{27} is chosen from hydrogen; straight chain or branched chain alkyl containing one to eight carbon atoms; straight chain or branched chain hydroxyalkyl containing one to six carbon atoms; alkoxyalkyl wherein the alkoxy moiety contains one to four carbon atoms and the alkyl moiety contains one to six carbon atoms; benzyl, (phenyl)ethyl and phenyl, the benzyl, (phenyl)ethyl and 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;

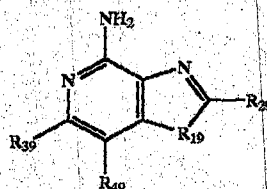
[0064] $-(CH_2)_a-C(R_D R_E)(CH_2)_b-$ wherein a and b are integers and $a+b$ is 0 to 3, R_D is hydrogen or alkyl of one to four carbon atoms, and R_E is chosen from alkyl of one to four carbon atoms, hydroxy, $-OR_F$ wherein R_F is alkyl of one to four carbon atoms, and $-NR_G R'_G$ wherein R_G and 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_9 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:



[0069] wherein:

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

[0071] R_{20} 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-N₃;

[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;

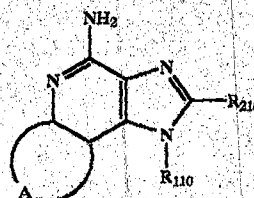
[0099] or when taken together, R_{39} and R_{49} form a fused aromatic, heteroaromatic, cycloalkyl or heterocyclic ring;

[0100] X is chosen from -O-, -S-, -NR₅₉-, -C(O)-, -C(O)O-, -OC(O)-, and a bond; and

[0101] each R_{59} is independently H or C₁₋₈alkyl;

[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:



[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] -C₁₋₂₀alkyl or C₂₋₂₀alkenyl that is unsubstituted or substituted by one or more substituents chosen from:

[0109] -aryl;

[0110] -heteroaryl;

[0111] -heterocyclyl;

[0112] -O-C₁₋₂₀alkyl;

[0113] -O-(C₁₋₂₀alkyl)₀₋₁-aryl;

[0114] -O-(C₁₋₂₀alkyl)₀₋₁-heteroaryl;

[0115] -O-(C₁₋₂₀alkyl)₀₋₁-heterocyclyl;

[0116] -CO-O-C₁₋₂₀alkyl;

[0117] -S(O)₀₋₂-C₁₋₂₀alkyl;

[0118] -S(O)₀₋₂-(C₁₋₂₀alkyl)₀₋₁-aryl;

[0119] -S(O)₀₋₂-(C₁₋₂₀alkyl)₀₋₁-heteroaryl;

[0120] -S(O)₀₋₂-(C₁₋₂₀alkyl)₀₋₁-heterocyclyl;

[0121] -N(R_{310})₂;

[0122] -N₃;

[0123] oxo;

[0124] -halogen;

[0125] $-\text{NO}_2$;[0126] $-\text{OH}$; and[0127] $-\text{SH}$; and

[0128] $-\text{C}_{1-20}\text{alkyl}-\text{NR}_{310}-\text{Q}-\text{X}-\text{R}_{410}$ or $-\text{C}_{2-20}\text{alkenyl}-\text{NR}_{310}-\text{Q}-\text{X}-\text{R}_{410}$ wherein Q is $-\text{CO}-$ or $-\text{SO}_2-$; X is a bond, $-\text{O}-$ or $-\text{NR}_{310}-$ and R_{410} is aryl; heteroaryl; heterocyclyl; or $-\text{C}_{1-20}\text{alkyl}$ or $\text{C}_{2-20}\text{alkenyl}$ that is unsubstituted or substituted by one or more substituents chosen from:

[0129] -aryl;

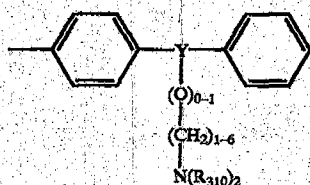
[0130] -heteroaryl;

[0131] -heterocyclyl;

[0132] $-\text{O}-\text{C}_{1-20}\text{alkyl}$;[0133] $-\text{O}-(\text{C}_{1-20}\text{alkyl})_{0-1}\text{-aryl}$;[0134] $-\text{O}-(\text{C}_{1-20}\text{alkyl})_{0-1}\text{-heteroaryl}$;[0135] $-\text{O}-(\text{C}_{1-20}\text{alkyl})_{0-1}\text{-heterocyclyl}$;[0136] $-\text{CO}-\text{O}-\text{C}_{1-20}\text{alkyl}$;[0137] $-\text{S}(\text{O})_{0-2}-\text{C}_{1-20}\text{alkyl}$;[0138] $-\text{S}(\text{O})_{0-2}-(\text{C}_{1-20}\text{alkyl})_{0-1}\text{-aryl}$;[0139] $-\text{S}(\text{O})_{0-2}-(\text{C}_{1-20}\text{alkyl})_{0-1}\text{-heteroaryl}$;[0140] $-\text{S}(\text{O})_{0-2}-(\text{C}_{1-20}\text{alkyl})_{0-1}\text{-heterocyclyl}$;[0141] $-\text{N}(\text{R}_{310})_2$;[0142] $-\text{NR}_{310}-\text{CO}-\text{O}-\text{C}_{1-20}\text{alkyl}$;[0143] $-\text{N}_3$;

[0144] oxo;

[0145] -halogen;

[0146] $-\text{NO}_2$;[0147] $-\text{OH}$; and[0148] $-\text{SH}$; or R_{410} is[0149] wherein Y is $-\text{N}-$ or $-\text{CR}-$;[0150] R_{210} is chosen from:

[0151] -hydrogen;

[0152] $-\text{C}_{1-10}\text{alkyl}$;[0153] $-\text{C}_{2-10}\text{alkenyl}$;

[0154] -aryl;

[0155] $-\text{C}_{1-10}\text{alkyl}-\text{O}-\text{C}_{1-10}\text{alkyl}$;[0156] $-\text{C}_{1-10}\text{alkyl}-\text{O}-\text{C}_{2-10}\text{alkenyl}$; and[0157] $-\text{C}_{1-10}\text{alkyl}$ or $\text{C}_{2-10}\text{alkenyl}$ substituted by one or more substituents chosen from:[0158] $-\text{OH}$;

[0159] -halogen;

[0160] $-\text{N}(\text{R}_{310})_2$;[0161] $-\text{CO}-\text{N}(\text{R}_{310})_2$;[0162] $-\text{CO}-\text{C}_{1-10}\text{alkyl}$;[0163] $-\text{N}_3$;

[0164] -aryl;

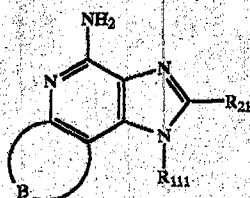
[0165] -heteroaryl;

[0166] -heterocyclyl;

[0167] $-\text{CO}-\text{aryl}$; and[0168] $-\text{CO}-\text{heteroaryl}$;[0169] each R_{310} is independently chosen from hydrogen and $\text{C}_{1-10}\text{alkyl}$; and[0170] each R is independently chosen from hydrogen, $\text{C}_{1-10}\text{alkyl}$, $\text{C}_{1-10}\text{alkoxy}$, halogen and trifluoromethyl,

[0171] and pharmaceutically acceptable salts thereof;

XI



[0172] wherein

[0173] B is $-\text{NR}-\text{C}(\text{R})_2-\text{C}(\text{R})_2-\text{C}(\text{R})_2-$, $-\text{C}(\text{R})_2-\text{NR}-\text{C}(\text{R})_2-\text{C}(\text{R})_2-$, $-\text{C}(\text{R})_2-\text{C}(\text{R})_2-\text{NR}-\text{C}(\text{R})_2-$ or $-\text{C}(\text{R})_2-\text{C}(\text{R})_2-\text{NR}-$;

[0174] R_{111} is chosen from:

[0175] -hydrogen;

[0176] $-\text{C}_{1-20}\text{alkyl}$ or $\text{C}_{2-20}\text{alkenyl}$ that is unsubstituted or substituted by one or more substituents chosen from:

[0177] -aryl;

[0178] -heteroaryl;

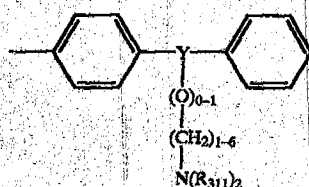
[0179] -heterocyclyl;

[0180] $-\text{O}-\text{C}_{1-20}\text{alkyl}$;[0181] $-\text{O}-(\text{C}_{1-20}\text{alkyl})_{0-1}\text{-aryl}$;[0182] $-\text{O}-(\text{C}_{1-20}\text{alkyl})_{0-1}\text{-heteroaryl}$;[0183] $-\text{O}-(\text{C}_{1-20}\text{alkyl})_{0-1}\text{-heterocyclyl}$;[0184] $-\text{CO}-\text{O}-\text{C}_{1-20}\text{alkyl}$;

- [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] -heterocyclyl;
 [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] $-CO-heteroaryl$;

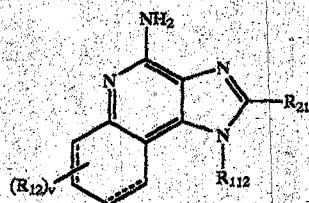
[0237] each R_{311} is independently chosen from hydrogen and $C_{1-10}alkyl$; and

[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:

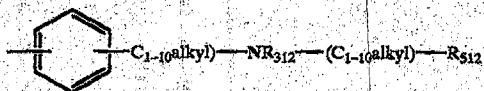
XII



[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)(OR₃₁₂)₂;
 [0268] -NR₃₁₂-CO-O-alkyl;
 [0269] -N₃;
 [0270] -halogen;
 [0271] -NO₂;
 [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 R₄₁₂ is



[0279] wherein R₅₁₂ is an aryl, (substituted aryl), heteroaryl, (substituted heteroaryl), heterocyclyl or (substituted heterocyclyl) group;

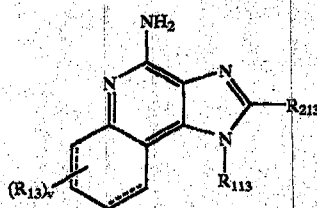
[0280] R₂₁₂ is chosen from:

- [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(R₃₁₂)₂;
 [0296] -CO-N(R₃₁₂)₂;
 [0297] -CO-C₁₋₁₀alkyl;
 [0298] -CO-O-C₁₋₁₀alkyl;
 [0299] -N₃;
 [0300] -aryl;
 [0301] -(substituted aryl);
 [0302] -heteroaryl;
 [0303] -(substituted heteroaryl);
 [0304] -heterocyclyl;
 [0305] -(substituted heterocyclyl);
 [0306] -CO-aryl; and
 [0307] -CO-heteroaryl;

[0308] each R₃₁₂ is independently chosen from hydrogen; C₁₋₁₀alkyl-heteroaryl; C₁₋₁₀alkyl-(substituted heteroaryl); C₁₋₁₀alkyl-aryl; C₁₋₁₀alkyl-(substituted aryl) and C₁₋₁₀alkyl;

[0309] v is 0 to 4;

[0310] and each R₁₂ present is independently chosen from C₁₋₁₀alkyl, C₁₋₁₀alkoxy, halogen and trifluoromethyl;



XIII

[0311] wherein

[0312] R_{113} is $\text{-alkyl-NR}_{313}\text{-SO}_2\text{-X-R}_{413}$ or $\text{-alkenyl-NR}_{313}\text{-SO}_2\text{-X-R}_{413}$;

[0313] X is a bond or $\text{-NR}_{513}\text{-}$;

[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-NR₃₁₃R₃₁₃;
- [0342] -(alkyl)₀₋₁-NR₃₁₃-CO-O-alkyl;

- [0343] -(alkyl)₀₋₁-NR₃₁₃-CO-alkyl;
- [0344] -(alkyl)₀₋₁-NR₃₁₃-CO-aryl;
- [0345] -(alkyl)₀₋₁-NR₃₁₃-CO-substituted aryl;
- [0346] -(alkyl)₀₋₁-NR₃₁₃-CO-heteroaryl;
- [0347] -(alkyl)₀₋₁-NR₃₁₃-CO-substituted heteroaryl;
- [0348] -N₃;
- [0349] -halogen;
- [0350] -haloalkyl;
- [0351] -haloalkoxy;
- [0352] -CO-haloalkyl;
- [0353] -CO-haloalkoxy;
- [0354] -NO₂;
- [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(R₃₁₃)₂;
 - [0372] -CO-N(R₃₁₃)₂;
 - [0373] -CO-C₁₋₁₀alkyl;
 - [0374] -CO-O-C₁₋₁₀alkyl;
 - [0375] -N₃;
 - [0376] -aryl;
 - [0377] -substituted aryl;
 - [0378] -heteroaryl;
 - [0379] -substituted heteroaryl;
 - [0380] -heterocyclyl;
 - [0381] -substituted heterocyclyl;
 - [0382] -CO-aryl;
 - [0383] -CO-(substituted aryl);

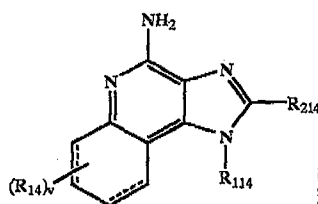
[0384] -CO-heteroaryl; and

[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-NR₃₁₄-CY-NR₅₁₄-X-R₄₁₄ or -alkenyl-NR₃₁₄-CY-NR₅₁₄-X-R₄₁₄

[0391] wherein

[0392] Y is =O or =S;

[0393] X is a bond, -CO- or -SO₂-;

[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 heterocyclyl;

[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-NR₃₁₄R₃₁₄;

[0421] -(alkyl)₀₋₁-NR₃₁₄-CO-O-alkyl;

[0422] -(alkyl)₀₋₁-NR₃₁₄-CO-alkyl;

[0423] -(alkyl)₀₋₁-NR₃₁₄-CO-aryl;

[0424] -(alkyl)₀₋₁-NR₃₁₄-CO-substituted aryl;

[0425] -(alkyl)₀₋₁-NR₃₁₄-CO-heteroaryl;

[0426] -(alkyl)₀₋₁-NR₃₁₄-CO-substituted heteroaryl;

[0427] -N₃;

[0428] -halogen;

[0429] -haloalkyl;

[0430] -haloalkoxy;

[0431] -CO-haloalkoxy;

[0432] -NO₂;

[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(R₃₁₄)₂;

[0450] -CO-N(R₃₁₄)₂;

- [0451] $-\text{CO}-\text{C}_{1-10}\text{alkyl}$;
 [0452] $-\text{CO}-\text{O}-\text{C}_{1-10}\text{alkyl}$;
 [0453] $-\text{N}_3$;
 [0454] -aryl;
 [0455] -substituted aryl;
 [0456] -heteroaryl;
 [0457] -substituted heteroaryl;
 [0458] -heterocyclyl;
 [0459] -substituted heterocyclyl;
 [0460] $-\text{CO}-\text{aryl}$;
 [0461] $-\text{CO}-(\text{substituted aryl})$;
 [0462] $-\text{CO}-\text{heteroaryl}$; and
 [0463] $-\text{CO}-(\text{substituted heteroaryl})$;

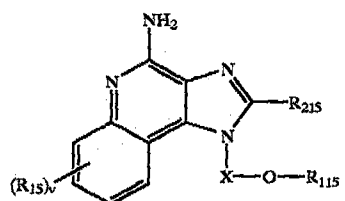
[0464] each R_{314} is independently chosen from hydrogen and $\text{C}_{1-10}\text{alkyl}$;

[0465] R_{514} is chosen from hydrogen, $\text{C}_{1-10}\text{alkyl}$, 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 $\text{C}_{1-10}\text{alkyl}$, $\text{C}_{1-10}\text{alkoxy}$, 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



[0469] wherein:

[0470] X is $-\text{CHR}_{515}-$, $-\text{CHR}_{515}\text{-alkyl}$ -, or $-\text{CHR}_{515}\text{-alkenyl}$ -;

[0471] R_{115} is chosen from:

- [0472] $-\text{R}_{415}-\text{CR}_{315}-\text{Z}-\text{R}_{615}\text{-alkyl}$;
 [0473] $-\text{R}_{415}-\text{CR}_{315}-\text{Z}-\text{R}_{615}\text{-alkenyl}$;
 [0474] $-\text{R}_{415}-\text{CR}_{315}-\text{Z}-\text{R}_{615}\text{-aryl}$;
 [0475] $-\text{R}_{415}-\text{CR}_{315}-\text{Z}-\text{R}_{615}\text{-heteroaryl}$;
 [0476] $-\text{R}_{415}-\text{CR}_{315}-\text{Z}-\text{R}_{615}\text{-heterocyclyl}$;
 [0477] $-\text{R}_{415}-\text{CR}_{315}-\text{Z}-\text{H}$;

- [0478] $-\text{R}_{415}-\text{NR}_{715}-\text{CR}_{315}-\text{R}_{615}\text{-alkyl}$;
 [0479] $-\text{R}_{415}-\text{NR}_{715}-\text{CR}_{315}-\text{R}_{615}\text{-alkenyl}$;
 [0480] $-\text{R}_{415}-\text{NR}_{715}-\text{CR}_{315}-\text{R}_{615}\text{-aryl}$;
 [0481] $-\text{R}_{415}-\text{NR}_{715}-\text{CR}_{315}-\text{R}_{615}\text{-heteroaryl}$;

[0482] $-\text{R}_{415}-\text{NR}_{715}-\text{CR}_{315}-\text{R}_{615}\text{-heterocyclyl}$; and

[0483] $-\text{R}_{415}-\text{NR}_{715}-\text{CR}_{315}-\text{R}_{815}$;

[0484] Z is $-\text{NR}_{515}-$, $-\text{O}-$, or $-\text{S}-$;

[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] $-\text{OH}$;
 [0497] -halogen;
 [0498] $-\text{N}(\text{R}_{515})_2$;
 [0499] $-\text{CO}-\text{N}(\text{R}_{515})_2$;
 [0500] $-\text{CO}-\text{C}_{1-10}\text{alkyl}$;
 [0501] $-\text{CO}-\text{O}-\text{C}_{1-10}\text{alkyl}$;
 [0502] $-\text{N}_3$;
 [0503] -aryl;
 [0504] -heteroaryl;
 [0505] -heterocyclyl;
 [0506] $-\text{CO}-\text{aryl}$; and
 [0507] $-\text{CO}-\text{heteroaryl}$;

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

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

[0510] each R_{515} is independently H or $\text{C}_{1-10}\text{alkyl}$;

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

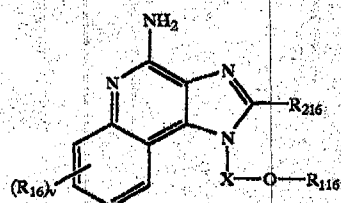
[0512] R_{715} is H, $\text{C}_{1-10}\text{alkyl}$, arylalkyl, or R_{415} and R_{715} can join together to form a 5 to 7 membered heterocyclic ring;

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

[0514] Y is $-\text{O}-$ or $-\text{S}(\text{O})_{0-2}-$;

[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 $-\text{CHR}_{516}-$, $-\text{CHR}_{516}\text{-alkyl-}$, or $-\text{CHR}_{516}\text{-alkenyl-}$;

[0519] R_{116} is chosen from:

[0520] $-\text{R}_{416}-\text{CR}_{316}-\text{Z-R}_{616}\text{-alkyl-}$;

[0521] $-\text{R}_{416}-\text{CR}_{316}-\text{Z-R}_{616}\text{-alkenyl-}$;

[0522] $-\text{R}_{416}-\text{CR}_{316}-\text{Z-R}_{616}\text{-aryl-}$;

[0523] $-\text{R}_{416}-\text{CR}_{316}-\text{Z-R}_{616}\text{-heteroaryl-}$;

[0524] $-\text{R}_{416}-\text{CR}_{316}-\text{Z-R}_{616}\text{-heterocyclyl-}$;

[0525] $-\text{R}_{416}-\text{CR}_{316}-\text{Z-H}$;

[0526] $-\text{R}_{416}-\text{NR}_{716}-\text{CR}_{316}-\text{R}_{616}\text{-alkyl-}$;

[0527] $-\text{R}_{416}-\text{NR}_{716}-\text{CR}_{316}-\text{R}_{616}\text{-alkenyl-}$;

[0528] $-\text{R}_{416}-\text{NR}_{716}-\text{CR}_{316}-\text{R}_{616}\text{-aryl-}$;

[0529] $-\text{R}_{416}-\text{NR}_{716}-\text{CR}_{316}-\text{R}_{616}\text{-heteroaryl-}$;

[0530] $-\text{R}_{416}-\text{NR}_{716}-\text{CR}_{316}-\text{R}_{616}\text{-heterocyclyl-}$; and

[0531] $-\text{R}_{416}-\text{NR}_{716}-\text{CR}_{316}-\text{R}_{616}$;

[0532] Z is $-\text{NR}_{516}-$, $-\text{O}-$, or $-\text{S}-$;

[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] $-\text{N}(\text{R}_{516})_2$;

[0547] $-\text{CO}-\text{N}(\text{R}_{516})_2$;

[0548] $-\text{CO}-\text{C}_{1-10}\text{alkyl}$;

[0549] $-\text{CO}-\text{O}-\text{C}_{1-10}\text{alkyl}$;

[0550] $-\text{N}_3$;

[0551] -aryl;

[0552] -heteroaryl;

[0553] -heterocyclyl;

[0554] $-\text{CO-aryl}$; and

[0555] $-\text{CO-heteroaryl}$;

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

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

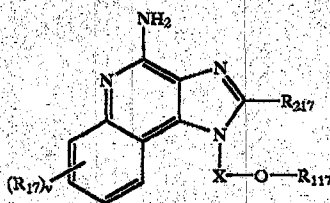
[0560] R_{716} is H, C_{1-10} alkyl, arylalkyl, or R_{416} and R_{716} can join together to form a 5 to 7 membered heterocyclic ring;

[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 $-\text{O}-$ or $-\text{S}(\text{O})_{0-2}-$;

[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 $-\text{CHR}_{317}-$, $-\text{CHR}_{317}\text{-alkyl-}$, or $-\text{CHR}_{317}\text{-alkenyl-}$;

[0567] R_{117} is chosen from:

[0568] -alkenyl;

[0569] -aryl; and

[0570] $-\text{R}_{417}\text{-aryl}$;

[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(R₃₁₇)₂;
 [0585] —CO—N(R₃₁₇)₂;
 [0586] —CO—C₁₋₁₀alkyl;
 [0587] —CO—O—C₁₋₁₀alkyl;
 [0588] —N₃;
 [0589] -aryl;
 [0590] -heteroaryl;
 [0591] -heterocyclyl;
 [0592] —CO-aryl; and
 [0593] —CO-heteroaryl;

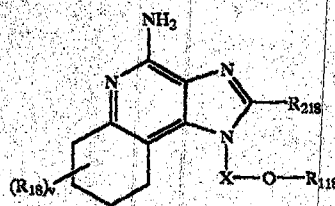
[0594] R₄₁₇ is alkyl or alkenyl, which may be interrupted by one or more —O— groups;

[0595] each R₃₁₇ is independently H or C₁₋₁₀alkyl;

[0596] each Y is independently —O— or —S(O)₀₋₂—;

[0597] v is 0 to 4; and

[0598] each R₁₇ present is independently chosen from C₁₋₁₀alkyl, C₁₋₁₀alkoxy, hydroxy, halogen and trifluoromethyl;



XVIII

[0599] wherein:

[0600] X is —CHR₃₁₈—, —CHR₃₁₈-alkyl-, or —CHR₃₁₈-alkenyl-;

[0601] R₁₁₈ is chosen from:

- [0602] -aryl;
 [0603] -alkenyl; and
 [0604] —R₄₁₈-aryl;

[0605] R₂₁₈ 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(R₃₁₈)₂;
 [0619] —CO—N(R₃₁₈)₂;
 [0620] —CO—C₁₋₁₀alkyl;
 [0621] —CO—O—C₁₋₁₀alkyl;
 [0622] —N₃;
 [0623] -aryl;
 [0624] -heteroaryl;
 [0625] -heterocyclyl;
 [0626] —CO-aryl; and
 [0627] —CO-heteroaryl;

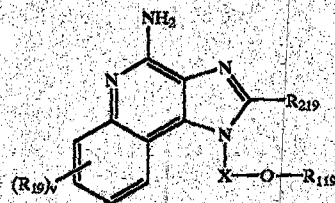
[0628] R₄₁₈ is alkyl or alkenyl, which may be interrupted by one or more —O— groups;

[0629] each R₃₁₈ is independently H or C₁₋₁₀alkyl;

[0630] each Y is independently —O— or —S(O)₀₋₂—;

[0631] v is 0 to 4; and

[0632] each R₁₈ present is independently chosen from C₁₋₁₀alkyl, C₁₋₁₀alkoxy, hydroxy, halogen and trifluoromethyl;



XIX

[0633] wherein:

[0634] X is —CHR₃₁₉—, —CHR₃₁₉-alkyl-, or —CHR₃₁₉-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] $-CO-heteroaryl$;

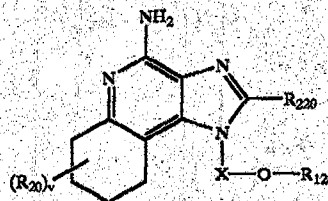
[0663] R_{419} is alkyl or alkenyl, which may be interrupted by one or more $-O-$ groups;

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

[0665] each Y is independently $-O-$ or $-S(O)_0$;

[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] $-CO-heteroaryl$;

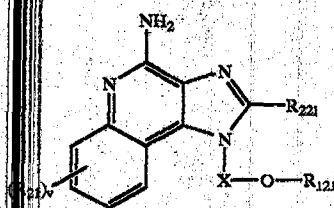
[0698] R_{420} is alkyl or alkenyl, which may be interrupted by one or more $-O-$ groups;

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

[0700] each Y is independently —O— or —S(O)_v—;

[0701] v is 0 to 4; and

[0702] each R₂₀ present is independently chosen from C₁₋₁₀alkyl, C₁₋₁₀alkoxy, hydroxy, halogen and trifluoromethyl;



XXI

[0703] wherein:

[0704] X is —CHR₅₂₁—, —CHR₅₂₁-alkyl-, or —CHR₅₂₁-alkenyl-;

[0705] R₁₂₁ is chosen from:

[0706] —R₄₂₁—NR₃₂₁—SO₂—R₆₂₁-alkyl;

[0707] —R₄₂₁—NR₃₂₁—SO₂—R₆₂₁-alkenyl;

[0708] —R₄₂₁—NR₃₂₁—SO₂—R₆₂₁-aryl;

[0709] —R₄₂₁—NR₃₂₁—SO₂—R₆₂₁-heteroaryl;

[0710] —R₄₂₁—NR₃₂₁—SO₂—R₆₂₁-heterocycl-

cyl;

[0711] —R₄₂₁—NR₃₂₁—SO₂—R₇₂₁;

[0712] —R₄₂₁—NR₃₂₁—SO₂—NR₅₂₁—R₆₂₁-alkyl;

[0713] —R₄₂₁—NR₃₂₁—SO₂—NR₅₂₁—R₆₂₁-alkenyl;

[0714] —R₄₂₁—NR₃₂₁—SO₂—NR₅₂₁—R₆₂₁-aryl;

[0715] —R₄₂₁—NR₃₂₁—SO₂—NR₅₂₁—R₆₂₁-heteroaryl;

[0716] —R₄₂₁—NR₃₂₁—SO₂—NR₅₂₁—R₆₂₁-heterocycl;

and

[0717] —R₄₂₁—NR₃₂₁—SO₂—NH₂;

[0718] R₂₂₁ is chosen from:

[0719] -hydrogen;

[0720] -alkyl;

[0721] -alkenyl;

[0722] -aryl;

[0723] -heteroaryl;

[0724] -heterocycl;

[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(R₅₂₁)₂;

[0732] —CO—N(R₅₂₁)₂;

[0733] —CO—C₁₋₁₀alkyl;

[0734] —CO—O—C₁₋₁₀alkyl;

[0735] —N₃;

[0736] -aryl;

[0737] -heteroaryl;

[0738] -heterocycl;

[0739] —CO-aryl; and

[0740] —CO-heteroaryl;

[0741] Y is —O— or —S(O)₀₋₂—;

[0742] R₃₂₁ is H, C₁₋₁₀alkyl, or arylalkyl;

[0743] each R₄₂₁ is independently alkyl or alkenyl, which may be interrupted by one or more —O— groups, or R₃₂₁ and R₄₂₁ can join together to form a 5 to 7 membered heterocyclic ring;

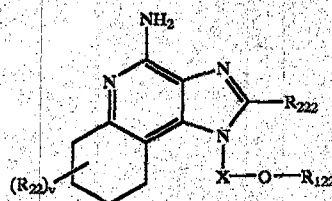
[0744] each R₅₂₁ is independently H, C₁₋₁₀alkyl, or C₂₋₁₀alkenyl;

[0745] R₆₂₁ is a bond, alkyl, or alkenyl, which may be interrupted by one or more —O— groups;

[0746] R₇₂₁ is C₁₋₁₀alkyl, or R₃₂₁ and R₇₂₁ can join together to form a 5 to 7 membered heterocyclic ring;

[0747] v is 0 to 4; and

[0748] each R₂₁ present is independently chosen from C₁₋₁₀alkyl, C₁₋₁₀alkoxy, hydroxy, halogen and trifluoromethyl;



XXII

[0749] wherein:

[0750] X is —CHR₅₂₂—, —CHR₅₂₂-alkyl-, or —CHR₅₂₂-alkenyl-;

[0751] R₁₂₂ is chosen from:

[0752] —R₄₂₂—NR₃₂₂—SO₂—R₆₂₂-alkyl;

[0753] —R₄₂₂—NR₃₂₂—SO₂—R₆₂₂-alkenyl;

[0754] —R₄₂₂—NR₃₂₂—SO₂—R₆₂₂-aryl;

[0755] —R₄₂₂—NR₃₂₂—SO₂—R₆₂₂-heteroaryl;

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- [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;

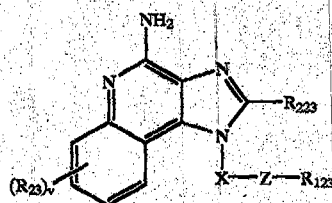
[0790] each R_{522} is independently H, C_{1-10} alkyl, or C_{2-10} alkenyl;

[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;



[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:

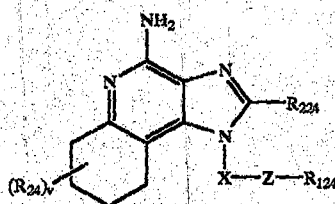
[0818] $-OH$;

[0819] -halogen;

[0820] $-N(R_{323})_2$;

- [0821] $-\text{CO}-\text{N}(\text{R}_{323})_2$;
 [0822] $-\text{CO}-\text{C}_{1-10}\text{alkyl}$;
 [0823] $-\text{CO}-\text{O}-\text{C}_{1-10}\text{alkyl}$;
 [0824] $-\text{N}_3$;
 [0825] -aryl;
 [0826] -heteroaryl;
 [0827] -heterocyclyl;
 [0828] $-\text{CO}-\text{aryl}$; and
 [0829] $-\text{CO}-\text{heteroaryl}$;

- [0830] each R_{323} is independently H or $\text{C}_{1-10}\text{alkyl}$;
 [0831] each R_{423} is independently alkyl or alkenyl;
 [0832] each Y is independently $-\text{O}-$ or $-\text{S}(\text{O})_0$;
 [0833] v is 0 to 4; and
 [0834] each R_{23} present is independently chosen from $\text{C}_{1-10}\text{alkyl}$, $\text{C}_{1-10}\text{alkoxy}$, hydroxy, halogen and trifluoromethyl;



XXIV

[0835] wherein:

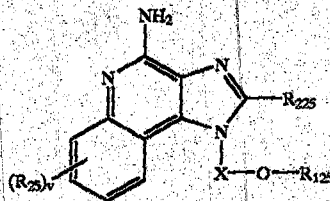
- [0836] X is $-\text{CHR}_{324}-$, $-\text{CHR}_{324}\text{-alkyl-}$, or $-\text{CHR}_{324}\text{-alkenyl-}$;
 [0837] Z is $-\text{S}-$, $-\text{SO}-$, or $-\text{SO}_2-$;
 [0838] R_{124} is chosen from:
 [0839] -alkyl;
 [0840] -aryl;
 [0841] -heteroaryl;
 [0842] -heterocyclyl;
 [0843] -alkenyl;
 [0844] $-\text{R}_{424}\text{-aryl}$;
 [0845] $-\text{R}_{424}\text{-heteroaryl}$; and
 [0846] $-\text{R}_{424}\text{-heterocyclyl}$;

[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] $-\text{OH}$;
 [0859] -halogen;
 [0860] $-\text{N}(\text{R}_{324})_2$;
 [0861] $-\text{CO}-\text{N}(\text{R}_{324})_2$;
 [0862] $-\text{CO}-\text{C}_{1-10}\text{alkyl}$;
 [0863] $-\text{CO}-\text{O}-\text{C}_{1-10}\text{alkyl}$;
 [0864] $-\text{N}_3$;
 [0865] -aryl;
 [0866] -heteroaryl;
 [0867] -heterocyclyl;
 [0868] $-\text{CO}-\text{aryl}$; and
 [0869] $-\text{CO}-\text{heteroaryl}$;

- [0870] each R_{324} is independently H or $\text{C}_{1-10}\text{alkyl}$;
 [0871] each R_{424} is independently alkyl or alkenyl;
 [0872] each Y is independently $-\text{O}-$ or $-\text{S}(\text{O})_0$;
 [0873] v is 0 to 4; and
 [0874] each R_{24} present is independently chosen from $\text{C}_{1-10}\text{alkyl}$, $\text{C}_{1-10}\text{alkoxy}$, hydroxy, halogen and trifluoromethyl;



XXV

[0875] wherein:

- [0876] X is $-\text{CHR}_{525}-$, $-\text{CHR}_{525}\text{-alkyl-}$, or $-\text{CHR}_{525}\text{-alkenyl-}$;
 [0877] R_{125} is chosen from:
 [0878] $-\text{R}_{425}-\text{NR}_{525}-\text{CR}_{325}-\text{NR}_{525}-\text{Z}-\text{R}_{625}$ -alkyl;
 [0879] $-\text{R}_{425}-\text{NR}_{525}-\text{CR}_{325}-\text{NR}_{525}-\text{Z}-\text{R}_{625}$ -alkenyl;
 [0880] $-\text{R}_{425}-\text{NR}_{525}-\text{CR}_{325}-\text{NR}_{525}-\text{Z}-\text{R}_{625}$ -aryl;
 [0881] $-\text{R}_{425}-\text{NR}_{525}-\text{CR}_{325}-\text{NR}_{525}-\text{Z}-\text{R}_{625}$ -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] $-CO-C_{1-10}alkyl$;

[0905] $-CO-O-C_{1-10}alkyl$;

[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 $C_{1-10}alkyl$;

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

[0916] R_{725} is H, $C_{1-10}alkyl$ 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, $C_{1-10}alkyl$, arylalkyl, or R_{425} and R_{825} can join together to form a 5 to 7 membered heterocyclic ring;

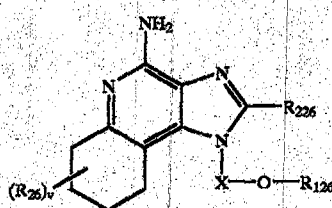
[0918] R_{925} is $C_{1-10}alkyl$ which can join together with R_{825} to form a 5 to 7 membered heterocyclic ring;

[0919] each Y is independently $-O-$ or $-S(O)_0$ -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 $C_{1-10}alkyl$, $C_{1-10}alkoxy$, 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(R₅₂₆)₂;
 [0951] —CO—N(R₅₂₆)₂;
 [0952] —CO—C₁₋₁₀alkyl;
 [0953] —CO—O—C₁₋₁₀alkyl;
 [0954] —N₃;
 [0955] -aryl;
 [0956] -heteroaryl;
 [0957] -heterocyclyl;
 [0958] —CO-aryl; and
 [0959] —CO-heteroaryl;

[0960] each R₃₂₆ is =O or =S;

[0961] each R₄₂₆ is independently alkyl or alkenyl, which may be interrupted by one or more —O— groups;

[0962] each R₅₂₆ is independently H or C₁₋₁₀alkyl;

[0963] R₆₂₆ is a bond, alkyl, or alkenyl, which may be interrupted by one or more —O— groups;

[0964] R₇₂₆ is H, C₁₋₁₀alkyl which may be interrupted by a hetero atom, or R₇₂₆ can join with R₅₂₆ to form a 5 to 7 membered heterocyclic ring;

[0965] R₈₂₆ is H, C₁₋₁₀alkyl, arylalkyl, or R₄₂₆ and R₈₂₆ can join together to form a 5 to 7 membered heterocyclic ring;

[0966] R₉₂₆ is C₁₋₁₀alkyl which can join together with R₈₂₆ 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 —SO₂—;

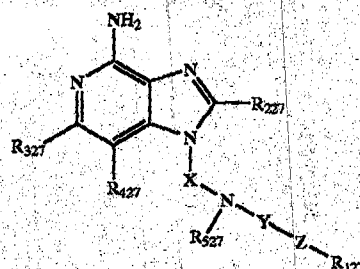
[0969] v is 0 to 4; and

[0970] each R₂₆ present is independently chosen from C₁₋₁₀alkyl, C₁₋₁₀alkoxy, 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] whercin

[0974] X is alkylene or alkenylene;

[0975] Y is —CO—, —CS—, or —SO₂—;

[0976] Z is a bond, —O—, —S—, or —NR₅₂₇—;

[0977] R₁₂₇ is aryl, heteroaryl, heterocyclyl, C₁₋₂₀alkyl or C₂₋₂₀alkenyl, 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(R₅₂₇)₂;

[0996] -(alkyl)₀₋₁-NR₅₂₇-CO—O-alkyl;

[0997] -(alkyl)₀₋₁-NR₅₂₇-CO-alkyl;

[0998] -(alkyl)₀₋₁-NR₅₂₇-CO-aryl;

[0999] -(alkyl)₀₋₁-NR₅₂₇-CO-heteroaryl;

[1000] —N₃;

[1001] -halogen;

- [1002] -haloalkyl;
- [1003] -haloalkoxy;
- [1004] —CO-haloalkyl;
- [1005] —CO-haloalkoxy;
- [1006] —NO₂;
- [1007] —CN;
- [1008] —OH;
- [1009] —SH; and in the case of alkyl, alkenyl, and heterocyclyl, oxo;
- [1010] R₂₂₇ 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(R₅₂₇)₂;
- [1024] —CO—N(R₅₂₇)₂;
- [1025] —CS—N(R₅₂₇)₂;
- [1026] —SO₂—N(R₅₂₇)₂;
- [1027] —NR₅₂₇—CO—C₁₋₁₀alkyl;
- [1028] —NR₅₂₇—CS—C₁₋₁₀alkyl;
- [1029] —NR₅₂₇—SO₂—C₁₋₁₀alkyl;
- [1030] —CO—C₁₋₁₀alkyl;
- [1031] —CO—O—C₁₋₁₀alkyl;
- [1032] —N₃;
- [1033] -aryl;
- [1034] -heteroaryl;
- [1035] -heterocyclyl;
- [1036] —CO-aryl; and
- [1037] —CO-heteroaryl;
- [1038] R₃₂₇ and R₄₂₇ are independently chosen from hydrogen, alkyl, alkenyl, halogen, alkoxy, amino, alkylamino, dialkylamino and alkylthio;
- [1039] each R₅₂₇ is independently H or C₁₋₁₀alkyl;
- [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, quinoxalyl, 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 qualities 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 compo-

ment, 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 myristate, 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 myristate, 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 pentaerythritol 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

Ingredient (Compendial Status)	Topical Cream (percentage weight-by-weight)							
	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)	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50
Solution, 20% w/w 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 μ L 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 Bio-Source 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	Control site
0	untreated	0	NA	96 $\pm$ 5
16	placebo	0	103 $\pm$ 8	71 $\pm$ 6
1	1%	6 $\pm$ 6	318 $\pm$ 33 ^c	96 $\pm$ 13
2	1%	0	1125 $\pm$ 74 ^c	124 $\pm$ 18
4	1%	0	1120 $\pm$ 51 ^c	129 $\pm$ 11
8	1%	24 $\pm$ 16	429 $\pm$ 56 ^c	91 $\pm$ 12
16	1%	6 $\pm$ 4	231 $\pm$ 22 ^c	87 $\pm$ 27
24	1%	32 $\pm$ 32	198 $\pm$ 28 ^c	103 $\pm$ 13
48	1%	49 $\pm$ 49	74 $\pm$ 10	69 $\pm$ 15
MCP-1				
0	untreated	81 $\pm$ 30	NA	44 $\pm$ 2
16	placebo	144 $\pm$ 9	144 $\pm$ 41	42 $\pm$ 3
1	1%	86 $\pm$ 29	40 $\pm$ 8	42 $\pm$ 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 $\pm$ 31	234 $\pm$ 29 ^c	50 $\pm$ 4
4	1%	101 $\pm$ 28	723 $\pm$ 89 ^c	41 $\pm$ 5
8	1%	438 $\pm$ 91 ^c	1474 $\pm$ 202 ^c	38 $\pm$ 3
16	1%	424 $\pm$ 96 ^c	1209 $\pm$ 325 ^c	31 $\pm$ 5
24	1%	187 $\pm$ 39	813 $\pm$ 151 ^c	39 $\pm$ 1
48	1%	141 $\pm$ 24	145 $\pm$ 48 ^c	36 $\pm$ 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 $\geq$ 650	<650
16	1%	<200	<650	<650
24	1%	<200	<650	<650
48	1%	<200	<650	<650

^aFemale hairless CD rats were dosed topically with cream formulated Compound 1.

^bTNF- 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 $\pm$ SEM.

^cIndicates $p < 0.05$ 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	Control Site
0	None (untreated)	89 $\pm$ 11	NA	20 $\pm$ 10
24	Placebo	41 $\pm$ 14	42 $\pm$ 15	28 $\pm$ 6
8	Multiple 0.1%	71 $\pm$ 13	784 $\pm$ 48 ^c	42 $\pm$ 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)	Post Dose	Dose	Cytokine Concentration ^b MCP-1	
			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

^aFemale hairless CD rats were dosed topically with cream formulated Compound 1.

^bMCP-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.

^cIndicates 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)	Post Dose	Dose	Cytokine Concentration ^b MCP-1	
			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

^aFemale hairless CD rats were dosed topically with cream formulated Compound 1.

^bMCP-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.

^cIndicates 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)		0.50	0.50	0.50	0.35	0.50 0.50
Solution, 20% w/w						
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 $\pm$ 15	NA	70 $\pm$ 11
16	placebo	42 $\pm$ 9	131 $\pm$ 32	69 $\pm$ 11
1	1%	38 $\pm$ 38	44 $\pm$ 14	35 $\pm$ 19
2	1%	2 $\pm$ 2	75 $\pm$ 20 ^c	33 $\pm$ 13
4	1%	3 $\pm$ 3	321 $\pm$ 18 ^c	62 $\pm$ 20
8	1%	0	894 $\pm$ 180 ^c	21 $\pm$ 9
16	1%	12 $\pm$ 12	377 $\pm$ 45 ^c	22 $\pm$ 12

TABLE 6-continued

Cytokine Concentrations in Rat Serum and Dermal Tissue Following Application of the Topical Formulation of Example 11 Full Time Course ^a				
24	1%	16 $\pm$ 8	285 $\pm$ 15 ^c	52 $\pm$ 14
48	1%	24 $\pm$ 7	74 $\pm$ 9	65 $\pm$ 13
MCP-1				
0	untreated	100 $\pm$ 20	NA	33 $\pm$ 7
16	placebo	144 $\pm$ 9	225 $\pm$ 106	22 $\pm$ 4
1	1%	117 $\pm$ 17	56 $\pm$ 9	55 $\pm$ 9
2	1%	126 $\pm$ 29	50 $\pm$ 13	54 $\pm$ 8
4	1%	136 $\pm$ 29	161 $\pm$ 18 ^c	71 $\pm$ 9
8	1%	189 $\pm$ 28	1020 $\pm$ 319	45 $\pm$ 15
16	1%	297 $\pm$ 35	1294 $\pm$ 122 ^c	40 $\pm$ 9
24	1%	217 $\pm$ 12	1044 $\pm$ 185 ^c	41 $\pm$ 11
48	1%	120 $\pm$ 22	134 $\pm$ 14 ^c	34 $\pm$ 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 $\pm$ 571	<650
16	1%	<65	1330 $\pm$ 386 ^c	<650
24	1%	<65	<650	<650
48	1%	<65	<650	<650

^aFemale hairless CD rats were dosed topically with cream formulated Compound 2.

^bTNF- 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 $\pm$ SEM.

^cIndicates $p < 0.05$ 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 $\pm$ 58	NA	80 $\pm$ 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	321 ± 62	1173 ± 117 ^c	86 ± 14
	0.1%			
24	Multiple	217 ± 43	388 ± 80 ^c	58 ± 5
	0.1%			
16	Single	205 ± 32	1448 ± 241 ^c	77 ± 15
	0.1%			
24	Single	279 ± 45	1172 ± 288 ^c	90 ± 15
	0.1%			

^aFemale hairless CD rats were dosed topically with cream formulated Compound 2.

^bMCP-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.

^cIndicates $p < 0.05$ 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	293 ± 76	44 ± 10	36 ± 12
	(Comparative Example C1)			
16	0.01%	276 ± 50	257 ± 85	57 ± 20
	(Example 8)			
16	0.03%	318 ± 86	210 ± 10	45 ± 9
	(Example 9)			
16	0.10%	529 ± 141	2622 ± 616 ^c	73 ± 9
	(Example 10)			
16	1.0%	345 ± 51	3166 ± 470 ^c	71 ± 11
	(Example 11)			
24	0.01%	298 ± 65	276 ± 87	94 ± 32
	(Example 8)			
24	0.03%	253 ± 34	427 ± 238	28 ± 14
	(Example 9)			
24	0.10%	331 ± 93	1461 ± 264 ^c	19 ± 7
	(Example 10)			

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%	358 ± 52	1952 ± 185 ^c	17 ± 6
	(Example 11)			

^aFemale hairless CD rats were dosed topically with cream formulated Compound 2.

^bMCP-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.

^cIndicates $p < 0.05$ 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

Ingredients	Topical Creams (percentage weight-by-weight)				
	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	10.00	10.00	10.00	10.00	10.00
USA - NF					
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

^aAvailable under the trade name PRIPURE 3786 from Uniqema, New Castle, DE

^bAvailable 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

Ingredients	Topical Creams (percentage weight-by-weight)					
	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	10.00	10.00	10.00	10.00	10.00	10.00
USA - NF	—	—	—	—	—	—
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	10	10	10	10
USA - NF	—	—	—	—
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

Ingredient	Model Formulation (percentage weight-by-weight)						
	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

Ingredient	Model Formulation (percentage weight-by-weight)					
	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

Ingredient	Model Formulation (percentage weight-by-weight)					
	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	B
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 3 rats 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 μ L 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 Bio-Source 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			24 hours			Placebo Cream		
Example	Serum	Untreated	Serum	Treated	Untreated	Serum	Untreated	
31	212	54	267	606	125	142	59	
32	26	59	79	82	69	54	56	
33	54	71	56	74	58	54	56	
34	72	58	59	319	69	54	56	
35	170	55	162	142	62	80	58	
36	94	46	86	1216	96	80	58	
37	153	38	136	2036	77	80	58	
38	178	120	211	121	86	142	59	
39	193	61	259	263	59	142	59	
40	226	58	284	1086	95	142	59	
41	54	96	45	88	71	73	96	
42	65	78	54	126	88	73	96	
43	77	68	89	1016	93	73	96	
44	86	*	177	498	*	128	**28	
45	172	*	157	1041	*	128	**28	
46	177	*	406	1023	*	128	**28	
47	58	59	81	95	73	37	73	
48	71	61	63	112	61	37	73	
49	92	62	83	1436	75	37	73	
50	170	56	*	655	56	88	*	
51	625	787	*	149	787	88	*	
52	811	314	*	86	314	88	*	
53	70	46	76	47	45	7	31	
54	68	27	71	26	24	7	31	
55	75	21	44	33	32	7	31	
56	115	*	115	425	*	201	**42	
57	119	*	267	1252	*	201	**42	
58	190	*	476	1508	*	201	**42	
59	155	36	271	41	53	107	54	
60	123	58	175	80	69	107	54	
61	133	52	151	1131	46	107	54	
62	143	55	174	428	61	96	26	
63	320	51	230	1217	74	96	26	
64	970	529	425	390	99	96	26	
65	43	57	46	81	61	83	59	
66	29	28	32	42	74	83	59	
67	19	61	25	34	72	83	59	
68	60	82	91	72	35	68	72	
69	143	52	99	73	59	68	72	
70	59	34	91	134	60	68	72	
71	259	62	134	84	57	177	53	
72	138	65	122	990	63	177	53	
73	251	63	293	1411	108	177	53	
74	99	71	73	99	89	61	91	
75	76	78	3	170	73	61	91	
76	66	54	188	4949	104	61	91	
77	28	95	21	43	40	30	38	
78	27	37	33	49	59	30	38	
79	24	40	27	50	38	30	38	
80	51	23	50	163	0	97	15	
81	9	15	83	34	10	97	15	
82***	61	0	121	303	45	97	15	
82***	50	140	79	225	76	93	120	
83	110	164	61	275	172	93	120	
84	59	177	98	629	40	93	120	
85	81	0	0	0	0	177	0	
86	116	0	0	0	0	177	0	
87	69	0	0	0	0	177	0	
88	114	56	87	43	42	141	33	
89	74	47	132	49	40	141	33	
90	91	96	111	109	41	141	33	
91	42	91	86	874	57	34	46	
92	83	1238	92	1087	67	34	46	
93	98	2037	114	1124	74	34	46	
94	102	98	48	136	133	110	100	
95	49	130	95	158	112	110	100	
96	68	253	132	528	81	110	100	
97	34	88	54	95	92	36	102	

TABLE 16-continued

MCP-1 (pg/ml)								
IRM Cream								
6 hours			24 hours			Placebo Cream		
Example	Serum	Treated	Untreated	Serum	Treated	Untreated	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 separate 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

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

TABLE 17-continued

Topical Creams (percentage weight-by-weight)					
Ingredients	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	—	—	—

nol (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 BioSource 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

<u>Cytokine Induction</u>										
IRM Cream Treated Animals							Normal Animals			
Cream of	<u>MCP-1 (pg/ml)</u>			<u>TNF-α (pg/ml)</u>			<u>MCP-1 (pg/ml)</u>		<u>TNF-α (pg/ml)</u>	
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

[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 μ L 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-mercaptoetha-

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 1 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-1-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}-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.

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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(19) **United States**(12) **Patent Application Publication**
Oommen et al.(10) **Pub. No.: US 2004/0089855 A1**(43) **Pub. Date: May 13, 2004**(54) **HIGH OLEIC ACID OIL COMPOSITIONS
AND METHODS OF MAKING AND
ELECTRICAL INSULATION FLUIDS AND
DEVICES COMPRISING THE SAME**Jan. 6, 1997, now Pat. No. 5,949,017, which is a
continuation-in-part of application No. 08/665,721,
filed on Jun. 18, 1996, now abandoned.(75) **Inventors: Thottathil V. Oommen, Raleigh, NC
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PHILADELPHIA, PA 19103 (US)**(73) **Assignee: ABB Technology AG**(21) **Appl. No.: 10/663,089**(22) **Filed: Sep. 15, 2003****Related U.S. Application Data**(63) **Continuation of application No. 09/928,000, filed on
Aug. 10, 2001, now Pat. No. 6,645,404, which is a
continuation of application No. 09/321,653, filed on
May 28, 1999, now Pat. No. 6,274,067, which is a
continuation of application No. 08/778,608, filed on****ABSTRACT**

High oleic acid triglyceride compositions that comprise fatty acid components of at least 75% oleic acid, less than 10% diunsaturated fatty acid component; less than 3% triunsaturated fatty acid component; and less than 8% saturated fatty acid component; and having the properties of a dielectric strength of at least 35 KV/100 mil gap, a dissipation factor of less than 0.05% at 25NC, acidity of less than 0.03 mg KOH/g, electrical conductivity of less than 1 pS/m at 25NC, a flash point of at least 250NC and a pour point of at least -15NC are disclosed. Electrical insulation fluids comprising the triglyceride composition are disclosed. Electrical insulation fluids that comprise the triglyceride composition and a combination of additives are disclosed. Electrical apparatuses comprising the electrical insulation fluids and the use of electrical insulation fluids to provide insulation in electrical apparatuses are disclosed. A process for preparing the high oleic acid triglyceride composition is disclosed.

HIGH OLEIC ACID OIL COMPOSITIONS AND METHODS OF MAKING AND ELECTRICAL INSULATION FLUIDS AND DEVICES COMPRISING THE SAME

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation in part application of Ser. No. 08/665,721 filed Jun. 18, 1996, pending, which is incorporated herein by reference.

FIELD OF THE INVENTION

[0002] The invention relates to a high oleic oil composition useful as an electrical insulation fluid, to electrical insulation fluid compositions and electrical apparatuses which comprise the same. The high oleic oil compositions of the invention have electrical properties which make them well suited as insulation fluids in electrical components.

BACKGROUND OF THE INVENTION

[0003] The electrical industry uses a variety of insulating fluids which are easily available and cost effective. Examples are mineral oil, silicone fluid, and synthetic hydrocarbon oils used in transformers, power cables and capacitors. Examples of such fluids include those described in U.S. Pat. No. 4,082,866 issued Apr. 4, 1978 to Link, U.S. Pat. No. 4,206,066 issued Jun. 3, 1980 to Rinehart, U.S. Pat. No. 4,621,302 issued Nov. 4, 1986 to Sato et al., U.S. Pat. No. 5,017,733 issued May 21, 1991 to Sato et al. U.S. Pat. No. 5,250,750 issued Oct. 5, 1993 to Shubkin et al., and U.S. Pat. No. 5,336,847 issued Aug. 9, 1994 to Nakagami, which are each incorporated herein by reference.

[0004] Many of these fluids are not considered to be biodegradable in a reasonable time frame. Some have electrical properties which render them less than optimal. In recent years regulatory agencies have become increasingly concerned about oil spills which can contaminate the ground soil and other areas. A biodegradable oil would be desirable for electrical apparatus such as transformers used in populated areas and shopping centers.

[0005] Vegetable oils are fully biodegradable, but the oils presently available in the market are not electrical grade. A few vegetable oils such as rapeseed oil and castor oil have been used in limited quantities, mostly in capacitors, but these are not oleic esters.

[0006] There is a need for a fully biodegradable electrical fluid. There is a need for electrical apparatuses which comprise such an oil. There is a need for a method of processing vegetable oil to electrical grade.

SUMMARY OF THE INVENTION

[0007] The present invention relates to high oleic acid triglyceride compositions that comprise fatty acid components of at least 75% oleic acid, less than 10% diunsaturated fatty acid component; less than 3% triunsaturated fatty acid component; and less than 8% saturated fatty acid component; and wherein said composition is further characterized by the properties of a dielectric strength of at least 35 KV/100 mil (2.5 mm) gap, a dissipation factor of less than 0.05% at 25NC, acidity of less than 0.03 mg KOH/g,

electrical conductivity of less than 1 pS/m at 25NC, a flash point of at least 250NC and a pour point of at least -15NC.

[0008] The present invention relates to an electrical insulation fluid comprising at least 75% of a high oleic acid triglyceride composition that comprise fatty acid components of at least 75% oleic acid, less than 10% diunsaturated fatty acid component; less than 3% triunsaturated fatty acid component; and less than 8% saturated fatty acid component; and wherein said composition is further characterized by the properties of a dielectric strength of at least 35 KV/100 mil gap, a dissipation factor of less than 0.05% at 25NC, acidity of less than 0.03 mg KOH/g, electrical conductivity of less than 1 pS/m at 25NC, a flash point of at least 250NC and a pour point of at least -15NC, and one or more additive selected from the group of an antioxidant additive, a pour point depressant additive and a copper deactivator.

[0009] In some preferred embodiments the electrical insulation fluid comprises a pour point depressant additive, which in some embodiments is polymethacrylate.

[0010] In some preferred embodiments the electrical insulation fluid comprises a combination of antioxidant additives. In some preferred embodiments, the electrical insulation fluid comprises a combination of IRGANOX L-57 antioxidant and IRGANOX L-109 antioxidant.

[0011] In some preferred embodiments the electrical insulation fluid comprises a copper deactivator. In some preferred embodiments, the copper deactivator is IRGAMET-30 metal deactivator.

[0012] In some preferred embodiments that antioxidant additives and copper deactivators make up about 0.2-2.0% of electrical insulation fluid. It is preferred that the additives comprise a combination of IRGANOX L-57 antioxidant, IRGANOX L-109 antioxidant and IRGAMET-30 metal deactivator. It is preferred that the combination is provided at a ratio of about 1 part IRGANOX L-57 antioxidant to 2-4 parts IRGANOX L-109 antioxidant to about 1 part IRGAMET-30 metal deactivator.

[0013] In some preferred embodiments, the electrical insulation fluid comprises at least 94% of the high oleic acid triglyceride composition. In some preferred embodiments, the electrical insulation fluid comprises fatty acid components of: at least 75% oleic acid, less than 10% linoleic acid, less than 3% linolenic acid, less than 4% stearic acid, and less than 4% palmitic acid. In some preferred embodiments the electrical insulation fluid is characterized by the properties of: a dielectric strength of at least 40 KV/100 mil gap, a dissipation factor of less than 0.02% at 25NC, acidity of less than 0.02 mg KOH/g, electrical conductivity of less than 0.25 pS/m at 25NC, a flash point of at least 300NC, and a pour point of at least -20NC, and in some embodiments, at least -40NC. In some preferred embodiments the electrical insulation fluid comprises 0.5-1.0%, in some embodiments 0.5%, of the combination of IRGANOX L-57 antioxidant, IRGANOX L-109 antioxidant and IRGAMET-30 metal deactivator. In some preferred embodiments the combination of IRGANOX L-57 antioxidant, IRGANOX L-109 antioxidant and IRGAMET-30 metal deactivator has a ratio of about 1 part IRGANOX L-57 antioxidant to about 3 parts IRGANOX L-109 antioxidant to about 1 part IRGAMET-30 metal deactivator.

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[0014] The present invention relates to electrical apparatuses comprising the electrical insulation fluid.

[0015] The present invention relates to the use of electrical insulation fluid to provide insulation in electrical apparatuses.

[0016] The present invention relates to a process for preparing the high oleic acid triglyceride composition comprising the steps of combining refined, bleached and deodorized high oleic acid triglyceride with clay to form a mixture and filtering the mixture to remove the clay.

DETAILED DESCRIPTION OF THE INVENTION

[0017] This present invention provides a novel application for high oleic vegetable oils as electrical insulation fluids. Vegetable oils usually have a high percent of triglyceride esters of saturated and unsaturated organic acids. When the acid is saturated, the triglyceride is either a semi-solid or a liquid with high freezing point. Unsaturated acids produce oils with low freezing points. However, monounsaturated acids are preferred over diunsaturated and triunsaturated acids because the latter tend to dry fast in air due to cross-linking with oxygen. Increasing the amount of diunsaturates and triunsaturates makes the oil more vulnerable to oxidation; increasing the saturates raises the pour point. Ideally, the higher the monosaturate content, the better the oil as an electrical fluid.

[0018] Oleic acid is a monounsaturated acid found as triglyceride ester in many natural oils such as sunflower, olive oil and safflower in relatively high proportions (above 60%). High oleic acid content is usually above 75% of the total acid content. Oleic acid content above 80% is achieved by genetic manipulation and breeding. Two oils that are currently available in the United States with high oleic acid content and low saturates are sunflower oil and canola oil. These oils are of value in producing high quality lubricating oils but have not been used in the production of electrical insulation fluids.

[0019] High oleic oils may be derived from plant seeds such as sunflower and canola which have been genetically modified to yield high oleic content. The pure oils are triglycerides of certain fatty acids with a carbon chain ranging from 16 to 22 carbon atoms. If the carbon chain has no double bonds, it is a saturated oil, and is designated Cn:0 where n is the number of carbon atoms. Chains with one double bond are monounsaturated and are designated Cn:1; with two double bonds, it will be Cn:2 and with three double bonds Cn:3. Oleic acid is a C18:1 acid while erucic acid is a C22:1 acid. The acids are in the combined state as triglycerides, and when the oils are hydrolyzed they are separated into the acid and glycerol components. High oleic oils contain more than 75% oleic acid (in combined state with glycerol), the remaining being composed mainly of C18:0, C18:2 and C18:3 acids (also in combined state with glycerol). These acids are known as stearic, linoleic and linolenic. Oils with a high percentage of double and triple unsaturated molecules are unsuitable for electrical application because they react with air and produce oxidation products. Monounsaturated oils such as oleic acid esters may also react with air, but much slower, and can be stabilized with oxidation inhibitors.

[0020] A typical 85% high oleic oil has the following approximate composition:

Saturates:	3-5%
monounsaturates:	84-85%
diunsaturates:	3-7%
triunsaturates:	1-3%

[0021] While the present invention provides for the use of vegetable oils, the invention may use synthetic oil having the same compositional characteristics of those oils isolated from plants. While plant derived material is suitable for almost all applications, synthetic material may provide a desirable alternative in some applications.

[0022] According to the present invention, high oleic acid content oils are used as starting materials for the production of an oil composition which has physical properties useful for electrical insulation fluids. The present invention provides the processed compositions having specific structural and physical characteristics and properties, methods of making such composition, electrical insulation fluids which comprise the composition, electrical apparatuses which comprise the electrical insulation fluids and methods of insulating electrical apparatuses using such fluids.

[0023] The present invention provides a high oleic acid triglyceride composition useful as an electrical insulation fluid and more particularly as a component material of an electrical insulation fluid. A triglyceride composition is a glycerol backbone linked to three fatty acid molecules. The triglyceride compositions of the invention comprise fatty acid components of at least 75% oleic acid. The remaining fatty acid components include less than 10% diunsaturated fatty acid component, less than 3% triunsaturated fatty acid component; and less than 8% saturated fatty acid component.

[0024] The triglyceride compositions of the invention preferably comprise fatty acid components of at least 80% oleic acid. The triglyceride compositions of the invention more preferably comprise fatty acid components of at least 85% oleic acid. In some embodiments, the triglyceride compositions of the invention comprise fatty acid components of 90% oleic acid. In some embodiments, the triglyceride compositions of the invention comprise fatty acid components of greater than 90% oleic acid.

[0025] Di-unsaturated, triunsaturated and saturated fatty acid components present in the triglyceride are preferably C16-C22. It is preferred that 80% or more of the remaining fatty acid components are C18 diunsaturated, triunsaturated and saturated fatty acids, i.e. linoleic, linolenic and stearic acids, respectively. In some embodiments, the diunsaturated, triunsaturated and saturated fatty acid components of the triglyceride comprise at least 75% oleic acid, less than 3% linoleic acid, less than 4% stearic acid and less than 4% palmitic acid (saturated C16).

[0026] The triglyceride compositions of the invention are of an electric grade. That is, they have specific physical properties which make them particularly suited for use as an electrical insulation fluid. The dielectric strength of a triglyceride composition of the invention is at least 35 KV/100 mil (2.5 mm) gap, the dissipation factor is less than 0.05%

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at 25NC, the acidity is less than 0.03 mg KOH/g, the electrical conductivity is less than 1 pS/m at 25NC, the flash point is at least 250NC and the pour point is at least -15NC.

[0027] The dielectric strength, dissipation factor, acidity, electrical conductivity, flash point and pour point are each measured using the published standards set forth in the Annual Book of ASTM Standards (in Volumes 5 and 10) published by the American Society for Testing Materials (ASTM), 100 Barr Harbor Drive West Conshohocken Pa. 19428, which is incorporated herein by reference. The dielectric strength is determined using ASTM test method D 877. The dissipation factor is determined using ASTM test method D 924. The acidity is determined using ASTM test method D 974. The electrical conductivity is determined using ASTM test method D 2624. The flash point is determined using ASTM test method D 92. The pour point is determined using ASTM test method D 97.

[0028] The dielectric strength is measured by taking 100-150 ml oil sample in a test cell and applying a voltage between test electrodes separated by a specified gap. The breakdown voltage is noted. The test is preferably run five times and the average value is calculated. The dielectric strength of a triglyceride composition of the invention is at least 35 KV/100 mil (2.5 mm) gap. In some preferred embodiments, it is 40 KV/100 mil (2.5 mm) gap.

[0029] The dissipation factor is a measure of the electrical loss due to conducting species and is tested by measuring the capacitance of fluids in a test cell using a capacitance bridge. The dissipation factor of a triglyceride composition of the invention is less than 0.05% at 25C. In some preferred embodiments, it is less than 0.02%. In some preferred embodiments, it is less than 0.01%.

[0030] The acidity is measured by titrating a known volume of oil with a solution of alcoholic KOH to neutralization point. The weight of the oil in grams per mg KOH is referred to interchangeably as the acidity number or the neutralization number. The acidity of a triglyceride composition of the invention is less than 0.03 mg KOH/g. In some preferred embodiments, it is less than 0.02 mg KOH/g.

[0031] The electrical conductivity is measured using a conductivity meter such as an Emcee meter. The electrical conductivity of a triglyceride composition of the invention is less than 1 pS/m at 25NC. In some preferred embodiments, it is less than 0.25 pS/m.

[0032] The flash point is determined by placing an oil sample in a flashpoint tester and determining the temperature at which it ignites. The flash point of a triglyceride composition of the invention is at least 250NC. In some preferred embodiments, it is at least 300NC.

[0033] The pour point is determined by cooling an oil sample with dry ice/acetone and determining the temperature at which the liquid becomes a semi-solid. The pour point of a triglyceride composition of the invention is not greater than -15NC. In some preferred embodiments, it is not greater than -20NC. In some preferred embodiments, it is not greater than -40NC.

[0034] In some preferred embodiments, the triglyceride composition of the invention is characterized by the properties of a dielectric strength of at least 40 KV/100 mil (2.5 mm) gap, a dissipation factor of less than 0.02% at 25NC,

acidity of less than 0.02 mg KOH/g, electrical conductivity of less than 0.25 pS/m at 25NC, a flash point of at least 300NC and a pour point of not greater than -20NC. In some preferred embodiments, the pour point is not greater than -40NC.

[0035] In some preferred embodiments, the triglyceride composition of the invention comprises fatty acid components of at least 75% oleic acid, linoleic acid at a proportion of less than 10%, linoleic acid at a proportion of less than 3%, stearic acid in a proportion of less than 4%, and palmitic acid in a proportion of less than 4%, and is characterized by the properties of a dielectric strength of at least 40 KV/100 mil (2.5 mm) gap, a dissipation factor of less than 0.02% at 25NC, acidity of less than 0.02 mg KOH/g, electrical conductivity of less than 0.25 pS/m at 25NC, a flash point of at least 300NC and a pour point of not greater than -20NC. In some preferred embodiments, the pour point is not greater than -40NC.

[0036] Triglycerides with high oleic acid oil content are described in U.S. Pat. No. 4,627,192 issued Dec. 4, 1986 to Fick and U.S. Pat. No. 4,743,402 issued May 10, 1988 to Fick, which are incorporated herein by reference. These oils or those with similar fatty acid component content according to the present invention may be processed to yield an oil with the desired physical properties. High oleic vegetable oils may be obtained from commercial suppliers as RBD oils (refined, bleached and deodorized) which are further processed according to the present invention to yield high oleic oils useful in electrical insulation fluid compositions. There are several suppliers of high oleic RBD oils in the USA and overseas. RBD oil useful as a starting material for further processing may be obtained from SVO Specialty Products, Eastlake Ohio, and Cargill Corp., Minneapolis Minn. The oil manufacturer goes through an elaborate process to obtain RBD oil during which all nonoil components (gums, phospholipids, pigments etc.) are removed. Further steps may involve winterization (chilling) to remove saturates, and stabilization using nontoxic additives. The processes for converting oil to RBD oil are described in *Bailey's Industrial Oil and Fat Products*, Vols. 1, 2 & 3, Fourth Edition 1979 John Wiley & Sons and in *Bleaching and Purifying Fats and Oils* by H. B. W. Patterson, AOCC Press, 1992, which are incorporated herein by reference.

[0037] RBD oils are further processed according to the present invention in order to yield an oil with the physical properties as defined herein. The purification of the as received oil designated RBD oil is necessary because trace polar compounds and acidic materials still remain in the oil, making it unfit as an electrical fluid. The purification process of the present invention uses clay treatment which involves essentially a bleaching process using neutral clay. RBD oil is combination with 10% by weight clay and mixed for at least about 20 minutes. It is preferred if the oil is heated to about 60-80NC. It is preferred if the mixture is agitated. The clay particles are removed subsequently by a filter press. Vacuum conditions or a neutral atmosphere (by nitrogen) during this process prevent oxidation. Slightly stabilized oil is preferable. More stabilizer is added at the end of the process. The purity is monitored by electrical conductivity, acidity and dissipation factor measurement. Further treatment by deodorization techniques is possible but not essential. The polar compounds that interfere most with electrical properties are organometallic compounds such as metallic

soaps, chlorophyll pigments and so on. The level of purification needed is determined by the measured properties and the limits used. An alternative embodiment provides passing RBD oil through a clay column. However, stirring with clay removes trace polar impurities better than passing through a clay column. In preferred embodiments, neutral Attapulgite clay, typically 30/60 mesh size, is used in a ratio of 1-10% clay by weight. In some embodiments, clay particles are removed using filters, preferably paper filters with a pore size of 1-5 μm . The clay is preferably mixed with hot oil and agitated for several minutes, after which the clay is filtered off using filters. Paper or synthetic filter sheets may be used if a filter separator is used. The filter sheets are periodically replaced.

[0038] Electrical insulation fluids of the invention comprise the triglyceride composition of the invention and may further comprise one or more additives. Additives include oxidation inhibitors, copper deactivators and pour point depressors.

[0039] Oxidation inhibitors may be added to the oils. Oxidation stability is desirable but in sealed units where there is no oxygen, it should not be critical. Commonly used oxidation inhibitors include butylated hydroxy toluene (BHT), butylated hydroxy anisole (BHA) and mono-tertiary butyl hydro quinone (TBHQ). In some embodiments, oxidation inhibitors are used in combinations such as BHA and BHT. Oxidation inhibitors may be present at levels of 0.1-3.0%. In some preferred embodiments, 0.2% TBHQ is used. Oxidation stability of the oil is determined by AOM or OSI methods well known to those skilled in the art. In the AOM method, the oil is oxidized by air at 100NC and the formation of peroxide is monitored. The time to reach 100 milliequivalents (meq) or any other limit is determined. The higher the value, the more stable the oil is. In the OSI method, the time to reach an induction period is determined by the measurement of conductivity.

[0040] Since copper is always present in the electrical environment, another type of additive is copper deactivators. Copper deactivators such as benzotriazole derivatives are commercially available. The use of these in small, such as below 1%, may be beneficial in reducing the catalytic activity of copper in electrical apparatus. In some embodiments, the electrical insulation fluid contains less than 1% of a copper deactivator. In some embodiments, the copper deactivator is a benzotriazole derivative.

[0041] According to some preferred embodiments the present invention, a combination of additives set forth herein particularly is effective when used in combination with high oleic acid triglyceride compositions to form electrical insulation fluids. The additives include a combination of combination of. The combination of additives included in the electrical insulation fluid of the invention include three additives: IRGANOX L-57 antioxidant, IRGANOX L-109 antioxidant and IRGAMET-30 metal deactivator which are each commercially available from CIBA-GEIGY, Inc. (Tarrytown, N.Y.). The combination of additives is present in a combined total in the fluid at between 0.2 and 2.0%, preferably between 0.5-1.0%. In some preferred embodiments, the combination of additives is present at about 0.5%.

[0042] The combination of additives may be present in a ratio of about 1 part IRGANOX L-57 antioxidant to about 24 parts IRGANOX L-109 antioxidant to about 1 part IRGA-

MET-30 metal deactivator. In some preferred embodiment, the combination of additives is present in a ratio of about 1 part IRGANOX L-57 antioxidant to about 3 parts IRGANOX L-109 antioxidant to about 1 part IRGAMET-30 metal deactivator.

[0043] IRGANOX L-57 antioxidant is commercially available from CIBA/GEIGY and is a liquid mixture of alkylated diphenylamines; specifically the reaction products of reacting N-Phenylbenzenamine with 2,4,4-trimethylpentane.

[0044] IRGANOX L-109 antioxidant is commercially available from CIBA/GEIGY and is a high molecular weight phenolic antioxidant, bis(3,5-di-tert-butyl-4-hydroxyhydrocinnamate. IRGANOX L-109 antioxidant is a bis(2,6-di-tert-butylphenol derivative.

[0045] IRGAMET-30 metal deactivator metal deactivator is commercially available from CIBA/GEIGY and is a triazole derivative, N,N-bis (2-Ethylhexyl)-1H-1,2,4-triazole-1 methanamine.

[0046] IRGANOX L-57 antioxidant and IRGANOX L-109 antioxidant are antioxidants, and IRGAMET-30 metal deactivation is a copper passivator. In electrical apparatuses, copper is widely used as conductor and copper has a catalytic effect in the oxidation of oil. The antioxidants react with free oxygen thereby preventing the latter from attacking the oil.

[0047] Pour point depressants may also be added if low pour points are needed. Commercially available products can be used which are compatible with vegetable-based oils. Only low percentages, such as 2% or below, are needed normally to bring down the pour point by 10 to 15NC. In some embodiments, the pour point depressant is polymethacrylate (PMA).

[0048] In some embodiments, the pour point may be further reduced by winterizing processed oil. Essentially, the oils are winterized by lowering the temperature to near or below 0NC and removing solidified components. The winterization process may be performed as a series of temperature reductions followed by removal of solids at the various temperature. In some embodiments, winterization is performed by reducing the temperature serially to 5N, 0N and -12NC for several hours, and filtering the solids with diatomaceous earth.

[0049] In some embodiments, the electrical insulation fluid of the invention that comprises at least 75 percent triglyceride composition of the invention as described above further comprises about 0.1-5% additives and then up to about 25% other insulating fluids such as mineral oil, synthetic esters, and synthetic hydrocarbons. In some embodiments, the electrical insulation fluid comprises 1-24% of insulating fluids selected from the group consisting of mineral oil, synthetic esters, synthetic hydrocarbons and combination of two or more of such materials. In some embodiments, the electrical insulation fluid comprises 5-15% of insulating fluids selected from the group consisting of mineral oil, synthetic esters, synthetic hydrocarbons and combination of two or more of such materials. Examples of mineral oils include poly alpha olefins. An example of a mineral oil which may be used as part of the present invention is RTEemp, Cooper Power Fluid Systems. Examples of synthetic esters include polyol esters. Com-

mercially available synthetic esters which can be used as part of the invention include those sold under the trade names MIDEL 7131 (The Micanite and Insulators Co., Manchester UK), REOLEC 138 (FMC, Manchester, UK) and ENVIROTEMP 200 (Cooper Power Fluid Systems). In some preferred embodiments, the electrical insulation fluid comprises at least 85% of the triglyceride composition of the invention. In some preferred embodiments, the electrical insulation fluid comprises at least 95% of the triglyceride composition of the invention.

[0050] According to some preferred embodiments of the present invention, high oleic acid content oils are used as starting materials for the production of an oil composition which has physical properties useful for electrical insulation fluids. The high oleic acid content oils are combined with a preferred combination of antioxidant and metal deactivating additives to provide electrical insulation fluids. Some preferred embodiments of the present invention relates to such electrical insulation fluids, to electrical apparatuses which comprise the electrical insulation fluids and methods of insulating electrical apparatuses using such fluids.

[0051] In some embodiments, the electrical insulation fluid of the invention that comprises at least 75 percent triglyceride composition of the invention as described above further comprises about 0.1-5% additives, including preferably 0.5-2.0% combination of IRGANOX L57 antioxidant, IRGANOX L-109 antioxidant and IRGAMET-30 metal deactivator, and then up to about 24.5% other insulating fluids such as mineral oil, synthetic esters, and synthetic hydrocarbons. In some embodiments, the electrical insulation fluid comprises 1-24% of insulating fluids selected from the group consisting of mineral oil, synthetic esters, synthetic hydrocarbons and combination of two or more of such materials. In some embodiments, the electrical insulation fluid comprises 3-20% of insulating fluids selected from the group consisting of mineral oil, synthetic esters, synthetic hydrocarbons and combination of two or more of such materials. In some embodiments, the electrical insulation fluid comprises 5-15% of insulating fluids selected from the group consisting of mineral oil, synthetic esters, synthetic hydrocarbons and combination of two or more of such materials.

[0052] The present invention relates to an electrical apparatus which comprises the electrical insulation fluid of the invention. The electrical apparatus may be an electrical transformer, an electrical capacitor or an electrical power cable. U.S. Pat. No. 4,082,866, U.S. Pat. No. 4,206,066, U.S. Pat. No. 4,621,302, U.S. Pat. No. 5,017,733, U.S. Pat. No. 5,250,750, and U.S. Pat. No. 5,336,847, which are referred to above and incorporated herein by reference describe various applications of electrical insulation fluids for which the electrical insulation fluid of the invention may be used. In addition, U.S. Pat. No. 4,993,141 issued Feb. 19, 1991 to Grimes et al., U.S. Pat. No. 4,890,086 issued Dec. 26, 1989 to Hill, U.S. Pat. No. 5,025,949 issued Jun. 25, 1991 to Adkins et al., U.S. Pat. No. 4,972,168 issued Nov. 20, 1990 to Grimes et al., U.S. Pat. No. 4,126,844, and U.S. Pat. No. 4,307,364 issued Dec. 22, 1981 to Lanoue et al., which are each hereby incorporated herein by reference contain descriptions of various electrical apparatuses in which the electrical insulation fluid of the invention may be used. In

some preferred embodiments, the electrical apparatus of the invention is a transformer, in particular, a power transformer or a distribution transformer.

EXAMPLES

Example 1

[0053] Several high oleic oils were further purified and stabilized according to the present invention to make them electrically suitable. Electrical tests showed that such purified oils had properties similar to currently used high temperature fluids in distribution transformers. Table 1 compares the properties of the purified oils of the present invention with currently used fluids.

TABLE 1

Comparison of Purified Vegetable Oils with High Temperature Fluids Used in Transformers			
	High Oleic Veg. Oil	High Temp. Mineral Oil ^a	Synthetic Ester Fluid ^b
Dielectric Strength, KV/100 mil gap	42.4	40-45	50
Dissipation Factor, % at 25 NC	0.02	0.01	0.1
Neutr. No. mg KOH/g	0.05	—	0.03
Electrical Conductivity pS/m, 25 NC	0.25-1.0	(0.1 to 10)*	(5.0)*
Flash Point	328 NC	275-300 NC	257 NC
Pour Point	-28 NC	-24 NC	-48 N

^aRTTemp, Cooper Power Fluid Systems

^bPolyol Esters (such as MIDEL 7131 and REOLEC 138) deduced from resistivity
The properties listed for the high oleic oil are for purified oils with no additives.

Example 2

[0054] The purification of the as received oil designated RBD oil (refined, bleached and deodorized) is necessary because trace polar compounds and acidic materials still remain in the oil, making it unfit as an electrical fluid. The purification we attempted involved clay treatment as follows: approximately 1 gal. of the RBD oil was treated with 10% Attapulgite clay. Oil was produced with electrical conductivity of less than 1 pS/m. The attapulgite treated oil showed conductivities as low as 0.25 pS/m. Commercial grade oils had conductivities in the range of 1.5 to 125 pS/m. Conductivity below 1 pS/m (or resistivity above 10¹⁴ ohm.cm) is desired for electrical grade oil. Other indicators of purity are dissipation factor and neutralization number (acid number). Dissipation factor is a measure of electrical losses due to conduction caused by conducting species, usually organometallic trace components, and should be below 0.05% at room temperature. The clay treated oils had dissipation factor of 0.02%. Untreated RBD oils had DF ranging from 0.06% to 2.0%. With a finer grade of clay, the same results could be achieved with only 2% of clay. A filter separator was preferred to a filter column.

Example 3

[0055] Oxidation stability tests were conducted on treated and untreated oil samples using ASTM and AOCS methods.

The untreated and treated RBD oils failed the tests. Oxidation inhibitors were added to the oils and the tests were repeated. Several oxidation inhibitors were tested: BHT (Butylated Hydroxy Toluene, BHA (Butylated Hydroxy Anisole) and TBHQ (mono-Tertiary Butyl Hydro Quinone) in 0.2% by weight in oil. In the AOCs method used (Cd 12.57) 100 ml samples are bubbled with air at 100C, and the peroxide formation was measured at several time intervals. Hours to reach 100 meq of peroxide were noted. Since copper is always present in the electrical environment, all oil samples had copper wire placed in them. With no additive, the time to reach the limit was 18 hours; with additive (0.2%), the times were 100 hours for BHT+BHA. With TBHQ, even after 400 hours, the peroxide value reached only 8.4 meq. TBHQ proved to be the best antioxidant of the three. Without an oxidation inhibitor the oils upon oxidation would produce hydroperoxide which is then converted to acids, alcohols, esters, aldehydes, ketones and polymer structures. Most electrical apparatus that use a fluid insulation operate in low oxygen or oxygen-free environment, so the concern over oxidation is not great.

Example 4

[0056] The pour point of the treated oil was typically -25NC. To lower the pour point further, the treated oils were winterized at 5N, 0N and -12NC for several hours, and the solids that separated were filtered with diatomaceous earth. The lowest pour point reached so far was -38NC, close to the specified value of -40NC for transformer oil. Further lowering is possible by extended winterization. Another approach is by the use of pour point depressants such as PMA (polymethacrylate) which has been used for mineral oil.

Example 5

[0057] A laboratory oxidation stability test was conducted using the OSI (Oil Stability Index) Method, AOCs Cd 12b-92. The additives were used in a 1:3:1 ratio at several concentrations in both the high oleic vegetable oil and in regular mineral oil used in transformers. In the OSI method, 50 ml of the oil is taken in a conductivity cell, and is placed in a bath kept at 110°C. Air is bubbled through it at 2.5 ml/min. The effluent air containing the volatile fatty acids is passed through a vessel containing deionized water. The conductivity of the water is monitored as a function of time. When the antioxidant is consumed, a sudden rise in conductivity is observed. This taken as the end point. The number of hours is noted as the OSI value at 110°C. It is usual to convert these values to a 97.8°C OSI value to correspond to the temperature used in another oil stability test, the AOM (Active Oxygen Method), A.O.C.S Cd 12-57.

[0058] Table 2 summarizes the test results:

TABLE 2

OSI Values in Hours for Various Oils			
	OSI, 110°C	OSI, 97.8°C	AOM, 97.8°C
High Oleic Veg. oil with Cu	1.3	3.0	3.1
Same, with 0.2% TBHQ	13.5	31.3	32.6
Same, with 0.2% CIBA	79.7	185.2	192.8
Same, with 0.5% CIBA	226	526	548

TABLE 2-continued

OSI Values in Hours for Various Oils			
	OSI, 110°C	OSI, 97.8°C	AOM, 97.8°C
Transformer oil (mineral oil) + Cu	162	377	392
High Temp. Mineral Oil + Cu	137	315	328

[0059] Compositions which comprise the additives at 0.5% concentration in oil is as effective as regular transformer oil, and more effective than the high temperature mineral oil used in some transformers. Another superiority of the combination of additives is that the oil conductivity at 0.5% concentration below 2 pS/m, compared to 4.5 pS/m for oil with 0.2% TBHQ.

EXAMPLE 6

[0060] Mixing the composition with other fluids can result in the lowering of pour point. For example, the electrical insulation fluid was mixed with regular mineral oil (pour point of -50°C or below) and at a 5% concentration in the mixture (i.e. final electrical insulator fluid includes 5% mineral oil), the pour point was reduced to -40°C. In another embodiment, the electrical insulation fluid was mixed with the synthetic ester Reolec 138 and at a 10% concentration in the mixture (i.e. final electrical insulator fluid includes 10% synthetic ester), the pour point was lowered to -42°C. The above fluid may, for example, be mixed with regular mineral oil.

What is claimed is:

1. A high oleic acid triglyceride composition comprising fatty acid components of

at least 75% oleic acid

less than 10% diunsaturated fatty acid component C16-C22;

less than 3% triunsaturated fatty acid C16-C22 component; and

less than 8% saturated fatty acid component C16-C22; and

wherein said composition is further characterized by the properties of:

a dielectric strength of at least 35 KV/100 mil gap

a dissipation factor of less than 0.05% at 25NC

acidity of less than 0.03 mg KOH/g

electrical conductivity of less than 1 pS/m at 25NC

a flash point of at least 250NC and

a pour point of at least -15NC.

2. The high oleic acid triglyceride composition of claim 1 comprising fatty acid components of

at least 75% oleic acid

less than 10% linoleic acid

less than 3% linolenic acid

less than 4% stearic acid, and

less than 4% palmitic acid.

3. The high oleic acid triglyceride composition of claim 2 wherein said composition is further characterized by the properties of:

- a dielectric strength of at least 40 KV/100 mil gap,
- a dissipation factor of less than 0.02% at 25NC,
- acidity of less than 0.02 mg KOH/g,
- electrical conductivity of less than 0.25 pS/m at 25NC,
- a flash point of at least 300NC, and
- a pour point of at least -20NC.

4. The high oleic acid triglyceride composition of claim 3 wherein said composition is further characterized by a pour point of at least -40NC.

5. The high oleic acid triglyceride composition of claim 1 comprising fatty acid components of

- at least 75% oleic acid
- less than 10% linoleic acid
- less than 3% linolenic acid
- less than 4% stearic acid, and
- less than 4% palmitic acid

wherein said composition is further characterized by the properties of:

- a dielectric strength of at least 40 KV/100 mil gap,
- a dissipation factor of less than 0.02% at 25NC,
- acidity of less than 0.02 mg KOH/g,
- electrical conductivity of less than 0.25 pS/m at 25NC,
- a flash point of at least 300NC, and
- a pour point of at least -20NC.

6. The high oleic acid triglyceride composition of claim 5 wherein said composition is further characterized by a pour point of at least 40NC.

7. An electrical insulation fluid comprising:

- at least 75% of the high oleic acid triglyceride composition of claim 1
- 0.1-3% antioxidant additive.

8. The electrical insulation fluid of claim 7 wherein said antioxidant additive is selected from the group consisting of butylated hydroxy toluene, butylated hydroxy anisole and mono-tertiary butyl hydro quinone.

9. The electrical insulation fluid of claim 7 wherein said antioxidant additive is mono-tetra hydro quinone.

10. The electrical insulation fluid of claim 9 comprising up to 2% mono-tetra hydro quinone.

11. The electrical insulation fluid of claim 7 comprising at least 94% of the high oleic acid triglyceride composition.

12. The electrical insulation fluid of claim 7 further comprising a pour point depressant additive.

13. The electrical insulation fluid of claim 12 wherein said pour point depressant is polymethacrylate.

14. The electrical insulation fluid of claim 7 further comprising a copper deactivator additive, said electrical insulation fluid comprising less than 1% of said copper deactivator.

15. The electrical insulation fluid of claim 7 wherein said copper deactivator is a benzotriazole derivative.

16. The electrical insulation fluid of claim 7 further comprising up to 25% of mineral oil, synthetic esters, synthetic hydrocarbons and combinations thereof.

17. The electrical insulation fluid of claim 16 comprising 3-20% mineral oil, synthetic esters and/or synthetic hydrocarbons.

18. The electrical insulation fluid of claim 17 comprising 5-15% mineral oil, synthetic esters and/or synthetic hydrocarbons.

19. The electrical insulation fluid of claim 18 comprising 5-15% synthetic esters and/or synthetic hydrocarbons.

20. An electrical apparatus comprising the electrical insulation fluid of claim 7.

21. The electrical apparatus of claim 20 wherein said apparatus is an electrical transformer, an electrical capacitor or an electrical power cable.

22. The electrical insulation fluid of claim 7 comprising 0.2-2.0% of a combination of IRGANOX L-57 antioxidant, IRGANOX L-109 antioxidant and IRGAMET-30 metal deactivator, said combination having a ratio of about 1 part IRGANOX L-57 antioxidant to 24 parts IRGANOX L-109 antioxidant to about 1 part IRGAMET-30 metal deactivator

23. The electrical insulation fluid of claim 22 wherein said electrical insulation fluid is further characterized by a pour point of at least 40NC.

24. The electrical insulation fluid of claim 22 comprising 0.5-1.0% of said combination of IRGANOX L-57 antioxidant, IRGANOX L-109 antioxidant and IRGAMET-30 metal deactivator.

25. The electrical insulation fluid of claim 24 wherein said combination of IRGANOX L57 antioxidant, IRGANOX L-109 antioxidant and IRGAMET-30 metal deactivator has a ratio of about 1 part IRGANOX L-57 antioxidant to about 3 parts IRGANOX L-109 antioxidant to about 1 part IRGAMET-30 metal deactivator.

26. The electrical insulation fluid of claim 22 wherein said combination of IRGANOX L57 antioxidant, IRGANOX L-109 antioxidant and IRGAMET-30 metal deactivator has a ratio of about 1 part IRGANOX L-57 antioxidant to about 3 parts IRGANOX L-109 antioxidant to about 1 part IRGAMET-30 metal deactivator.

27. The electrical insulation fluid of claim 22 comprising about 0.5% of said combination of IRGANOX L-57 antioxidant, IRGANOX L-109 antioxidant and IRGAMET-30 metal deactivator.

28. The electrical insulation fluid of claim 27 comprising fatty acid components of

- at least 75% oleic acid
- less than 10% linoleic acid
- less than 3% linolenic acid
- less than 4% stearic acid, and
- less than 4% palmitic acid

wherein said composition is further characterized by the properties of:

- a dielectric strength of at least 40 KV/100 mil gap,
- a dissipation factor of less than 0.02% at 25NC,
- acidity of less than 0.02 mg KOH/g,
- electrical conductivity of less than 0.25 pS/m at 25NC,
- a flash point of at least 300NC, and
- a pour point of at least -20NC.

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29. The electrical insulation fluid of claim 28 wherein said composition is further characterized by a pour point of at least -40NC.

30. The electrical insulation fluid of claim 28 comprising at least 94% of the high oleic acid triglyceride composition.

31. The electrical insulation fluid of claim 30 further comprising a pour point depressant additive.

32. The electrical insulation fluid of claim 31 wherein said pour point depressant is polymethacrylate.

33. The electrical insulation fluid of claim 22 comprising about 0.5% of said combination of IRGANOX L-57 antioxidant, IRGANOX L-109 antioxidant and IRGAMET-30 metal deactivator.

34. The electrical insulation fluid of claim 22 further comprising a pour point depressant additive.

35. The electrical insulation fluid of claim 34 wherein said pour point depressant is polymethacrylate.

36. The electrical insulation fluid of claim 22 further comprising 1-24% mineral oil, synthetic esters and/or synthetic hydrocarbons.

37. The electrical insulation fluid of claim 36 comprising 3-30% mineral oil, synthetic esters and/or synthetic hydrocarbons.

38. The electrical insulation fluid of claim 37 comprising 5-15% mineral oil, synthetic esters and/or synthetic hydrocarbons.

39. The electrical insulation fluid of claim 38 comprising 5-15% synthetic esters and/or synthetic hydrocarbons.

40. An electrical apparatus comprising the electrical insulation fluid of claim 22.

41. The electrical apparatus of claim 40 wherein said apparatus is an electrical transformer, an electrical capacitor or an electrical power cable.

42. An electrical apparatus comprising the electrical insulation fluid of claim 28.

43. A process for preparing the high oleic acid triglyceride composition of claim 1 comprising the steps of:

mixing 10 parts refined, bleached and deodorized high oleic acid triglyceride with 1 part or less by weight neutral clay to form a mixture

maintaining said mixture for at least about 20 minutes, and

filtering said mixture to remove said clay.

44. The process of claim 43 wherein said clay is 30/60 mesh size clay.

* * * * *

2020
Bogotá, D.C.,

Doctor:
Juan Pablo Cadena Sarmiento
Apoderado

Oficio N°: 09210

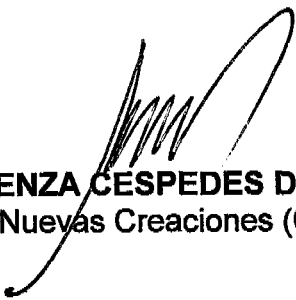
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Radicación PCT N°	08-88449
Trámite	011
Evento	378
Actuación	440
Folios	010

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 Cielo Ángela Peña Rodríguez, en su calidad de apoderada de Procaps 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 N° 10 de 2001.


LIX CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (C).

El anterior oficio fue notificado por fijación en lista de fecha, 23 JUL. 2010.

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