

**(19) AUSTRALIAN PATENT OFFICE**

(54) Title  
Immune response modifier formulations and methods

(51)<sup>6</sup> International Patent Classification(s)  
**A61K** 31/44 (2006.01) 20060101AFI2006092  
A61K 31/44 2BHAU  
PCT/US2005/008576

(21) Application No: 2005222995 (22) Application Date: 2005 .03 .14

(87) WIPO No: W005/089317

(30) Priority Data

(31) Number	(32) Date	(33) Country
60/553,148	2004 .03 .15	US

(43) Publication Date : 2005 .09 .29

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(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
29 September 2005 (29.09.2005)

PCT

(10) International Publication Number  
WO 2005/089317 A3

(51) International Patent Classification:  
A61K 31/44 (2006.01)

(21) International Application Number:  
PCT/US2005/008576

(22) International Filing Date: 14 March 2005 (14.03.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
60/553,148 15 March 2004 (15.03.2004) US

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM,

AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CI, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GII, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))

Published:

- with international search report

(88) Date of publication of the international search report:  
27 July 2006

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: IMMUNE RESPONSE MODIFIER FORMULATIONS AND METHODS

(57) Abstract: Pharmaceutical formulations including an immune response modifier (IRM) compound having a 2-aminopyridine moiety fused to a five-membered nitrogen-containing heterocyclic ring; a preservative system including a sorbic acid preservative selected from the group consisting of sorbic acid, esters thereof, salts thereof, and combinations thereof; an antioxidant; and an optional chelating agent.

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5 **IMMUNE RESPONSE MODIFIER FORMULATIONS AND METHODS****CROSS-REFERENCE TO RELATED APPLICATIONS**

The present invention claims priority to U.S. Provisional Patent Application  
Serial No. 60/553148, filed on March 15, 2004, which is incorporated herein by  
10 reference.

**BACKGROUND**

There has been a major effort in recent years to find compounds that modulate  
the immune system. Examples of such compounds, which have demonstrated cytokine  
15 inducing and immunomodulating activity, are disclosed in U.S. Patent Nos. 4,689,338;  
4,929,624; 5,266,575; 5,268,376; 5,346,905; 5,352,784; 5,389,640; 5,446,153;  
5,482,936; 5,756,747; 6,110,929; 6,194,425; 6,331,539; 6,376,669; 6,451,810;  
6,525,064; 6,541,485; 6,545,016; 6,545,017; 6,573,273; 6,656,938; 6,660,735;  
6,660,747; 6,664,260; 6,664,264; 6,664,265; 6,667,312; 6,670,372; 6,677,347;  
20 6,677,348; 6,677,349; 6,683,088; 6,756,382; 6,797,718; and 6,818,650; and U.S. Patent  
Publication Nos. 2004/0091491; 2004/0147543; and 2004/0176367. .

Many of these compounds, also known as immune response modifiers (IRMs),  
are small organic molecules, for example, imidazoquinoline amine derivatives (see, e.g.,  
U.S. 4,689,338), but a number of other compound classes are known as well (see, e.g.,  
25 U.S. 5,446,153), and more are still being discovered.

Pharmaceutical formulations containing IRM compounds are disclosed in U.S.  
Patent Nos. 5,238,944; 5,939,090; and 6,425,776; European Patent 0 394 026; and U.S.  
Patent Publication 2003/0199538. Many such formulations include preservatives such  
as methylparaben, sorbic acid, propylene glycol, etc.

30 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)- $\alpha$  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.

Accordingly, in view of their importance and potential benefit, there is a continuing need for new formulations of these unique compounds.

#### SUMMARY OF THE INVENTION

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, e.g., 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); degradation of excipients; poor permeation; and undesired systemic delivery of the topically applied IRM compound.

It has now been found that formulations of IRM compounds containing a 2-aminopyridine moiety fused to a five-membered nitrogen-containing heterocyclic ring in combination with sorbic acid may suffer impaired stability of both the IRM compound and the sorbic acid. However, it has further been found that addition of a pharmaceutically acceptable antioxidant compound to the formulation can reduce degradation of the IRM compound and sorbic acid, thereby providing improved stability. Sorbic acid and related salts and esters are often used as preservative systems

and can be particularly suitable for use in a multi-dose dispenser formulation (see, for example, U.S. Patent No. 6,245,776 (Skwicrzynski et al.)), but stability is an important issue for formulations and can reduce shelf life of a product or even jeopardize regulatory approvability.

5           In particular, it appears that IRMs containing a 2-aminopyridine moiety fused to a five-membered nitrogen-containing heterocyclic ring interact with preservatives such as sorbic acid, resulting in decreased concentrations (relative to the initial concentrations in the freshly prepared formulation) of both the IRM and preservative, with the resulting formation of unwanted impurities. Although not intending to be  
10 bound to any particular theory or mechanism, it is hypothesized that these IRMs interact with intermediates and products resulting from autoxidation of the sorbic acid preservative.

          It has been discovered that stability can be improved through the addition of a compound acting as an antioxidant. The antioxidant may beneficially have hydrogen  
15 atom donating functionality. Moreover, when an antioxidant compound is included with the IRM compound and sorbic acid, stability of the formulation may be further improved by adding a chelating agent.

          In one embodiment, the present invention provides a pharmaceutical formulation that includes: an immune response modifier (IRM) compound having a 2-  
20 aminopyridine moiety fused to a five-membered nitrogen-containing heterocyclic ring; a preservative system that includes sorbic acid, esters thereof, salts thereof, or combinations thereof; and an antioxidant.

          A chelating agent may also beneficially be included in any of the formulations described herein. Furthermore, a fatty acid, a hydrophobic, aprotic component miscible  
25 with the fatty acid and including a hydrocarbyl group of 7 or more carbon atoms, or combinations thereof, may also be included in any of the formulations described herein.

          For example, in another embodiment, the present invention provides a pharmaceutical formulation that includes: an immune response modifier (IRM) compound having a 2-aminopyridine moiety fused to a five-membered nitrogen-  
30 containing heterocyclic ring; a preservative system that includes a sorbic acid

preservative selected from the group consisting of sorbic acid, esters thereof, salts thereof, and combinations thereof; an antioxidant having hydrogen atom donating functionality; a fatty acid; and a hydrophobic, aprotic component miscible with the fatty acid and having a hydrocarbyl group of 7 or more carbon atoms. A chelating agent may also beneficially be included.

In another embodiment, the present invention provides a pharmaceutical formulation that includes: 0.001% by weight to 5.0% by weight of an immune response modifier (IRM) compound having a 2-aminopyridine moiety fused to a five-membered nitrogen-containing heterocyclic ring (preferably, an imidazonaphthyridine amine, and more preferably 2-methyl-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine); a preservative system; 0.001% by weight to 0.2% by weight of an antioxidant having hydrogen atom donating functionality; 0 to 0.1% by weight of a chelating agent; 1% by weight to 30% by weight of a fatty acid; 1% by weight to 15% by weight of a medium-chain triglyceride; 0.2% by weight to 2.0% by weight of a viscosity enhancing agent; 0.1% by weight to 6.0% by weight of an emulsifier; and water; wherein the formulation has a pH of 4.0 to 6.0 and the weight percentages are based on the total weight of the formulation. In this embodiment, the preservative system includes: 0.02% by weight to 0.2% by weight of a sorbic acid preservative selected from the group consisting of sorbic acid, esters thereof, salts thereof, and combinations thereof; 0 to 10.0% by weight of a preservative enhancing solubilizer; and 0.05% by weight to 0.2% by weight of a secondary preservative compound.

Certain embodiments of the present invention include a hydrophilic viscosity agent, such as those selected from cellulose ethers and carbomers. If used, the hydrophilic viscosity agent is preferably present in an amount of 0.2% by weight to 2.0% by weight. Other useful additives include, for example, a pH adjuster, an emulsifier, or combinations thereof.

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In a further embodiment, the present invention provides a pharmaceutical formulation that includes:

- 0.001% by weight to 5.0% by weight of an imidazonaphthyridine amine;
- 0.02% by weight to 0.2% by weight of a sorbic acid preservative selected
- 5 from the group consisting of sorbic acid, esters thereof, salts thereof, and combinations thereof;
- 0 to 10.0% by weight of propylene glycol;
- 0.05% by weight to 0.2% by weight of methylparaben;
- 0.001% by weight to 0.2% by weight of butylated hydroxyanisole, butylated
- 10 hydroxytoluene, or combinations thereof;
- 0 to 0.1% by weight of ethylenediaminetetraacetic acid, a hydrate thereof, a salt thereof, a hydrate of the salt thereof, or combinations thereof;
- 1% by weight to 30% by weight of isostearic acid;
- 1% by weight to 15% by weight of a medium-chain triglyceride;
- 15 0.2% by weight to 2.0% by weight of a carbomer;
- 0.1% by weight to 6.0% by weight of a poloxamer; and
- water.

In this embodiment, the formulation has a pH of 4.0 to 6.0 and the weight percentages are based on the total weight of the formulation.

- 20 The present invention also provides methods.

In one embodiment, the present invention provides a method of stabilizing a pharmaceutical formulation that includes: an immune response modifier (IRM) compound having a 2-aminopyridine moiety fused to a five-membered nitrogen-

containing heterocyclic ring; and a preservative system that includes a sorbic acid preservative selected from the group consisting of sorbic acid, esters thereof, salts thereof, and combinations thereof. The method includes adding an antioxidant and optionally a chelating agent to the formulation.

5 In another embodiment, the present invention provides a method for delivering an immune response modifier (IRM) to a dermal surface. The method includes selecting a formulation of the present invention and applying the selected formulation to the dermal and/or mucosal surface.

10 In another embodiment, the present invention provides a method of treating a dermal associated condition (particularly, actinic keratosis). The method includes applying to a dermal surface of a patient in need thereof a pharmaceutical formulation of the present invention.

As used herein, a "sorbic acid preservative" means sorbic acid, esters of sorbic acid, salts of sorbic acid, or combinations thereof.

15 As used herein "remains substantially constant" means that the concentration of sorbic acid preservative in an IRM-containing formulation does not decrease by more than 15% of the initial concentration (i.e., its concentration when initially formulated) when stored for at least 6 months at 40°C and 75% relative humidity.

20 As used herein, "a" or "an" or "the" are used interchangeably with "at least one," to mean "one or more" of the listed element.

The above summary of the present invention is not intended to describe each disclosed embodiment or every implementation of the present invention. The description that follows more particularly exemplifies illustrative embodiments. In several places throughout the application, guidance is provided through lists of  
25 examples, which examples can be used in various combinations. In each instance, the recited list serves only as a representative group and should not be interpreted as an exclusive list.



## DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

The present invention provides pharmaceutical formulations that include an immune response modifier containing a 2-aminopyridine fused to a five-membered nitrogen-containing heterocyclic ring, a preservative system that includes a sorbic acid preservative (i.e., sorbic acid, esters of sorbic acid, salts of sorbic acid, or combinations thereof). Surprisingly, such formulations are stabilized through the incorporation of an antioxidant, more preferably an antioxidant having hydrogen atom donating functionality. Additional stability, particularly of the antioxidant, can be obtained through the incorporation of a chelating agent.

Through the use of an antioxidant and an optional chelating agent, the concentration of the sorbic acid preservative in an IRM-containing formulation remains substantially constant relative to its initial concentration (i.e., its concentration when initially formulated) when stored for at least 6 months at 40°C and 75% relative humidity.

As used herein "remains substantially constant" means that the concentration of sorbic acid preservative in an IRM-containing formulation does not decrease by more than 15% of the initial concentration (i.e., its concentration when initially formulated) when stored for at least 6 months at 40°C and 75% relative humidity. Preferably, the concentration of the sorbic acid preservative in an IRM-containing formulation does not decrease by more than 10% of the initial concentration when stored for at least 6 months at 40°C and 75% relative humidity. More preferably, the concentration of the sorbic acid preservative in an IRM-containing formulation does not decrease by more than 5% of the initial concentration when stored for at least 6 months at 40°C and 75% relative humidity.

In certain embodiments, formulations described herein can be in the form of an oil-in-water emulsion such as a cream or a lotion. Such an emulsion can include an oil phase that includes one or more IRM compounds, a fatty acid in an amount sufficient to solubilize the IRM compound(s), a hydrophobic, aprotic component; and an aqueous phase that includes a preservative system, and a hydrophilic viscosity enhancing agent. Such components, as well as all others of the formulations described herein, are

preferably pharmaceutically acceptable.

#### Immune Response Modifiers

In one aspect, the present invention provides a formulation that includes an  
5 immune response modifier containing a 2-aminopyridine moiety fused to a five-  
membered nitrogen-containing heterocyclic ring.

Immune response modifier compounds ("IRMs") include compounds that  
possess potent immunomodulating activity including but not limited to antiviral and  
antitumor activity. Certain IRMs modulate the production and secretion of cytokines.  
10 For example, certain IRM compounds induce the production and secretion of cytokines  
such as, e.g., Type I interferons, TNF- $\alpha$ , IL-1, IL-6, IL-8, IL-10, IL-12, MIP-1, and/or  
MCP-1. As another example, certain IRM compounds can inhibit production and  
secretion of certain T<sub>H</sub>2 cytokines, such as IL-4 and IL-5. Additionally, some IRM  
compounds are said to suppress IL-1 and TNF (U.S. Patent No. 6,518,265).

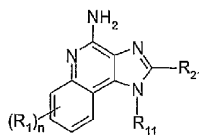
15 IRM compounds suitable for use in the invention include compounds having a  
2-aminopyridine fused to a five-membered nitrogen-containing heterocyclic ring. Such  
compounds include, for example, imidazoquinoline amines including, but not limited to,  
substituted imidazoquinoline amines such as, for example, amide substituted  
imidazoquinoline amines, sulfonamide substituted imidazoquinoline amines, urea  
20 substituted imidazoquinoline amines, aryl ether substituted imidazoquinoline amines,  
heterocyclic ether substituted imidazoquinoline amines, amido ether substituted  
imidazoquinoline amines, sulfonamido ether substituted imidazoquinoline amines, urea  
substituted imidazoquinoline ethers, thioether substituted imidazoquinoline amines, and  
6-, 7-, 8-, or 9-aryl or heteroaryl substituted imidazoquinoline amines;  
25 tetrahydroimidazoquinoline amines including, but not limited to, amide substituted  
tetrahydroimidazoquinoline amines, sulfonamide substituted  
tetrahydroimidazoquinoline amines, urea substituted tetrahydroimidazoquinoline  
amines, aryl ether substituted tetrahydroimidazoquinoline amines, heterocyclic ether  
substituted tetrahydroimidazoquinoline amines, amido ether substituted  
30 tetrahydroimidazoquinoline amines, sulfonamido ether substituted

5 tetrahydroimidazoquinoline amines, urea substituted tetrahydroimidazoquinoline ethers,  
and thioether substituted tetrahydroimidazoquinoline amines; imidazopyridine amines  
including, but not limited to, amide substituted imidazopyridine amines, sulfonamide  
substituted imidazopyridine amines, urea substituted imidazopyridine amines, aryl ether  
10 substituted imidazopyridine amines, heterocyclic ether substituted imidazopyridine  
amines, amido ether substituted imidazopyridine amines, sulfonamido ether substituted  
imidazopyridine amines, urea substituted imidazopyridine ethers, and thioether  
substituted imidazopyridine amines; 1,2-bridged imidazoquinoline amines; 6,7-fused  
cycloalkylimidazopyridine amines; imidazonaphthyridine amines;  
15 tetrahydroimidazonaphthyridine amines; oxazoloquinoline amines; thiazoloquinoline  
amines; oxazolopyridine amines; thiazolopyridine amines; oxazolophthyridine  
amines; thiazolonaphthyridine amines; imidazoquinoline-1,4-diamines; and 1*H*-imidazo  
dimers fused to pyridine amines, quinoline amines, tetrahydroquinoline amines,  
naphthyridine amines, or tetrahydronaphthyridine amines.

15 These immune response modifier compounds, methods of making them,  
methods of using them and compositions containing them are disclosed in U.S. Patent  
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; 6,069,149;  
20 6,083,505; 6,110,929; 6,194,425; 6,245,776; 6,331,539; 6,376,669; 6,451,810;  
6,525,064; 6,541,485; 6,545,016; 6,545,017; 6,558,951; 6,573,273; 6,656,938;  
6,660,735; 6,660,747; 6,664,260; 6,664,264; 6,664,265; 6,667,312; 6,670,372;  
6,677,347; 6,677,348; 6,677,349; 6,683,088; 6,743,920; 6,756,382; 6,797,718; and  
6,818,650; European Patent 0 394 026; U.S. Patent Publication Nos. 2002/0016332;  
25 2002/0055517; 2002/0110840; 2003/0133913; 2003/0161797; 2003/0199538;  
2004/0014779; 2004/0147543; 2004/0175336; 2004/0176367; 2004/0180919;  
2004/0181130; 2004/0181211; and 2004/0192585.

As noted above, many of the IRM compounds useful in the present invention  
have demonstrated immunomodulating activity. In certain embodiments of the present

invention the IRM compound can be chosen from 1H-imidazo[4,5-c]quinolin-4-amines defined by one of Formulas I-V below:



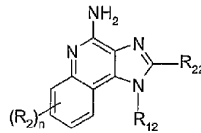
I

5 wherein

$R_{11}$  is selected 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 benzyloxy, and the alkyl moiety contains one to six carbon atoms, benzyl, (phenyl)ethyl and phenyl, said benzyl, (phenyl)ethyl or phenyl substituent being  
 10 optionally substituted on the benzene ring by one or two moieties independently selected 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;

$R_{21}$  is selected from hydrogen, alkyl of one to eight carbon atoms, benzyl, (phenyl)ethyl and phenyl, the benzyl, (phenyl)ethyl or phenyl substituent being  
 15 optionally substituted on the benzene ring by one or two moieties independently selected 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

20 each  $R_1$  is independently selected 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;



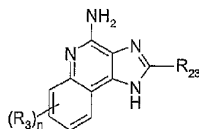
II

wherein

$R_{12}$  is selected 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 selected 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

$R_{22}$  is selected 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 selected 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

each  $R_2$  is independently selected 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;

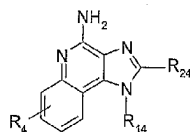


III

wherein

R<sub>23</sub> is selected 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 selected 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

each R<sub>3</sub> is independently selected 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<sub>3</sub> groups together contain no more than six carbon atoms;



IV

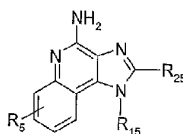
wherein

R<sub>14</sub> is -CHR<sub>x</sub>R<sub>y</sub> wherein R<sub>y</sub> is hydrogen or a carbon-carbon bond, with the proviso that when R<sub>y</sub> is hydrogen R<sub>x</sub> 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<sub>y</sub> is a carbon-carbon bond R<sub>y</sub> and R<sub>x</sub> together

form a tetrahydrofuranyl group optionally substituted with one or more substituents independently selected from hydroxy and hydroxyalkyl of one to four carbon atoms;

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

$R_4$  is selected 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;



10

V

wherein

$R_{15}$  is selected 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 selected 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 selected 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 selected from alkyl of one to four carbon

25

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;

R<sub>25</sub> is



5

wherein

R<sub>5</sub> and R<sub>7</sub> are independently selected from hydrogen, alkyl of one to four carbon atoms, phenyl, and substituted phenyl wherein the substituent is selected from alkyl of one to four carbon atoms, alkoxy of one to four carbon atoms, and halogen;

10

X is selected 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, alkythio of one to four carbon atoms; and

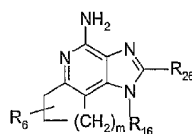
15

R<sub>5</sub> is selected 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;

20

and pharmaceutically acceptable salts of any of the foregoing.

In another embodiment, the IRM compound can be chosen from 6,7 fused cycloalkylimidazopyridine amines defined by Formula VI below:



VI

25

wherein



m is 1, 2, or 3;

$R_{16}$  is selected 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, 5 wherein the substituent is selected 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 10 substituted straight chain or branched chain alkenyl containing two to ten carbon atoms, wherein the substituent is selected 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 15 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 20 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 selected 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 25 no more than six carbon atoms; and  $-CHR_xR_y$  wherein

$R_y$  is hydrogen or a carbon-carbon bond, with the proviso that when  $R_y$  is hydrogen  $R_x$  is alkoxy of one to four carbon atoms, hydroxyalkoxy of one to four carbon atoms, 1-alkynyl of two to ten carbon atoms, tetrahydropyranyl, alkoxyalkyl 30 wherein the alkoxy moiety contains one to four carbon atoms and the alkyl moiety

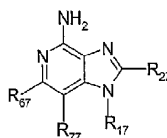
contains one to four carbon atoms, 2-, 3-, or 4-pyridyl, and with the further proviso that when R<sub>y</sub> is a carbon-carbon bond R<sub>y</sub> and R<sub>x</sub> together form a tetrahydrofuranyl group optionally substituted with one or more substituents independently selected from hydroxy and hydroxyalkyl of one to four carbon atoms,

5           R<sub>26</sub> is selected 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 selected from methyl, methoxy, and halogen; and -C(R<sub>S</sub>)(R<sub>T</sub>)(X)  
10           wherein R<sub>S</sub> and R<sub>T</sub> are independently selected from hydrogen, alkyl of one to four carbon atoms, phenyl, and substituted phenyl wherein the substituent is selected from alkyl of one to four carbon atoms, alkoxy of one to four carbon atoms, and halogen;

          X is selected from alkoxy containing one to four carbon atoms, alkoxyalkyl wherein the alkoxy moiety contains one to four carbon atoms and the alkyl moiety  
15           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

20           R<sub>6</sub> is selected 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.

In another embodiment, the IRM compound can be chosen from imidazopyridine amines defined by Formula VII below:



VII

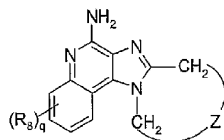
5 wherein

$R_{17}$  is selected from hydrogen;  $-CH_2R_w$  wherein  $R_w$  is selected 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  
10 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;

$R_{27}$  is selected from hydrogen; straight chain or branched chain alkyl containing one to eight carbon atoms; straight chain or branched chain hydroxyalkyl containing  
15 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 selected from methyl, methoxy, and halogen; and morpholinoalkyl wherein the alkyl moiety contains one to four carbon  
20 atoms;

$R_{67}$  and  $R_{77}$  are independently selected 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  
25 proviso that when  $R_{67}$  is hydrogen then  $R_{77}$  and  $R_{27}$  are other than hydrogen; and pharmaceutically acceptable salts thereof.

In another embodiment, the IRM compound can be chosen from 1,2-bridged imidazoquinoline amines defined by Formula VIII below:



VIII

5 wherein

Z is selected from

$-(\text{CH}_2)_p-$  wherein p is 1 to 4;

10  $-(\text{CH}_2)_a-\text{C}(\text{R}_D\text{R}_E)(\text{CH}_2)_b-$ , wherein a and b are integers and a+b is 0 to 3,  $\text{R}_D$  is hydrogen or alkyl of one to four carbon atoms, and  $\text{R}_E$  is selected from alkyl of one to four carbon atoms, hydroxy,  $-\text{OR}_F$  wherein  $\text{R}_F$  is alkyl of one to four carbon atoms, and  $-\text{NR}_G\text{R}'_G$  wherein  $\text{R}_G$  and  $\text{R}'_G$  are independently hydrogen or alkyl of one to four carbon atoms; and

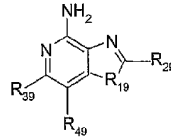
$-(\text{CH}_2)_c-(\text{Y})-(\text{CH}_2)_d-$  wherein a and b are integers and a+b is 0 to 3, and Y is O, S, or  $-\text{NR}_I-$  wherein  $\text{R}_I$  is hydrogen or alkyl of one to four carbon atoms;

15 q is 0 or 1; and

$\text{R}_8$  is selected from alkyl of one to four carbon atoms, alkoxy of one to four carbon atoms, and halogen, and pharmaceutically acceptable salts thereof.

In another embodiment, the IRM compound can be chosen from thiazoloquinoline amines, oxazoloquinoline amines, thiazolopyridine amines, oxazolopyridine amines, thiazolonaphthyridine amines and oxazolonaphthyridine amines defined by Formula IX below:

5



IX

wherein:

R<sub>19</sub> is selected from oxygen, sulfur and selenium;

10

R<sub>29</sub> is selected from

15

-hydrogen;

-alkyl;

-alkyl-OH;

-haloalkyl;

-alkenyl;

-alkyl-X-alkyl;

-alkyl-X-alkenyl;

-alkenyl-X-alkyl;

-alkenyl-X-alkenyl;

20

-alkyl-N(R<sub>59</sub>)<sub>2</sub>;

-alkyl-N<sub>3</sub>;

-alkyl-O-C(O)-N(R<sub>59</sub>)<sub>2</sub>;

-heterocyclyl;

-alkyl-X-heterocyclyl;

25

-alkenyl-X-heterocyclyl;

-aryl;

-alkyl-X-aryl;

-alkenyl-X-aryl;  
 -heteroaryl;  
 -alkyl-X-heteroaryl; and  
 -alkenyl-X-heteroaryl;

5 R<sub>39</sub> and R<sub>49</sub> are each independently:

-hydrogen;  
 -X-alkyl;  
 -halo;  
 -haloalkyl;

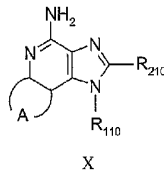
10 -N(R<sub>59</sub>)<sub>2</sub>;

or when taken together, R<sub>39</sub> and R<sub>49</sub> form a fused aromatic, heteroaromatic, cycloalkyl or heterocyclic ring;

X is selected from -O-, -S-, -NR<sub>59</sub>-, -C(O)-, -C(O)O-, -OC(O)-, and a bond; and

15 each R<sub>59</sub> is independently H or C<sub>1-8</sub>alkyl;  
 and pharmaceutically acceptable salts thereof.

In another embodiment, the IRM compound can be chosen from imidazonaphthyridine amines and imidazotetrahydronaphthyridine amines defined by Formulas X and XI below:



wherein

A is =N-CR=CR-CR=; =CR-N=CR-CR=; =CR-CR=N-CR=; or  
 =CR-CR=CR-N=;

25 R<sub>110</sub> is selected from:

- hydrogen;

-C<sub>1-20</sub> alkyl or C<sub>2-20</sub> alkenyl that is unsubstituted or substituted by one or more substituents selected from:

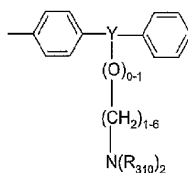
- aryl;
- heteroaryl;
- 5 -heterocyclyl;
- O-C<sub>1-20</sub> alkyl;
- O-(C<sub>1-20</sub> alkyl)<sub>0-1</sub>-aryl;
- O-(C<sub>1-20</sub> alkyl)<sub>0-1</sub>-heteroaryl;
- O-(C<sub>1-20</sub> alkyl)<sub>0-1</sub>-heterocyclyl;
- 10 -CO-O-C<sub>1-20</sub> alkyl;
- S(O)<sub>0-2</sub>-C<sub>1-20</sub> alkyl;
- S(O)<sub>0-2</sub>-(C<sub>1-20</sub> alkyl)<sub>0-1</sub>-aryl;
- S(O)<sub>0-2</sub>-(C<sub>1-20</sub> alkyl)<sub>0-1</sub>-heteroaryl;
- S(O)<sub>0-2</sub>-(C<sub>1-20</sub> alkyl)<sub>0-1</sub>-heterocyclyl;
- 15 -N(R<sub>310</sub>)<sub>2</sub>;
- N<sub>3</sub>;
- oxo;
- halogen;
- NO<sub>2</sub>;
- 20 -OH; and
- SH; and

-C<sub>1-20</sub> alkyl-NR<sub>310</sub>-Q-X-R<sub>410</sub> or -C<sub>2-20</sub> alkenyl-NR<sub>310</sub>-Q-X-R<sub>410</sub> wherein Q is -CO- or -SO<sub>2</sub>-; X is a bond, -O- or -NR<sub>310</sub>- and R<sub>410</sub> is aryl; heteroaryl; heterocyclyl; or -C<sub>1-20</sub> alkyl or C<sub>2-20</sub> alkenyl that is unsubstituted or substituted by one or more

25 substituents selected from:

- aryl;
- heteroaryl;
- heterocyclyl;
- O-C<sub>1-20</sub> alkyl;
- 30 -O-(C<sub>1-20</sub> alkyl)<sub>0-1</sub>-aryl;

- O-(C<sub>1-20</sub> alkyl)<sub>0-1</sub>-heteroaryl;
- O-(C<sub>1-20</sub> alkyl)<sub>0-1</sub>-heterocyclyl;
- CO-O-C<sub>1-20</sub> alkyl;
- S(O)<sub>0-2</sub>-C<sub>1-20</sub> alkyl;
- 5 -S(O)<sub>0-2</sub>-(C<sub>1-20</sub> alkyl)<sub>0-1</sub>-aryl;
- S(O)<sub>0-2</sub>-(C<sub>1-20</sub> alkyl)<sub>0-1</sub>-heteroaryl;
- S(O)<sub>0-2</sub>-(C<sub>1-20</sub> alkyl)<sub>0-1</sub>-heterocyclyl;
- N(R<sub>310</sub>)<sub>2</sub>;
- NR<sub>310</sub>-CO-O-C<sub>1-20</sub> alkyl;
- 10 -N<sub>3</sub>;
- oxo;
- halogen;
- NO<sub>2</sub>;
- OH; and
- 15 -SH; or R<sub>410</sub> is



wherein Y is -N- or -CR-;

R<sub>210</sub> is selected from:

- hydrogen;
- 20 -C<sub>1-10</sub> alkyl;
- C<sub>2-10</sub> alkenyl;
- aryl;
- C<sub>1-10</sub> alkyl-O-C<sub>1-10</sub> alkyl;
- C<sub>1-10</sub> alkyl-O-C<sub>2-10</sub> alkenyl; and
- 25 -C<sub>1-10</sub> alkyl or C<sub>2-10</sub> alkenyl substituted by one or more substituents selected

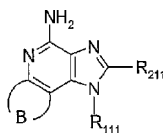


from:

- OH;
- halogen;
- N(R<sub>310</sub>)<sub>2</sub>;
- 5 -CO-N(R<sub>310</sub>)<sub>2</sub>;
- CO-C<sub>1-10</sub> alkyl;
- N<sub>3</sub>;
- aryl;
- heteroaryl;
- 10 -heterocyclyl;
- CO-aryl; and
- CO-heteroaryl;

each R<sub>310</sub> is independently selected from hydrogen and C<sub>1-10</sub> alkyl; and

- each R is independently selected from hydrogen, C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkoxy,
- 15 halogen and trifluoromethyl;



XI

wherein

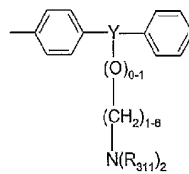
- B is -NR-C(R)<sub>2</sub>-C(R)<sub>2</sub>-C(R)<sub>2</sub>-; -C(R)<sub>2</sub>-NR-C(R)<sub>2</sub>-C(R)<sub>2</sub>-;
- 20 -C(R)<sub>2</sub>-C(R)<sub>2</sub>-NR-C(R)<sub>2</sub>- or -C(R)<sub>2</sub>-C(R)<sub>2</sub>-C(R)<sub>2</sub>-NR-;

R<sub>111</sub> is selected from:

- hydrogen;
- C<sub>1-20</sub> alkyl or C<sub>2-20</sub> alkenyl that is unsubstituted or substituted by one or more
- substituents selected from:
- 25 -aryl;
- heteroaryl;

- heterocyclyl;  
 -O-C<sub>1-20</sub> alkyl;  
 -O-(C<sub>1-20</sub> alkyl)<sub>0-1</sub>-aryl;  
 -O-(C<sub>1-20</sub> alkyl)<sub>0-1</sub>-heteroaryl;  
 5 -O-(C<sub>1-20</sub> alkyl)<sub>0-1</sub>-heterocyclyl;  
 -CO-O-C<sub>1-20</sub> alkyl;  
 -S(O)<sub>0-2</sub>-C<sub>1-20</sub> alkyl;  
 -S(O)<sub>0-2</sub>-(C<sub>1-20</sub> alkyl)<sub>0-1</sub>-aryl;  
 -S(O)<sub>0-2</sub>-(C<sub>1-20</sub> alkyl)<sub>0-1</sub>-heteroaryl;  
 10 -S(O)<sub>0-2</sub>-(C<sub>1-20</sub> alkyl)<sub>0-1</sub>-heterocyclyl;  
 -N(R<sub>311</sub>)<sub>2</sub>;  
 -N<sub>3</sub>;  
 oxo;  
 -halogen;  
 15 -NO<sub>2</sub>;  
 -OH; and  
 -SH; and  
 -C<sub>1-20</sub> alkyl-NR<sub>311</sub>-Q-X-R<sub>411</sub> or -C<sub>2-20</sub> alkenyl-NR<sub>311</sub>-Q-X-R<sub>411</sub> wherein Q is -  
 CO- or -SO<sub>2</sub>-; X is a bond, -O- or -NR<sub>311</sub>- and R<sub>411</sub> is aryl; heteroaryl; heterocyclyl; or -  
 20 C<sub>1-20</sub> alkyl or C<sub>2-20</sub> alkenyl that is unsubstituted or substituted by one or more  
 substituents selected from:  
 -aryl;  
 -heteroaryl;  
 -heterocyclyl;  
 25 -O-C<sub>1-20</sub> alkyl;  
 -O-(C<sub>1-20</sub> alkyl)<sub>0-1</sub>-aryl;  
 -O-(C<sub>1-20</sub> alkyl)<sub>0-1</sub>-heteroaryl;  
 -O-(C<sub>1-20</sub> alkyl)<sub>0-1</sub>-heterocyclyl;  
 -CO-O-C<sub>1-20</sub> alkyl;  
 30 -S(O)<sub>0-2</sub>-C<sub>1-20</sub> alkyl;

- S(O)<sub>0-2</sub>-(C<sub>1-20</sub> alkyl)<sub>0-1</sub>-aryl;
- S(O)<sub>0-2</sub>-(C<sub>1-20</sub> alkyl)<sub>0-1</sub>-heteroaryl;
- S(O)<sub>0-2</sub>-(C<sub>1-20</sub> alkyl)<sub>0-1</sub>-heterocyclyl;
- N(R<sub>311</sub>)<sub>2</sub>;
- 5 -NR<sub>311</sub>-CO-O-C<sub>1-20</sub> alkyl;
- N<sub>3</sub>;
- oxo;
- halogen;
- NO<sub>2</sub>;
- 10 -OH; and
- SH; or R<sub>411</sub> is



wherein Y is -N- or -CR-;

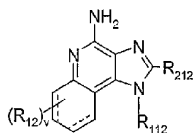
R<sub>211</sub> is selected from:

- 15 -hydrogen;
- C<sub>1-10</sub> alkyl;
- C<sub>2-10</sub> alkenyl;
- aryl;
- C<sub>1-10</sub> alkyl -O-C<sub>1-10</sub>-alkyl;
- 20 -C<sub>1-10</sub> alkyl-O-C<sub>2-10</sub> alkenyl; and
- C<sub>1-10</sub> alkyl or C<sub>2-10</sub> alkenyl substituted by one or more substituents selected from:
- OH;
- halogen;
- 25 -N(R<sub>311</sub>)<sub>2</sub>;

-CO-N(R<sub>311</sub>)<sub>2</sub>;  
 -CO-C<sub>1-10</sub> alkyl;  
 -N<sub>3</sub>;  
 -aryl;  
 5 -heteroaryl;  
 -heterocyclyl;  
 -CO-aryl; and  
 -CO-heteroaryl;

each R<sub>311</sub> is independently selected from hydrogen and C<sub>1-10</sub> alkyl; and  
 10 each R is independently selected from hydrogen, C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkoxy,  
 halogen, and trifluoromethyl;  
 and pharmaceutically acceptable salts thereof.

In another embodiment, the IRM compound can be chosen from 1*H*-  
 imidazo[4,5-*c*]quinolin-4-amines and tetrahydro- 1*H*-imidazo[4,5-*c*]quinolin-4-amines  
 15 defined by Formulas XII, XIII and XIV below:



XII

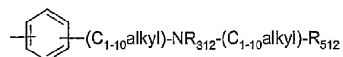
wherein

20 R<sub>112</sub> is -alkyl-NR<sub>312</sub>-CO-R<sub>412</sub> or -alkenyl-NR<sub>312</sub>-CO- R<sub>412</sub> wherein R<sub>412</sub> is aryl,  
 heteroaryl, alkyl or alkenyl, each of which may be unsubstituted or substituted by one or  
 more substituents selected from:

-alkyl;  
 -alkenyl;  
 25 -alkynyl;  
 -(alkyl)<sub>0-1</sub>-aryl;

-(alkyl)<sub>0-1</sub>-(substituted aryl);  
 -(alkyl)<sub>0-1</sub>-heteroaryl;  
 -(alkyl)<sub>0-1</sub>-(substituted heteroaryl);  
 -O-alkyl;  
 5      -O-(alkyl)<sub>0-1</sub>-aryl;  
        -O-(alkyl)<sub>0-1</sub>-(substituted aryl);  
        -O-(alkyl)<sub>0-1</sub>-heteroaryl;  
        -O-(alkyl)<sub>0-1</sub>-(substituted heteroaryl);  
        -CO-aryl;  
 10      -CO-(substituted aryl);  
        -CO-heteroaryl;  
        -CO-(substituted heteroaryl);  
        -COOH;  
        -CO-O-alkyl;  
 15      -CO-alkyl;  
        -S(O)<sub>0-2</sub>-alkyl;  
        -S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-aryl;  
        -S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-(substituted aryl);  
        -S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-heteroaryl;  
 20      -S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-(substituted heteroaryl);  
        -P(O)(OR<sub>312</sub>)<sub>2</sub>;  
        -NR<sub>312</sub>-CO-O-alkyl;  
        -N<sub>3</sub>;  
        -halogen;  
 25      -NO<sub>2</sub>;  
        -CN;  
        -haloalkyl;  
        -O-haloalkyl;  
        -CO-haloalkyl;  
 30      -OH;

-SH; and in the case that R<sub>412</sub> is alkyl, alkenyl, or heterocyclyl, oxo;  
or R<sub>412</sub> is



5            wherein R<sub>512</sub> is an aryl, (substituted aryl), heteroaryl, (substituted heteroaryl),  
heterocyclyl or (substituted heterocyclyl) group;

R<sub>212</sub> is selected from:

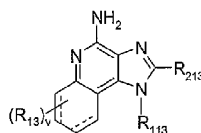
- hydrogen;
- alkyl;
- 10        -alkenyl;
- aryl;
- (substituted aryl);
- heteroaryl;
- (substituted heteroaryl);
- 15        -heterocyclyl;
- (substituted heterocyclyl);
- alkyl-O-alkyl;
- alkyl-O-alkenyl; and
- alkyl or alkenyl substituted by one or more substituents selected
- 20        from:
- OH;
- halogen;
- N(R<sub>312</sub>)<sub>2</sub>;
- CO-N(R<sub>312</sub>)<sub>2</sub>;
- 25        -CO-C<sub>1-10</sub> alkyl;
- CO-O-C<sub>1-10</sub> alkyl;
- N<sub>3</sub>;
- aryl;

- 5
- (substituted aryl);
  - heteroaryl;
  - (substituted heteroaryl);
  - heterocyclyl;
  - (substituted heterocyclyl);
  - CO-aryl; and
  - CO-heteroaryl;

10 each  $R_{312}$  is independently selected from hydrogen;  $C_{1-10}$  alkyl-heteroaryl;  $C_{1-10}$  alkyl-(substituted heteroaryl);  $C_{1-10}$  alkyl-aryl;  $C_{1-10}$  alkyl-(substituted aryl) and  $C_{1-10}$  alkyl;

$v$  is 0 to 4;

and each  $R_{12}$  present is independently selected from  $C_{1-10}$  alkyl,  $C_{1-10}$  alkoxy, halogen, and trifluoromethyl;



XIII

wherein

$R_{113}$  is -alkyl-NR<sub>313</sub>-SO<sub>2</sub>-X-R<sub>413</sub> or -alkenyl-NR<sub>313</sub>-SO<sub>2</sub>-X-R<sub>413</sub>;

X is a bond or -NR<sub>513</sub>-;

20  $R_{413}$  is aryl, heteroaryl, heterocyclyl, alkyl or alkenyl, each of which may be unsubstituted or substituted by one or more substituents selected from:

- 25
- alkyl;
  - alkenyl;
  - aryl;
  - heteroaryl;
  - heterocyclyl;

-substituted cycloalkyl;  
 -substituted aryl;  
 -substituted heteroaryl;  
 -substituted heterocyclyl;  
 5     -O-alkyl;  
       -O-(alkyl)<sub>0-1</sub>-aryl;  
       -O-(alkyl)<sub>0-1</sub>-substituted aryl;  
       -O-(alkyl)<sub>0-1</sub>-heteroaryl;  
       -O-(alkyl)<sub>0-1</sub>-substituted heteroaryl;  
 10     -O-(alkyl)<sub>0-1</sub>-heterocyclyl;  
       -O-(alkyl)<sub>0-1</sub>-substituted heterocyclyl;  
       -COOH;  
       -CO-O-alkyl;  
       -CO-alkyl;  
 15     -S(O)<sub>0-2</sub>-alkyl;  
       -S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-aryl;  
       -S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-substituted aryl;  
       -S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-heteroaryl;  
       -S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-substituted heteroaryl;  
 20     -S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-heterocyclyl;  
       -S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-substituted heterocyclyl;  
       -(alkyl)<sub>0-1</sub>-NR<sub>313</sub>R<sub>313</sub>;  
       -(alkyl)<sub>0-1</sub>-NR<sub>313</sub>-CO-O-alkyl;  
       -(alkyl)<sub>0-1</sub>-NR<sub>313</sub>-CO-alkyl;  
 25     -(alkyl)<sub>0-1</sub>-NR<sub>313</sub>-CO-aryl;  
       -(alkyl)<sub>0-1</sub>-NR<sub>313</sub>-CO-substituted aryl;  
       -(alkyl)<sub>0-1</sub>-NR<sub>313</sub>-CO-heteroaryl;  
       -(alkyl)<sub>0-1</sub>-NR<sub>313</sub>-CO-substituted heteroaryl;  
       -N<sub>3</sub>;  
 30     -halogen;



- haloalkyl;  
 -haloalkoxy;  
 -CO-haloalkyl;  
 -CO-haloalkoxy;  
 5 -NO<sub>2</sub>;  
 -CN;  
 -OH;  
 -SH; and in the case that R<sub>413</sub> is alkyl, alkenyl, or heterocyclyl, oxo;
- R<sub>213</sub> is selected from:
- 10 -hydrogen;  
 -alkyl;  
 -alkenyl;  
 -aryl;  
 -substituted aryl;  
 15 -heteroaryl;  
 -substituted heteroaryl;  
 -alkyl-O-alkyl;  
 -alkyl-O-alkenyl; and  
 -alkyl or alkenyl substituted by one or more substituents selected
- 20 from:  
 -OH;  
 -halogen;  
 -N(R<sub>313</sub>)<sub>2</sub>;  
 -CO-N(R<sub>313</sub>)<sub>2</sub>;  
 25 -CO-C<sub>1-10</sub> alkyl;  
 -CO-O-C<sub>1-10</sub> alkyl;  
 -N<sub>3</sub>;  
 -aryl;  
 -substituted aryl;  
 30 -heteroaryl;

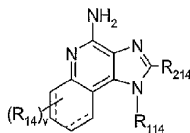
- 5
- substituted heteroaryl;
  - heterocyclyl;
  - substituted heterocyclyl;
  - CO-aryl;
  - CO-(substituted aryl);
  - CO-heteroaryl; and
  - CO-(substituted heteroaryl);

10 each  $R_{313}$  is independently selected from hydrogen and  $C_{1-10}$  alkyl; or when X is a bond  $R_{313}$  and  $R_{413}$  can join to form a 3 to 7 membered heterocyclic or substituted heterocyclic ring;

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

v is 0 to 4;

15 and each  $R_{13}$  present is independently selected from  $C_{1-10}$  alkyl,  $C_{1-10}$  alkoxy, halogen, and trifluoromethyl;



XIV

wherein

20  $R_{114}$  is -alkyl-NR<sub>314</sub>-CY-NR<sub>514</sub>-X-R<sub>414</sub> or -alkenyl-NR<sub>314</sub>-CY- NR<sub>514</sub>-X- R<sub>414</sub>

wherein

Y is =O or =S;

X is a bond, -CO- or -SO<sub>2</sub>-;

25  $R_{414}$  is aryl, heteroaryl, heterocyclyl, alkyl or alkenyl, each of which may be unsubstituted or substituted by one or more substituents selected from:

-alkyl;

-alkenyl;  
 -aryl;  
 -heteroaryl;  
 -heterocyclyl;  
 5 -substituted aryl;  
 -substituted heteroaryl;  
 -substituted heterocyclyl;  
 -O-alkyl;  
 -O-(alkyl)<sub>0-1</sub>-aryl;  
 10 -O-(alkyl)<sub>0-1</sub>-substituted aryl;  
 -O-(alkyl)<sub>0-1</sub>-heteroaryl;  
 -O-(alkyl)<sub>0-1</sub>-substituted heteroaryl;  
 -O-(alkyl)<sub>0-1</sub>-heterocyclyl;  
 -O-(alkyl)<sub>0-1</sub>-substituted heterocyclyl;  
 15 -COOH;  
 -CO-O-alkyl;  
 -CO-alkyl;  
 -S(O)<sub>0-2</sub>-alkyl;  
 -S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-aryl;  
 20 -S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-substituted aryl;  
 -S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-heteroaryl;  
 -S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-substituted heteroaryl;  
 -S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-heterocyclyl;  
 -S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-substituted heterocyclyl;  
 25 -(alkyl)<sub>0-1</sub>-NR<sub>314</sub>R<sub>314</sub>;  
 -(alkyl)<sub>0-1</sub>-NR<sub>314</sub>-CO-O-alkyl;  
 -(alkyl)<sub>0-1</sub>-NR<sub>314</sub>-CO-alkyl;  
 -(alkyl)<sub>0-1</sub>-NR<sub>314</sub>-CO-aryl;  
 -(alkyl)<sub>0-1</sub>-NR<sub>314</sub>-CO-substituted aryl;  
 30 -(alkyl)<sub>0-1</sub>-NR<sub>314</sub>-CO-heteroaryl;

- (alkyl)<sub>0-1</sub>-NR<sub>314</sub>-CO-substituted heteroaryl;  
 -N<sub>3</sub>;  
 -halogen;  
 -haloalkyl;  
 5        - haloalkoxy;  
        -CO-haloalkoxy;  
        -NO<sub>2</sub>;  
        -CN;  
        -OH;  
 10       -SH; and, in the case that R<sub>414</sub> is alkyl, alkenyl or heterocyclyl, oxo;  
 with the proviso that when X is a bond R<sub>414</sub> can additionally be hydrogen;  
 R<sub>214</sub> is selected from:  
        -hydrogen;  
        -alkyl;  
 15       -alkenyl;  
        -aryl;  
        -substituted aryl;  
        -heteroaryl;  
        -substituted heteroaryl;  
 20       -alkyl-O-alkyl;  
        -alkyl-O-alkenyl; and  
        -alkyl or alkenyl substituted by one or more substituents selected  
 from:  
        -OH;  
 25       -halogen;  
        -N(R<sub>314</sub>)<sub>2</sub>;  
        -CO-N(R<sub>314</sub>)<sub>2</sub>;  
        -CO-C<sub>1-10</sub> alkyl;  
        -CO-O-C<sub>1-10</sub> alkyl;  
 30       -N<sub>3</sub>;

- aryl;  
 -substituted aryl;  
 -heteroaryl;  
 -substituted heteroaryl;  
 5 -heterocyclyl;  
 -substituted heterocyclyl;  
 -CO-aryl;  
 -CO-(substituted aryl);  
 -CO-heteroaryl; and  
 10 -CO-(substituted heteroaryl);

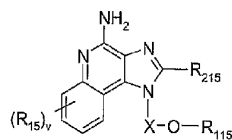
each  $R_{314}$  is independently selected from hydrogen and  $C_{1-10}$  alkyl;

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

$v$  is 0 to 4;

- 15 and each  $R_{14}$  present is independently selected from  $C_{1-10}$  alkyl,  $C_{1-10}$  alkoxy, halogen, and trifluoromethyl;  
 and pharmaceutically acceptable salts thereof.

- In another embodiment, the IRM compound can be chosen from *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:



25

XV

wherein: X is  $-CHR_{515}-$ ,  $-CHR_{515}$ -alkyl-, or  $-CHR_{515}$ -alkenyl-;  
 $R_{115}$  is selected from:

34

- 5  
10
- R<sub>415</sub>-CR<sub>315</sub>-Z-R<sub>615</sub>-alkyl;
  - R<sub>415</sub>-CR<sub>315</sub>-Z-R<sub>615</sub>-alkenyl;
  - R<sub>415</sub>-CR<sub>315</sub>-Z-R<sub>615</sub>-aryl;
  - R<sub>415</sub>-CR<sub>315</sub>-Z-R<sub>615</sub>-heteroaryl;
  - R<sub>415</sub>-CR<sub>315</sub>-Z-R<sub>615</sub>-heterocyclyl;
  - R<sub>415</sub>-CR<sub>315</sub>-Z-H;
  - R<sub>415</sub>-NR<sub>715</sub>-CR<sub>315</sub>-R<sub>615</sub>-alkyl;
  - R<sub>415</sub>-NR<sub>715</sub>-CR<sub>315</sub>-R<sub>615</sub>-alkenyl;
  - R<sub>415</sub>-NR<sub>715</sub>-CR<sub>315</sub>-R<sub>615</sub>-aryl;
  - R<sub>415</sub>-NR<sub>715</sub>-CR<sub>315</sub>-R<sub>615</sub>-heteroaryl;
  - R<sub>415</sub>-NR<sub>715</sub>-CR<sub>315</sub>-R<sub>615</sub>-heterocyclyl; and
  - R<sub>415</sub>-NR<sub>715</sub>-CR<sub>315</sub>-R<sub>815</sub>;

Z is -NR<sub>515</sub>-, -O-, or -S-;

R<sub>215</sub> is selected from:

- 15  
20  
25  
30
- hydrogen;
  - alkyl;
  - alkenyl;
  - aryl;
  - heteroaryl;
  - heterocyclyl;
  - alkyl-Y-alkyl;
  - alkyl-Y-alkenyl;
  - alkyl-Y-aryl; and
  - alkyl or alkenyl substituted by one or more substituents selected from:
  - OH;
  - halogen;
  - N(R<sub>515</sub>)<sub>2</sub>;
  - CO-N(R<sub>515</sub>)<sub>2</sub>;
  - CO-C<sub>1-10</sub> alkyl;

-CO-O-C<sub>1-10</sub> alkyl;  
 -N<sub>3</sub>;  
 -aryl;  
 -heteroaryl;  
 5 -heterocyclyl;  
 -CO-aryl; and  
 -CO-heteroaryl;

R<sub>315</sub> is =O or =S;

R<sub>415</sub> is alkyl or alkenyl, which may be interrupted by one or more  
 10 -O- groups;

each R<sub>515</sub> is independently H or C<sub>1-10</sub> alkyl;

R<sub>615</sub> is a bond, alkyl, or alkenyl, which may be interrupted by one or  
 more -O- groups;

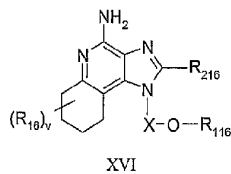
R<sub>715</sub> is H, C<sub>1-10</sub> alkyl, or arylalkyl; or R<sub>415</sub> and R<sub>715</sub> can join together to  
 15 form a ring;

R<sub>815</sub> is H or C<sub>1-10</sub> alkyl; or R<sub>715</sub> and R<sub>815</sub> can join together to form a ring;

Y is -O- or -S(O)<sub>0-2</sub>;

v is 0 to 4; and

each R<sub>15</sub> present is independently selected from C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkoxy,  
 20 hydroxy, halogen, and trifluoromethyl;



25 wherein: X is -CHR<sub>516</sub>-, -CHR<sub>516</sub>-alkyl-, or -CHR<sub>516</sub>-alkenyl-;

R<sub>116</sub> is selected from:

-R<sub>416</sub>-CR<sub>316</sub>-Z-R<sub>616</sub>-alkyl;

- 5
- R<sub>416</sub>-CR<sub>316</sub>-Z-R<sub>616</sub>-alkenyl;
  - R<sub>416</sub>-CR<sub>316</sub>-Z-R<sub>616</sub>-aryl;
  - R<sub>416</sub>-CR<sub>316</sub>-Z-R<sub>616</sub>-heteroaryl;
  - R<sub>416</sub>-CR<sub>316</sub>-Z-R<sub>616</sub>-heterocyclyl;
  - R<sub>416</sub>-CR<sub>316</sub>-Z-H;
  - R<sub>416</sub>-NR<sub>716</sub>-CR<sub>316</sub>-R<sub>616</sub>-alkyl;
  - R<sub>416</sub>-NR<sub>716</sub>-CR<sub>316</sub>-R<sub>616</sub>-alkenyl;
  - R<sub>416</sub>-NR<sub>716</sub>-CR<sub>316</sub>-R<sub>616</sub>-aryl;
  - R<sub>416</sub>-NR<sub>716</sub>-CR<sub>316</sub>-R<sub>616</sub>-heteroaryl;
  - 10 -R<sub>416</sub>-NR<sub>716</sub>-CR<sub>316</sub>-R<sub>616</sub>-heterocyclyl; and
  - R<sub>416</sub>-NR<sub>716</sub>-CR<sub>316</sub>-R<sub>816</sub>;

Z is -NR<sub>516</sub>-, -O-, or -S-;

R<sub>216</sub> is selected from:

- 15
- hydrogen;
  - alkyl;
  - alkenyl;
  - aryl;
  - heteroaryl;
  - heterocyclyl;
  - 20 -alkyl-Y-alkyl;
  - alkyl-Y-alkenyl;
  - alkyl-Y-aryl; and
  - alkyl or alkenyl substituted by one or more substituents selected
  - 25 from:
  - OH;
  - halogen;
  - N(R<sub>516</sub>)<sub>2</sub>;
  - CO-N(R<sub>516</sub>)<sub>2</sub>;
  - CO-C<sub>1-10</sub> alkyl;
  - 30 -CO-O-C<sub>1-10</sub> alkyl;



-N<sub>3</sub>;  
 -aryl;  
 -heteroaryl;  
 -heterocyclyl;  
 5 -CO-aryl; and  
 -CO-heteroaryl;

R<sub>316</sub> is =O or =S;

R<sub>416</sub> is alkyl or alkenyl, which may be interrupted by one or more  
 -O- groups;

10 each R<sub>516</sub> is independently H or C<sub>1-10</sub> alkyl;

R<sub>616</sub> is a bond, alkyl, or alkenyl, which may be interrupted by one or  
 more -O- groups;

R<sub>716</sub> is H, C<sub>1-10</sub> alkyl, arylalkyl; or R<sub>416</sub> and R<sub>716</sub> can join together to form  
 a ring;

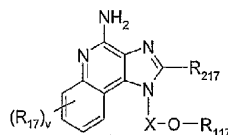
15 R<sub>816</sub> is H or C<sub>1-10</sub> alkyl; or R<sub>716</sub> and R<sub>816</sub> can join together to form a ring;

Y is -O- or -S(O)<sub>0-2</sub>;

v is 0 to 4; and

each R<sub>16</sub> present is independently selected from C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkoxy,  
 hydroxy, halogen, and trifluoromethyl;

20



XVII

wherein: X is -CHR<sub>317</sub>-, -CHR<sub>317</sub>-alkyl-, or -CHR<sub>317</sub>-alkenyl-;

25 R<sub>117</sub> is selected from:

-alkenyl;  
 -aryl; and

-R<sub>417</sub>-aryl;

R<sub>217</sub> is selected from:

-hydrogen;

-alkyl;

5

-alkenyl;

-aryl;

-heteroaryl;

-heterocyclyl;

-alkyl-Y-alkyl;

10

-alkyl-Y-alkenyl;

-alkyl-Y-aryl; and

-alkyl or alkenyl substituted by one or more substituents selected from:

-OH;

15

-halogen;

-N(R<sub>317</sub>)<sub>2</sub>;

-CO-N(R<sub>317</sub>)<sub>2</sub>;

-CO-C<sub>1-10</sub> alkyl;

-CO-O-C<sub>1-10</sub> alkyl;

20

-N<sub>3</sub>;

-aryl;

-heteroaryl;

-heterocyclyl;

-CO-aryl; and

25

-CO-heteroaryl;

R<sub>417</sub> is alkyl or alkenyl, which may be interrupted by one or more -O- groups;

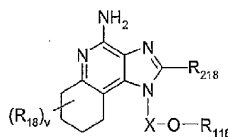
each R<sub>317</sub> is independently H or C<sub>1-10</sub> alkyl;

each Y is independently -O- or -S(O)<sub>0-2</sub>;

30

v is 0 to 4; and

each R<sub>17</sub> present is independently selected from C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkoxy, hydroxy, halogen, and trifluoromethyl;



XVIII

5

wherein: X is -CHR<sub>318</sub>-, -CHR<sub>318</sub>-alkyl-, or -CHR<sub>318</sub>-alkenyl-;

R<sub>118</sub> is selected from:

- aryl;
- alkenyl; and
- R<sub>418</sub>-aryl;

10

R<sub>218</sub> is selected from:

- hydrogen;
- alkyl;
- alkenyl;
- aryl;
- heteroaryl;
- heterocyclyl;
- alkyl-Y-alkyl;
- alkyl-Y-aryl;
- alkyl-Y-alkenyl; and
- alkyl or alkenyl substituted by one or more substituents selected from:

15

20

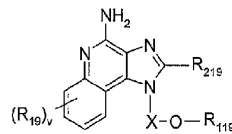
25

- OH;
- halogen;
- N(R<sub>318</sub>)<sub>2</sub>;
- CO-N(R<sub>318</sub>)<sub>2</sub>;

40

- CO-C<sub>1-10</sub> alkyl;
- CO-O-C<sub>1-10</sub> alkyl;
- N<sub>3</sub>;
- aryl;
- 5 -heteroaryl;
- heterocyclyl;
- CO-aryl; and
- CO-heteroaryl;

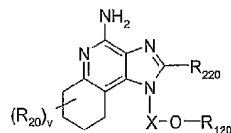
R<sub>418</sub> is alkyl or alkenyl, which may be interrupted by one or more  
 10 -O- groups;  
 each R<sub>318</sub> is independently H or C<sub>1-10</sub> alkyl;  
 each Y is independently -O- or -S(O)<sub>0,2</sub>;  
 v is 0 to 4; and  
 each R<sub>18</sub> present is independently selected C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkoxy,  
 15 hydroxy, halogen, and trifluoromethyl;



XIX

20 wherein: X is -CHR<sub>319</sub>-, -CHR<sub>319</sub>-alkyl-, or -CHR<sub>319</sub>-alkenyl-;  
 R<sub>119</sub> is selected from:  
 -heteroaryl;  
 -heterocyclyl;  
 -R<sub>419</sub>- heteroaryl; and  
 25 -R<sub>419</sub>-heterocyclyl;  
 R<sub>219</sub> is selected from:  
 -hydrogen;

-alkyl;  
 -alkenyl;  
 -aryl;  
 -heteroaryl;  
 5 -heterocyclyl;  
 -alkyl-Y-alkyl;  
 -alkyl-Y-alkenyl;  
 -alkyl-Y-aryl; and  
 -alkyl or alkenyl substituted by one or more substituents selected  
 10 from:  
 -OH;  
 -halogen;  
 -N(R<sub>319</sub>)<sub>2</sub>;  
 -CO-N(R<sub>319</sub>)<sub>2</sub>;  
 15 -CO-C<sub>1-10</sub> alkyl;  
 -CO-O-C<sub>1-10</sub> alkyl;  
 -N<sub>3</sub>;  
 -aryl;  
 -heteroaryl;  
 20 -heterocyclyl;  
 -CO-aryl; and  
 -CO-heteroaryl;  
 R<sub>419</sub> is alkyl or alkenyl, which may be interrupted by one or more  
 -O- groups;  
 25 each R<sub>319</sub> is independently H or C<sub>1-10</sub> alkyl;  
 each Y is independently -O- or -S(O)<sub>0-2</sub>;  
 v is 0 to 4; and  
 each R<sub>19</sub> present is independently selected from C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkoxy,  
 hydroxy, halogen, and trifluoromethyl;  
 30



XX

wherein: X is  $-\text{CHR}_{320}-$ ,  $-\text{CHR}_{320}\text{-alkyl-}$ , or  $-\text{CHR}_{320}\text{-alkenyl-}$ ;

5

$\text{R}_{120}$  is selected from:

- heteroaryl;
- heterocyclyl;
- $-\text{R}_{420}$ -heteroaryl; and
- $-\text{R}_{420}$ -heterocyclyl;

10

$\text{R}_{220}$  is selected from:

- hydrogen;
- alkyl;
- alkenyl;
- aryl;
- heteroaryl;
- heterocyclyl;
- alkyl-Y-alkyl;
- alkyl-Y-alkenyl;
- alkyl-Y-aryl; and

20

- alkyl or alkenyl substituted by one or more substituents selected from:

- OH;
- halogen;
- $-\text{N}(\text{R}_{320})_2$ ;
- $-\text{CO}-\text{N}(\text{R}_{320})_2$ ;
- $-\text{CO}-\text{C}_{1-10}$  alkyl;
- $-\text{CO}-\text{O}-\text{C}_{1-10}$  alkyl;

25

-N<sub>3</sub>;  
 -aryl;  
 -heteroaryl;  
 -heterocyclyl;  
 -CO-aryl; and  
 -CO-heteroaryl;

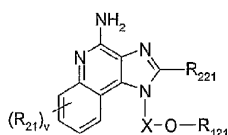
R<sub>420</sub> is alkyl or alkenyl, which may be interrupted by one or more  
 -O- groups;

each R<sub>320</sub> is independently H or C<sub>1-10</sub> alkyl;

each Y is independently -O- or -S(O)<sub>0-2</sub>;

v is 0 to 4; and

each R<sub>20</sub> present is independently selected from C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkoxy,  
 hydroxy, halogen, and trifluoromethyl;



XXI

wherein: X is -CHR<sub>521</sub>-, -CHR<sub>521</sub>-alkyl-, or -CHR<sub>521</sub>-alkenyl-;

R<sub>121</sub> is selected from:

-R<sub>421</sub>-NR<sub>321</sub>-SO<sub>2</sub>-R<sub>621</sub>-alkyl;  
 -R<sub>421</sub>-NR<sub>321</sub>-SO<sub>2</sub>-R<sub>621</sub>-alkenyl;  
 -R<sub>421</sub>-NR<sub>321</sub>-SO<sub>2</sub>-R<sub>621</sub>-aryl;  
 -R<sub>421</sub>-NR<sub>321</sub>-SO<sub>2</sub>-R<sub>621</sub>-heteroaryl;  
 -R<sub>421</sub>-NR<sub>321</sub>-SO<sub>2</sub>-R<sub>621</sub>-heterocyclyl;  
 -R<sub>421</sub>-NR<sub>321</sub>-SO<sub>2</sub>-R<sub>721</sub>;  
 -R<sub>421</sub>-NR<sub>321</sub>-SO<sub>2</sub>-NR<sub>521</sub>-R<sub>621</sub>-alkyl;  
 -R<sub>421</sub>-NR<sub>321</sub>-SO<sub>2</sub>-NR<sub>521</sub>-R<sub>621</sub>-alkenyl;

-R<sub>421</sub>-NR<sub>321</sub>-SO<sub>2</sub>-NR<sub>521</sub>-R<sub>621</sub>-aryl;  
 -R<sub>421</sub>-NR<sub>321</sub>-SO<sub>2</sub>-NR<sub>521</sub>-R<sub>621</sub>-heteroaryl;  
 -R<sub>421</sub>-NR<sub>321</sub>-SO<sub>2</sub>-NR<sub>521</sub>-R<sub>621</sub>-heterocyclyl; and  
 -R<sub>421</sub>-NR<sub>321</sub>-SO<sub>2</sub>-NH<sub>2</sub>;

5

R<sub>221</sub> is selected from:

-hydrogen;  
 -alkyl;  
 -alkenyl;  
 -aryl;  
 -heteroaryl;  
 -heterocyclyl;  
 -alkyl-Y-alkyl;  
 -alkyl-Y-alkenyl;  
 -alkyl-Y-aryl; and

10

15

- alkyl or alkenyl substituted by one or more substituents selected from:

-OH;  
 -halogen;  
 -N(R<sub>521</sub>)<sub>2</sub>;  
 -CO-N(R<sub>521</sub>)<sub>2</sub>;  
 -CO-C<sub>1-10</sub> alkyl;  
 -CO-O-C<sub>1-10</sub> alkyl;  
 -N<sub>3</sub>;  
 -aryl;  
 -heteroaryl;  
 -heterocyclyl;  
 -CO-aryl; and  
 -CO-heteroaryl;

20

25

Y is -O- or -S(O)<sub>0-2</sub>;

30

R<sub>321</sub> is H, C<sub>1-10</sub> alkyl, or arylalkyl;



each  $R_{421}$  is independently alkyl or alkenyl, which may be interrupted by one or more -O- groups; or  $R_{321}$  and  $R_{421}$  can join together to form a ring;

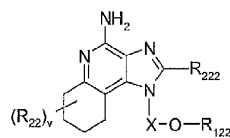
each  $R_{521}$  is independently H,  $C_{1-10}$  alkyl, or  $C_{2-10}$  alkenyl;

5  $R_{621}$  is a bond, alkyl, or alkenyl, which may be interrupted by one or more -O- groups;

$R_{721}$  is  $C_{1-10}$  alkyl; or  $R_{321}$  and  $R_{721}$  can join together to form a ring;

$v$  is 0 to 4; and

10 each  $R_{21}$  present is independently selected from  $C_{1-10}$  alkyl,  $C_{1-10}$  alkoxy, hydroxy, halogen, and trifluoromethyl;



XXII

15 wherein: X is -CHR<sub>522</sub>-, -CHR<sub>522</sub>-alkyl-, or -CHR<sub>522</sub>-alkenyl-;

$R_{122}$  is selected from:

- $R_{422}$ -NR<sub>322</sub>-SO<sub>2</sub>- $R_{622}$ -alkyl;

- $R_{422}$ -NR<sub>322</sub>-SO<sub>2</sub>- $R_{622}$ -alkenyl;

- $R_{422}$ -NR<sub>322</sub>-SO<sub>2</sub>- $R_{622}$ -aryl;

20 - $R_{422}$ -NR<sub>322</sub>-SO<sub>2</sub>- $R_{622}$ -heteroaryl;

- $R_{422}$ -NR<sub>322</sub>-SO<sub>2</sub>- $R_{622}$ -heterocyclyl;

- $R_{422}$ -NR<sub>322</sub>-SO<sub>2</sub>- $R_{722}$ ;

- $R_{422}$ -NR<sub>322</sub>-SO<sub>2</sub>-NR<sub>522</sub>- $R_{622}$ -alkyl;

- $R_{422}$ -NR<sub>322</sub>-SO<sub>2</sub>-NR<sub>522</sub>- $R_{622}$ -alkenyl;

25 - $R_{422}$ -NR<sub>322</sub>-SO<sub>2</sub>-NR<sub>522</sub>- $R_{622}$ -aryl;

- $R_{422}$ -NR<sub>322</sub>-SO<sub>2</sub>-NR<sub>522</sub>- $R_{622}$ -heteroaryl;

- $R_{422}$ -NR<sub>322</sub>-SO<sub>2</sub>-NR<sub>522</sub>- $R_{622}$ -heterocyclyl; and

-R<sub>422</sub>-NR<sub>322</sub>-SO<sub>2</sub>-NH<sub>2</sub>;

R<sub>222</sub> is selected from:

-hydrogen;

-alkyl;

5

-alkenyl;

-aryl;

-heteroaryl;

-heterocyclyl;

-alkyl-Y-alkyl;

10

-alkyl-Y-alkenyl;

-alkyl-Y-aryl; and

-alkyl or alkenyl substituted by one or more substituents selected from:

-OH;

15

-halogen;

-N(R<sub>522</sub>)<sub>2</sub>;

-CO-N(R<sub>522</sub>)<sub>2</sub>;

-CO-C<sub>1-10</sub> alkyl;

-CO-O-C<sub>1-10</sub> alkyl;

20

-N<sub>3</sub>;

-aryl;

-heteroaryl;

-heterocyclyl;

-CO-aryl; and

25

-CO-heteroaryl;

Y is -O- or -S(O)<sub>0-2</sub>;

R<sub>322</sub> is H, C<sub>1-10</sub> alkyl, or arylalkyl;

each R<sub>422</sub> is independently alkyl or alkenyl, which may be interrupted by one or more -O- groups; or R<sub>322</sub> and R<sub>422</sub> can join together to form a

30

ring;

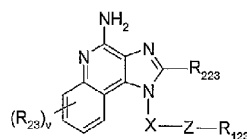
each  $R_{522}$  is independently H,  $C_{1-10}$  alkyl, or  $C_{2-10}$  alkenyl;

$R_{622}$  is a bond, alkyl, or alkenyl, which may be interrupted by one or more -O- groups;

$R_{722}$  is  $C_{1-10}$  alkyl; or  $R_{322}$  and  $R_{722}$  can join together to form a ring;

5  $v$  is 0 to 4; and

each  $R_{22}$  present is independently selected from  $C_{1-10}$  alkyl,  $C_{1-10}$  alkoxy, hydroxy, halogen, and trifluoromethyl;



10

XXIII

wherein: X is  $-CHR_{323}$ -,  $-CHR_{323}$ -alkyl-, or  $-CHR_{323}$ -alkenyl-;

Z is  $-S$ -,  $-SO$ -, or  $-SO_2$ -;

$R_{123}$  is selected from:

15

-alkyl;

-aryl;

-heteroaryl;

-heterocyclyl;

-alkenyl;

20

$-R_{423}$ -aryl;

$-R_{423}$ -heteroaryl; and

$-R_{423}$ -heterocyclyl;

$R_{223}$  is selected from:

25

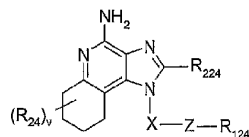
-hydrogen;

-alkyl;

-alkenyl;

-aryl;

- heteroaryl;  
 -heterocyclyl;  
 -alkyl-Y-alkyl;  
 - alkyl-Y- alkenyl;  
 5 -alkyl-Y-aryl; and  
 -alkyl or alkenyl substituted by one or more substituents selected  
 from:  
 -OH;  
 -halogen;  
 10 -N(R<sub>323</sub>)<sub>2</sub>;  
 -CO-N(R<sub>323</sub>)<sub>2</sub>;  
 -CO-C<sub>1-10</sub> alkyl;  
 -CO-O-C<sub>1-10</sub> alkyl;  
 -N<sub>3</sub>;  
 15 -aryl;  
 -heteroaryl;  
 -heterocyclyl;  
 -CO-aryl; and  
 -CO-heteroaryl;  
 20 each R<sub>323</sub> is independently H or C<sub>1-10</sub> alkyl;  
 each R<sub>423</sub> is independently alkyl or alkenyl;  
 each Y is independently -O- or -S(O)<sub>0,2</sub>;  
 v is 0 to 4; and  
 each R<sub>23</sub> present is independently selected from C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkoxy,  
 25 hydroxy, halogen, and trifluoromethyl;



XXIV

- wherein: X is  $-\text{CHR}_{324}-$ ,  $-\text{CHR}_{324}\text{-alkyl-}$ , or  $-\text{CHR}_{324}\text{-alkenyl-}$ ;
- 5 Z is  $-\text{S-}$ ,  $-\text{SO-}$ , or  $-\text{SO}_2-$ ;
- R<sub>124</sub> is selected from:
- alkyl;
  - aryl;
  - heteroaryl;
  - 10 -heterocyclyl;
  - alkenyl;
  - R<sub>424</sub>-aryl;
  - R<sub>424</sub>-heteroaryl; and
  - R<sub>424</sub>-heterocyclyl;
- 15 R<sub>224</sub> is selected from:
- hydrogen;
  - alkyl;
  - alkenyl;
  - aryl;
  - 20 -heteroaryl;
  - heterocyclyl;
  - alkyl-Y-alkyl;
  - alkyl-Y-alkenyl;
  - alkyl-Y-aryl; and
  - 25 -alkyl or alkenyl substituted by one or more substituents selected from:
  - OH;

- halogen;
- N(R<sub>324</sub>)<sub>2</sub>;
- CO-N(R<sub>324</sub>)<sub>2</sub>;
- CO-C<sub>1-10</sub> alkyl;
- 5 -CO-O-C<sub>1-10</sub> alkyl;
- N<sub>3</sub>;
- aryl;
- heteroaryl;
- heterocyclyl;
- 10 -CO-aryl; and
- CO-heteroaryl;

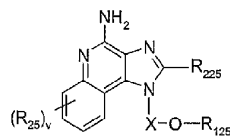
each R<sub>324</sub> is independently H or C<sub>1-10</sub> alkyl;

each R<sub>424</sub> is independently alkyl or alkenyl;

each Y is independently -O- or -S(O)<sub>0-2</sub>;

15 v is 0 to 4; and

each R<sub>24</sub> present is independently selected from C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkoxy, hydroxy, halogen, and trifluoromethyl;



20

XXV

wherein: X is -CHR<sub>525</sub>-, -CHR<sub>525</sub>-alkyl-, or -CHR<sub>525</sub>-alkenyl-;

R<sub>125</sub> is selected from:

- R<sub>425</sub>-NR<sub>825</sub>-CR<sub>325</sub>-NR<sub>525</sub>-Z-R<sub>625</sub>-alkyl;
- 25 -R<sub>425</sub>-NR<sub>825</sub>-CR<sub>325</sub>-NR<sub>525</sub>-Z-R<sub>625</sub>-alkenyl;
- R<sub>425</sub>-NR<sub>825</sub>-CR<sub>325</sub>-NR<sub>525</sub>-Z-R<sub>625</sub>-aryl;
- R<sub>425</sub>-NR<sub>825</sub>-CR<sub>325</sub>-NR<sub>525</sub>-Z-R<sub>625</sub>-heteroaryl;

-R<sub>425</sub>-NR<sub>825</sub>-CR<sub>325</sub>-NR<sub>525</sub>-Z-R<sub>625</sub>-heterocyclyl;

-R<sub>425</sub>-NR<sub>825</sub>-CR<sub>325</sub>-NR<sub>525</sub>R<sub>725</sub>;

-R<sub>425</sub>-NR<sub>825</sub>-CR<sub>325</sub>-NR<sub>925</sub>-Z-R<sub>625</sub>-alkyl;

-R<sub>425</sub>-NR<sub>825</sub>-CR<sub>325</sub>-NR<sub>925</sub>-Z-R<sub>625</sub>-alkenyl;

5

-R<sub>425</sub>-NR<sub>825</sub>-CR<sub>325</sub>-NR<sub>925</sub>-Z-R<sub>625</sub>-aryl;

-R<sub>425</sub>-NR<sub>825</sub>-CR<sub>325</sub>-NR<sub>925</sub>-Z-R<sub>625</sub>-heteroaryl; and

-R<sub>425</sub>-NR<sub>825</sub>-CR<sub>325</sub>-NR<sub>925</sub>-Z-R<sub>625</sub>-heterocyclyl;

R<sub>225</sub> is selected from:

-hydrogen;

10

-alkyl;

-alkenyl;

-aryl;

-heteroaryl;

-heterocyclyl;

15

-alkyl-Y-alkyl;

-alkyl-Y-alkenyl;

-alkyl-Y-aryl; and

-alkyl or alkenyl substituted by one or more substituents selected

from:

20

-OH;

-halogen;

-N(R<sub>525</sub>)<sub>2</sub>;

-CO-N(R<sub>525</sub>)<sub>2</sub>;

-CO-C<sub>1-10</sub> alkyl;

25

-CO-O-C<sub>1-10</sub> alkyl;

-N<sub>3</sub>;

-aryl;

-heteroaryl;

-heterocyclyl;

30

-CO-aryl; and

-CO-heteroaryl];

each R<sub>325</sub> is =O or =S;

each R<sub>425</sub> is independently alkyl or alkenyl, which may be interrupted by one or more -O- groups;

5 each R<sub>525</sub> is independently H or C<sub>1-10</sub> alkyl;

R<sub>625</sub> is a bond, alkyl, or alkenyl, which may be interrupted by one or more -O- groups;

R<sub>725</sub> is H or C<sub>1-10</sub> alkyl which may be interrupted by a hetero atom, or R<sub>725</sub> can join with R<sub>525</sub> to form a ring;

10 R<sub>825</sub> is H, C<sub>1-10</sub> alkyl, or arylalkyl; or R<sub>425</sub> and R<sub>825</sub> can join together to form a ring;

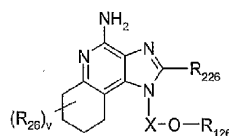
R<sub>925</sub> is C<sub>1-10</sub> alkyl which can join together with R<sub>825</sub> to form a ring;

each Y is independently -O- or -S(O)<sub>0-2</sub>;

Z is a bond, -CO-, or -SO<sub>2</sub>-;

15 v is 0 to 4; and

each R<sub>25</sub> present is independently selected C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkoxy, hydroxy, halogen, and trifluoromethyl;



20

XXVI

wherein: X is -CHR<sub>326</sub>-, -CHR<sub>326</sub>-alkyl-, or -CHR<sub>326</sub>-alkenyl-;

R<sub>126</sub> is selected from:

- 25
- R<sub>426</sub>-NR<sub>326</sub>-CR<sub>326</sub>-NR<sub>526</sub>-Z-R<sub>626</sub>-alkyl;
  - R<sub>426</sub>-NR<sub>326</sub>-CR<sub>326</sub>-NR<sub>526</sub>-Z-R<sub>626</sub>-alkenyl;
  - R<sub>426</sub>-NR<sub>326</sub>-CR<sub>326</sub>-NR<sub>526</sub>-Z-R<sub>626</sub>-aryl;
  - R<sub>426</sub>-NR<sub>326</sub>-CR<sub>326</sub>-NR<sub>526</sub>-Z-R<sub>626</sub>-heteroaryl;



-R<sub>426</sub>-NR<sub>826</sub>-CR<sub>326</sub>-NR<sub>926</sub>-Z-R<sub>626</sub>-heterocyclyl;

-R<sub>426</sub>-NR<sub>826</sub>-CR<sub>326</sub>-NR<sub>926</sub>-R<sub>726</sub>;

-R<sub>426</sub>-NR<sub>826</sub>-CR<sub>326</sub>-NR<sub>926</sub>-Z-R<sub>626</sub>-alkyl;

-R<sub>426</sub>-NR<sub>826</sub>-CR<sub>326</sub>-NR<sub>926</sub>-Z-R<sub>626</sub>-alkenyl;

5

-R<sub>426</sub>-NR<sub>826</sub>-CR<sub>326</sub>-NR<sub>926</sub>-Z-R<sub>626</sub>-aryl;

-R<sub>426</sub>-NR<sub>826</sub>-CR<sub>326</sub>-NR<sub>926</sub>-Z-R<sub>626</sub>-heteroaryl; and

-R<sub>426</sub>-NR<sub>826</sub>-CR<sub>326</sub>-NR<sub>926</sub>-Z-R<sub>626</sub>-heterocyclyl;

R<sub>226</sub> is selected from:

-hydrogen;

10

-alkyl;

-alkenyl;

-aryl;

-heteroaryl;

-heterocyclyl;

15

-alkyl-Y-alkyl;

-alkyl-Y-alkenyl;

-alkyl-Y-aryl; and

-alkyl or alkenyl substituted by one or more substituents selected

from:

20

-OH;

-halogen;

-N(R<sub>526</sub>)<sub>2</sub>;

-CO-N(R<sub>526</sub>)<sub>2</sub>;

-CO-C<sub>1-10</sub> alkyl;

25

-CO-O-C<sub>1-10</sub> alkyl;

-N<sub>3</sub>;

-aryl;

-heteroaryl;

-heterocyclyl;

30

-CO-aryl; and

-CO-heteroaryl;

each R<sub>326</sub> is =O or =S;

each R<sub>426</sub> is independently alkyl or alkenyl, which may be interrupted by one or more -O- groups;

5 each R<sub>526</sub> is independently H or C<sub>1-10</sub> alkyl;

R<sub>626</sub> is a bond, alkyl, or alkenyl, which may be interrupted by one or more -O- groups;

R<sub>726</sub> is H or C<sub>1-10</sub> alkyl which may be interrupted by a hetero atom, or

R<sub>726</sub> can join with R<sub>526</sub> to form a ring;

10 R<sub>826</sub> is H, C<sub>1-10</sub> alkyl, or arylalkyl; or R<sub>426</sub> and R<sub>826</sub> can join together to form a ring;

R<sub>926</sub> is C<sub>1-10</sub> alkyl which can join together with R<sub>826</sub> to form a ring;

each Y is independently -O- or -S(O)<sub>0-2</sub>-;

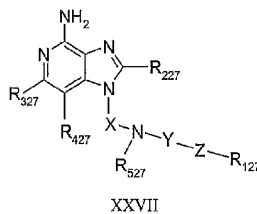
Z is a bond, -CO-, or -SO<sub>2</sub>-;

15 v is 0 to 4; and

each R<sub>26</sub> present is independently selected from C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkoxy, hydroxy, halogen, and trifluoromethyl;

and pharmaceutically acceptable salts of any of the foregoing.

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



25 wherein X is alkylene or alkenylene;  
Y is -CO- or -CS-;  
Z is a bond, -O-, or -S-;

R<sub>127</sub> is aryl, heteroaryl, heterocyclyl, alkyl or  
alkenyl, each of which may be unsubstituted or substituted by one or more  
substituents independently selected from:

- alkyl;
- 5        -alkenyl;
- aryl;
- heteroaryl;
- heterocyclyl;
- substituted cycloalkyl;
- 10        -substituted aryl;
- substituted heteroaryl;
- substituted heterocyclyl;
- O-alkyl;
- O-(alkyl)<sub>0-1</sub>-aryl;
- 15        -O-(alkyl)<sub>0-1</sub>-(substituted aryl);
- O-(alkyl)<sub>0-1</sub>-heteroaryl;
- O-(alkyl)<sub>0-1</sub>-(substituted heteroaryl);
- O-(alkyl)<sub>0-1</sub>-heterocyclyl;
- O-(alkyl)<sub>0-1</sub>-(substituted heterocyclyl);
- 20        -COOH;
- CO-O-alkyl;
- CO-alkyl;
- S(O)<sub>0-2</sub>-alkyl;
- S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-aryl;
- 25        -S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-(substituted aryl);
- S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-heteroaryl;
- S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-(substituted heteroaryl);
- S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-heterocyclyl;
- S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-(substituted heterocyclyl);
- 30        -(alkyl)<sub>0-1</sub>-N(R<sub>627</sub>)<sub>2</sub>;

- 5
- (alkyl)<sub>0-1</sub>-NR<sub>627</sub>-CO-O-alkyl;
  - (alkyl)<sub>0-1</sub>-NR<sub>627</sub>-CO-alkyl;
  - (alkyl)<sub>0-1</sub>-NR<sub>627</sub>-CO-aryl;
  - (alkyl)<sub>0-1</sub>-NR<sub>627</sub>-CO-(substituted aryl);
  - (alkyl)<sub>0-1</sub>-NR<sub>627</sub>-CO-heteroaryl;
  - (alkyl)<sub>0-1</sub>-NR<sub>627</sub>-CO-(substituted heteroaryl);
  - N<sub>3</sub>;
  - halogen;
  - haloalkyl;
  - 10
  - haloalkoxy;
  - CO-haloalkyl;
  - CO-haloalkoxy;
  - NO<sub>2</sub>;
  - CN;
  - 15
  - OH;
  - SH; and in the case of alkyl, alkenyl, and heterocyclyl, oxo;
- R<sub>227</sub> is selected from:
- hydrogen;
  - alkyl;
  - 20
  - alkenyl;
  - aryl;
  - substituted aryl;
  - heteroaryl;
  - substituted heteroaryl;
  - 25
  - alkyl-O-alkyl;
  - alkyl-S-alkyl;
  - alkyl-O-aryl;
  - alkyl-S-aryl;
  - alkyl-O- alkenyl;
  - 30
  - alkyl-S- alkenyl; and

-alkyl or alkenyl substituted by one or more substituents selected from:

- OH;
- halogen;
- 5 -N(R<sub>627</sub>)<sub>2</sub>;
- CO-N(R<sub>627</sub>)<sub>2</sub>;
- CS-N(R<sub>627</sub>)<sub>2</sub>;
- SO<sub>2</sub>-N(R<sub>627</sub>)<sub>2</sub>;
- NR<sub>627</sub>-CO-C<sub>1-10</sub> alkyl;
- 10 -NR<sub>627</sub>-CS-C<sub>1-10</sub> alkyl;
- NR<sub>627</sub>-SO<sub>2</sub>-C<sub>1-10</sub> alkyl;
- CO-C<sub>1-10</sub> alkyl;
- CO-O-C<sub>1-10</sub> alkyl;
- N<sub>3</sub>;
- 15 -aryl;
- substituted aryl;
- heteroaryl;
- substituted heteroaryl;
- heterocyclyl;
- 20 -substituted heterocyclyl;
- CO-aryl;
- CO-(substituted aryl);
- CO-heteroaryl; and
- CO-(substituted heteroaryl);

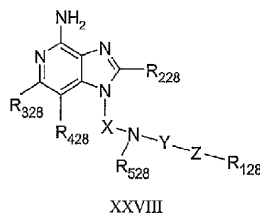
25 R<sub>327</sub> and R<sub>427</sub> are independently selected from hydrogen, alkyl, alkenyl, halogen, alkoxy, amino, alkylamino, dialkylamino, and alkylthio;

R<sub>527</sub> is H or C<sub>1-10</sub> alkyl, or R<sub>527</sub> can join with X to form a ring that contains one or two heteroatoms; or when R<sub>127</sub> is alkyl, R<sub>527</sub> and R<sub>127</sub> can join to form a ring;

30 each R<sub>627</sub> is independently H or C<sub>1-10</sub>alkyl;

and pharmaceutically acceptable salts thereof.

In another embodiment, the IRM compound can be chosen from 1*H*-imidazo[4,5-*c*]pyridin-4-amines defined by Formula XXVIII below:



5

wherein X is alkylene or alkenylene;  
 Y is -SO<sub>2</sub>-;  
 Z is a bond or -NR<sub>528</sub>-;  
 R<sub>128</sub> is aryl, heteroaryl, heterocyclyl, alkyl or  
 alkenyl, each of which may be unsubstituted or substituted by one or more  
 substituents independently selected from:

10

15

20

25

- alkyl;
- alkenyl;
- aryl;
- heteroaryl;
- heterocyclyl;
- substituted cycloalkyl;
- substituted aryl;
- substituted heteroaryl;
- substituted heterocyclyl;
- O-alkyl;
- O-(alkyl)<sub>0-1</sub>-aryl;
- O-(alkyl)<sub>0-1</sub>-(substituted aryl);
- O-(alkyl)<sub>0-1</sub>-heteroaryl;
- O-(alkyl)<sub>0-1</sub>-(substituted heteroaryl);

- O-(alkyl)<sub>0-1</sub>-heterocyclyl;  
 -O-(alkyl)<sub>0-1</sub>-(substituted heterocyclyl);  
 -COOH;  
 -CO-O-alkyl;  
 5 -CO-alkyl;  
 -S(O)<sub>0-2</sub>-alkyl;  
 -S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-aryl;  
 -S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-(substituted aryl);  
 -S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-heteroaryl;  
 10 -S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-(substituted heteroaryl);  
 -S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-heterocyclyl;  
 -S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-(substituted heterocyclyl);  
 -(alkyl)<sub>0-1</sub>-N(R<sub>628</sub>)<sub>2</sub>;  
 -(alkyl)<sub>0-1</sub>-NR<sub>628</sub>-CO-O-alkyl;  
 15 -(alkyl)<sub>0-1</sub>-NR<sub>628</sub>-CO-alkyl;  
 -(alkyl)<sub>0-1</sub>-NR<sub>628</sub>-CO-aryl;  
 -(alkyl)<sub>0-1</sub>-NR<sub>628</sub>-CO-(substituted aryl);  
 -(alkyl)<sub>0-1</sub>-NR<sub>628</sub>-CO-heteroaryl;  
 -(alkyl)<sub>0-1</sub>-NR<sub>628</sub>-CO-(substituted heteroaryl);  
 20 -N<sub>3</sub>;  
 -halogen;  
 -haloalkyl;  
 -haloalkoxy;  
 -CO-haloalkyl;  
 25 -CO-haloalkoxy;  
 -NO<sub>2</sub>;  
 -CN;  
 -OH;  
 -SH; and in the case of alkyl, alkenyl, and heterocyclyl, oxo;
- 30 R<sub>228</sub> is selected from:

- 5
- hydrogen;  
-alkyl;  
-alkenyl;  
-aryl;  
-substituted aryl;  
-heteroaryl;  
-substituted heteroaryl;  
-alkyl-O-alkyl;  
-alkyl-S-alkyl;  
10 -alkyl-O-aryl;  
-alkyl-S-aryl;  
-alkyl-O-alkenyl;  
-alkyl-S-alkenyl; and  
-alkyl or alkenyl substituted by one or more substituents selected  
15 from:
- OH;  
-halogen;  
-N(R<sub>628</sub>)<sub>2</sub>;  
-CO-N(R<sub>628</sub>)<sub>2</sub>;  
20 -CS-N(R<sub>628</sub>)<sub>2</sub>;  
-SO<sub>2</sub>-N(R<sub>628</sub>)<sub>2</sub>;  
-NR<sub>628</sub>-CO-C<sub>1-10</sub> alkyl;  
-NR<sub>628</sub>-CS-C<sub>1-10</sub> alkyl;  
-NR<sub>628</sub>-SO<sub>2</sub>-C<sub>1-10</sub> alkyl;  
25 -CO-C<sub>1-10</sub> alkyl;  
-CO-O-C<sub>1-10</sub> alkyl;  
-N<sub>3</sub>;  
-aryl;  
-substituted aryl;  
30 -heteroaryl;



-substituted heteroaryl;  
 -heterocyclyl;  
 -substituted heterocyclyl;  
 -CO-aryl;  
 5 -CO-(substituted aryl);  
 -CO-heteroaryl; and  
 -CO-(substituted heteroaryl);

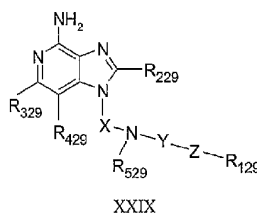
$R_{328}$  and  $R_{428}$  are independently selected from hydrogen, alkyl, alkenyl, halogen, alkoxy, amino, alkylamino, dialkylamino, and alkylthio;

10  $R_{528}$  is H or  $C_{1-10}$  alkyl, or  $R_{528}$  can join with X to form a ring; or when  $R_{128}$  is alkyl,  $R_{528}$  and  $R_{128}$  can join to form a ring;

each  $R_{628}$  is independently H or  $C_{1-10}$ alkyl;

and pharmaceutically acceptable salts thereof.

15 In another embodiment, the IRM compound can be chosen from 1*H*-imidazo[4,5-*c*]pyridin-4-amines defined by Formula XXIX below:



wherein X is alkylene or alkenylene;

20 Y is -CO- or -CS;

Z is -NR<sub>629</sub>-, -NR<sub>629</sub>-CO-, -NR<sub>629</sub>-SO<sub>2</sub>-, or -NR<sub>729</sub>-;

R<sub>129</sub> is aryl, heteroaryl, heterocyclyl, alkyl or alkenyl, each of which may be unsubstituted or substituted by one or more substituents independently selected from:

25 -alkyl;  
 -alkenyl;

-aryl;  
 -heteroaryl;  
 -heterocyclyl;  
 -substituted cycloalkyl;  
 5 -substituted aryl;  
 -substituted heteroaryl;  
 -substituted heterocyclyl;  
 -O-alkyl;  
 -O-(alkyl)<sub>0-1</sub>-aryl;  
 10 -O-(alkyl)<sub>0-1</sub>-(substituted aryl);  
 -O-(alkyl)<sub>0-1</sub>-heteroaryl;  
 -O-(alkyl)<sub>0-1</sub>-(substituted heteroaryl);  
 -O-(alkyl)<sub>0-1</sub>-heterocyclyl;  
 -O-(alkyl)<sub>0-1</sub>-(substituted heterocyclyl);  
 15 -COOH;  
 -CO-O-alkyl;  
 -CO-alkyl;  
 -S(O)<sub>0-2</sub>-alkyl;  
 -S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-aryl;  
 20 -S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-(substituted aryl);  
 -S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-heteroaryl;  
 -S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-(substituted heteroaryl);  
 -S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-heterocyclyl;  
 -S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-(substituted heterocyclyl);  
 25 -(alkyl)<sub>0-1</sub>-N(R<sub>629</sub>)<sub>2</sub>;  
 -(alkyl)<sub>0-1</sub>-NR<sub>629</sub>-CO-O-alkyl;  
 -(alkyl)<sub>0-1</sub>-NR<sub>629</sub>-CO-alkyl;  
 -(alkyl)<sub>0-1</sub>-NR<sub>629</sub>-CO-aryl;  
 -(alkyl)<sub>0-1</sub>-NR<sub>629</sub>-CO-(substituted aryl);  
 30 -(alkyl)<sub>0-1</sub>-NR<sub>629</sub>-CO-heteroaryl;

- (alkyl)<sub>0-1</sub>-NR<sub>629</sub>-CO-(substituted heteroaryl);  
 -P(O)(O-alkyl)<sub>2</sub>;  
 -N<sub>3</sub>;  
 -halogen;  
 5        -haloalkyl;  
           -haloalkoxy;  
           -CO-haloalkyl;  
           -CO-haloalkoxy;  
 10        -NO<sub>2</sub>;  
           -CN;  
           -OH;  
           -SH; and in the case of alkyl, alkenyl, and heterocyclyl, oxo;
- R<sub>229</sub> is selected from:
- 15        -hydrogen;  
           -alkyl;  
           -alkenyl;  
           -aryl;  
           -substituted aryl;  
           -heteroaryl;  
 20        -substituted heteroaryl;  
           -alkyl-O-alkyl;  
           -alkyl-S-alkyl;  
           -alkyl-O-aryl;  
           -alkyl-S-aryl;  
 25        -alkyl-O- alkenyl;  
           -alkyl-S- alkenyl; and  
           -alkyl or alkenyl substituted by one or more substituents selected  
           from:  
 30        -OH;  
           -halogen;

5                   -N(R<sub>629</sub>)<sub>2</sub>;  
                   -CO-N(R<sub>629</sub>)<sub>2</sub>;  
                   -CS-N(R<sub>629</sub>)<sub>2</sub>;  
                   -SO<sub>2</sub>-N(R<sub>629</sub>)<sub>2</sub>;  
                   -NR<sub>629</sub>-CO-C<sub>1-10</sub> alkyl;  
                   -NR<sub>629</sub>-CS-C<sub>1-10</sub> alkyl;  
                   -NR<sub>629</sub>-SO<sub>2</sub>-C<sub>1-10</sub> alkyl;  
                   -CO-C<sub>1-10</sub> alkyl;  
 10                  -CO-O-C<sub>1-10</sub> alkyl;  
                   -N<sub>3</sub>;  
                   -aryl;  
                   -substituted aryl;  
                   -heteroaryl;  
                   -substituted heteroaryl;  
 15                  -heterocyclyl;  
                   -substituted heterocyclyl;  
                   -CO-aryl;  
                   -CO-(substituted aryl);  
                   -CO-heteroaryl; and  
 20                  -CO-(substituted heteroaryl);

R<sub>329</sub> and R<sub>429</sub> are independently selected from hydrogen, alkyl, alkenyl, halogen, alkoxy, amino, alkylamino, dialkylamino, and alkylthio;

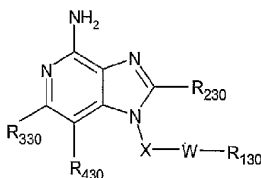
R<sub>529</sub> is H or C<sub>1-10</sub> alkyl, or R<sub>529</sub> can join with X to form a ring that contains one or two heteroatoms;

25                  each R<sub>629</sub> is independently H or C<sub>1-10</sub>alkyl;

R<sub>729</sub> is H or C<sub>1-10</sub> alkyl which may be interrupted by a heteroatom; or when R<sub>129</sub> is alkyl, R<sub>729</sub> and R<sub>129</sub> can join to form a ring;

and pharmaceutically acceptable salts thereof.

In another embodiment, the IRM compound can be chosen from 1-position ether or thioether substituted 1*H*-imidazo[4,5-*c*]pyridin-4-amines defined by Formula XXX below:



5

XXX

wherein:

10 X is -CH(R<sub>530</sub>)-, -CH(R<sub>530</sub>)-alkylene-, -CH(R<sub>530</sub>)-alkenylene-,  
or CH(R<sub>530</sub>)-alkylene-Y-alkylene-;

Y is -O-, or -S(O)<sub>0-2</sub>-;

-W-R<sub>130</sub> is selected from -O-R<sub>130-1-5</sub> and -S(O)<sub>0-2</sub>-R<sub>130-6</sub>;

R<sub>130-1-5</sub> is selected from

15 -R<sub>630</sub>-C(R<sub>730</sub>)-Z-R<sub>830</sub>-alkyl;  
-R<sub>630</sub>-C(R<sub>730</sub>)-Z-R<sub>830</sub>-alkenyl;  
-R<sub>630</sub>-C(R<sub>730</sub>)-Z-R<sub>830</sub>-aryl;  
-R<sub>630</sub>-C(R<sub>730</sub>)-Z-R<sub>830</sub>-heteroaryl;  
-R<sub>630</sub>-C(R<sub>730</sub>)-Z-R<sub>830</sub>-heterocyclyl;  
20 -R<sub>630</sub>-C(R<sub>730</sub>)-Z-H;  
-R<sub>630</sub>-N(R<sub>930</sub>)-C(R<sub>730</sub>)-R<sub>830</sub>-alkyl;  
-R<sub>630</sub>-N(R<sub>930</sub>)-C(R<sub>730</sub>)-R<sub>830</sub>-alkenyl;  
-R<sub>630</sub>-N(R<sub>930</sub>)-C(R<sub>730</sub>)-R<sub>830</sub>-aryl;  
-R<sub>630</sub>-N(R<sub>930</sub>)-C(R<sub>730</sub>)-R<sub>830</sub>-heteroaryl;  
25 -R<sub>630</sub>-N(R<sub>930</sub>)-C(R<sub>730</sub>)-R<sub>830</sub>-heterocyclyl;  
-R<sub>630</sub>-N(R<sub>930</sub>)-C(R<sub>730</sub>)-R<sub>1030</sub>;  
-R<sub>630</sub>-N(R<sub>930</sub>)-SO<sub>2</sub>-R<sub>830</sub>-alkyl;

66

- R<sub>630</sub>-N(R<sub>930</sub>)-SO<sub>2</sub>-R<sub>830</sub>-alkenyl;
- R<sub>630</sub>-N(R<sub>930</sub>)-SO<sub>2</sub>-R<sub>830</sub>-aryl;
- R<sub>630</sub>-N(R<sub>930</sub>)-SO<sub>2</sub>-R<sub>830</sub>-heteroaryl;
- R<sub>630</sub>-N(R<sub>930</sub>)-SO<sub>2</sub>-R<sub>830</sub>-heterocyclyl;
- 5 -R<sub>630</sub>-N(R<sub>930</sub>)-SO<sub>2</sub>-R<sub>1030</sub>;
- R<sub>630</sub>-N(R<sub>930</sub>)-SO<sub>2</sub>-N(R<sub>530</sub>)-R<sub>830</sub>-alkyl;
- R<sub>630</sub>-N(R<sub>930</sub>)-SO<sub>2</sub>-N(R<sub>530</sub>)-R<sub>830</sub>-alkenyl;
- R<sub>630</sub>-N(R<sub>930</sub>)-SO<sub>2</sub>-N(R<sub>530</sub>)-R<sub>830</sub>-aryl;
- R<sub>630</sub>-N(R<sub>930</sub>)-SO<sub>2</sub>-N(R<sub>530</sub>)-R<sub>830</sub>-heteroaryl;
- 10 -R<sub>630</sub>-N(R<sub>930</sub>)-SO<sub>2</sub>-N(R<sub>530</sub>)-R<sub>830</sub>-heterocyclyl;
- R<sub>630</sub>-N(R<sub>930</sub>)-SO<sub>2</sub>-NH<sub>2</sub>;
- R<sub>630</sub>-N(R<sub>930</sub>)-C(R<sub>730</sub>)-N(R<sub>530</sub>)-Q-R<sub>830</sub>-alkyl;
- R<sub>630</sub>-N(R<sub>930</sub>)-C(R<sub>730</sub>)-N(R<sub>530</sub>)-Q-R<sub>830</sub>-alkenyl;
- R<sub>630</sub>-N(R<sub>930</sub>)-C(R<sub>730</sub>)-N(R<sub>530</sub>)-Q-R<sub>830</sub>-aryl;
- 15 -R<sub>630</sub>-N(R<sub>930</sub>)-C(R<sub>730</sub>)-N(R<sub>530</sub>)-Q-R<sub>830</sub>-heteroaryl;
- R<sub>630</sub>-N(R<sub>930</sub>)-C(R<sub>730</sub>)-N(R<sub>530</sub>)-Q-R<sub>830</sub>-heterocyclyl;
- R<sub>630</sub>-N(R<sub>930</sub>)-C(R<sub>730</sub>)-N(R<sub>530</sub>)<sub>2</sub>;
- R<sub>630</sub>-N(R<sub>930</sub>)-C(R<sub>730</sub>)-N  $\begin{matrix} \text{A} \\ \text{A} \end{matrix}$  ;
- R<sub>630</sub>-N(R<sub>930</sub>)-C(R<sub>730</sub>)-N(R<sub>1130</sub>)-Q-R<sub>830</sub>-alkyl;
- 20 -R<sub>630</sub>-N(R<sub>930</sub>)-C(R<sub>730</sub>)-N(R<sub>1130</sub>)-Q-R<sub>830</sub>-alkenyl;
- R<sub>630</sub>-N(R<sub>930</sub>)-C(R<sub>730</sub>)-N(R<sub>1130</sub>)-Q-R<sub>830</sub>-aryl;
- R<sub>630</sub>-N(R<sub>930</sub>)-C(R<sub>730</sub>)-N(R<sub>1130</sub>)-Q-R<sub>830</sub>-heteroaryl;
- R<sub>630</sub>-N(R<sub>930</sub>)-C(R<sub>730</sub>)-N(R<sub>1130</sub>)-Q-R<sub>830</sub>-heterocyclyl;
- R<sub>630</sub>-N(R<sub>930</sub>)-C(R<sub>730</sub>)-N(R<sub>1130</sub>)H;
- 25 -alkenyl;
- aryl;
- R<sub>630</sub>-aryl;
- heteroaryl;
- heterocyclyl;

-R<sub>630</sub>- heteroaryl; and

-R<sub>630</sub>-heterocyclyl;

Z is -N(R<sub>530</sub>)-, -O-, or -S-;

Q is a bond, -CO-, or -SO<sub>2</sub>-;

5 A represents the atoms necessary to provide a 5- or 6-membered heterocyclic or heteroaromatic ring that contains up to three heteroatoms;

R<sub>130-6</sub> is selected from:

-alkyl;

-aryl;

10 -heteroaryl;

-heterocyclyl;

-alkenyl;

-R<sub>630</sub>-aryl;

-R<sub>630</sub>- heteroaryl; and

15 -R<sub>630</sub>-heterocyclyl;

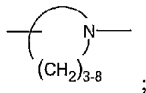
each R<sub>530</sub> is independently hydrogen, C<sub>1-10</sub> alkyl, or C<sub>2-10</sub> alkenyl;

R<sub>630</sub> is alkylene, alkenylene, or alkynylene, which may be interrupted by one or more -O- groups;

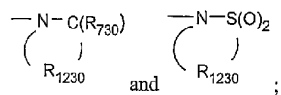
R<sub>730</sub> is =O or =S;

20 R<sub>830</sub> is a bond, alkylene, alkenylene, or alkynylene, which may be interrupted by one or more -O- groups;

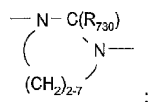
R<sub>930</sub> is hydrogen, C<sub>1-10</sub> alkyl, or arylalkyl; or R<sub>930</sub> can join together with any carbon atom of R<sub>630</sub> to form a ring of the formula



25 R<sub>1030</sub> is hydrogen or C<sub>1-10</sub> alkyl; or R<sub>930</sub> and R<sub>1030</sub> can join together to form a ring selected from



R<sub>1130</sub> is C<sub>1-10</sub> alkyl; or R<sub>930</sub> and R<sub>1130</sub> can join together to form a ring having the structure



5 R<sub>1230</sub> is C<sub>2-7</sub> alkylene which is straight chain or branched, wherein the branching does not prevent formation of the ring; and

R<sub>230</sub>, R<sub>330</sub> and R<sub>430</sub> are independently selected from hydrogen and non-interfering substituents;

and pharmaceutically acceptable salts thereof.

10 Illustrative non-interfering R<sub>230</sub> substituents include:

- alkyl;
- alkenyl;
- aryl;
- heteroaryl;
- 15 -heterocyclyl;
- alkylene-Y-alkyl;
- alkylene-Y-alkenyl;
- alkylene-Y-aryl; and
- alkyl or alkenyl substituted by one or more substituents selected from

20 the group consisting of:

- OH;
- halogen;
- N(R<sub>530</sub>)<sub>2</sub>;
- C(O)-C<sub>1-10</sub> alkyl;
- 25 -C(O)-O-C<sub>1-10</sub> alkyl;
- N<sub>3</sub>;



-aryl;  
 -heteroaryl;  
 -heterocyclyl;  
 -C(O)-aryl; and  
 -C(O)-heteroaryl.

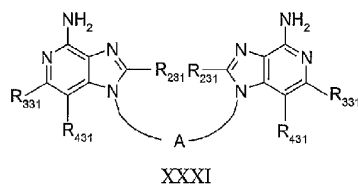
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Illustrative non-interfering  $R_{330}$  and  $R_{430}$  substituents include:

$C_{1-10}$  alkyl,  $C_{2-10}$  alkenyl,  $C_{2-10}$  alkynyl,  $C_{1-10}$  alkoxy,  $C_{1-10}$  alkylthio, amino, alkylamino, dialkylamino, halogen, and nitro.

In another embodiment, the IRM compound can be chosen from *1H*-imidazo dimers of the formula (XXXI):

10



wherein:

15

A is a divalent linking group selected from the group consisting of:

straight or branched chain  $C_{4-20}$  alkylene;  
 straight or branched chain  $C_{4-20}$  alkenylene;  
 straight or branched chain  $C_{4-20}$  alkynylene; and  
 -Z-Y-W-Y-Z-;

20

each Z is independently selected from the group consisting of:

straight or branched chain  $C_{2-20}$  alkylene;  
 straight or branched chain  $C_{4-20}$  alkenylene; and  
 straight or branched chain  $C_{4-20}$  alkynylene;

25

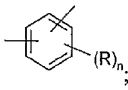
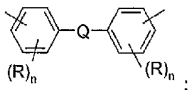
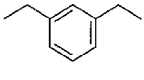
any of which may be optionally interrupted by -O-, -N( $R_{531}$ )-, or -S(O)<sub>2</sub>-;

each Y is independently selected from the group consisting of:

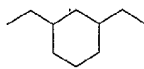
a bond;

- N(R<sub>531</sub>)C(O)-;
- C(O)N(R<sub>531</sub>)-;
- N(R<sub>531</sub>)C(O)N(R<sub>531</sub>)-;
- N(R<sub>531</sub>)S(O)<sub>2</sub>-;
- S(O)<sub>2</sub>N(R<sub>531</sub>)-;
- OC(O)O-;
- OC(O)-;
- C(O)O-;
- N(R<sub>531</sub>)C(O)O-; and
- OC(O)N(R<sub>531</sub>)-;

W is selected from the group consisting of:

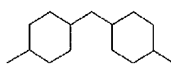
- straight or branched chain C<sub>2-20</sub> alkylene;
- straight or branched chain C<sub>2-20</sub> alkenylene;
- straight or branched chain C<sub>4-20</sub> alkynylene;
- straight or branched chain perfluoro C<sub>2-20</sub> alkylene;
- C<sub>1,4</sub> alkylene-O-C<sub>1,4</sub> alkylene;
- C(O)-;
- S(O)<sub>2</sub>-;
- OC(O)O-;
- N(R<sub>531</sub>)C(O)N(R<sub>531</sub>)-;
- ;
- ;
- ;
- 1,5-naphthylene;
- 2,6-pyridinylene;

1,2-cyclohexylene;  
 1,3-cyclohexylene;  
 1,4-cyclohexylene;  
 trans-1,4-cyclohexylene;



5

;



; and

trans-5-norbornen-2,3-diyl;

wherein n is 0 - 4; each R is independently selected from the group consisting of C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy, and halogen; and Q is selected from the group consisting of a bond, -CH<sub>2</sub>-, and -O-;

10

R<sub>231</sub> is selected from the group consisting of:

-hydrogen;

-alkyl;

-alkenyl;

15

-aryl;

-substituted aryl;

-heteroaryl;

-substituted heteroaryl;

-alkyl-X-alkyl;

20

-alkyl-X-aryl;

-alkyl-X-alkenyl; and

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

-OH;

25

-halogen;

-N(R<sub>631</sub>)<sub>2</sub>;

-C(O)-N(R<sub>631</sub>)<sub>2</sub>;

- C(S)-N(R<sub>631</sub>)<sub>2</sub>;
- S(O)<sub>2</sub>-N(R<sub>631</sub>)<sub>2</sub>;
- N(R<sub>631</sub>)-C(O)-C<sub>1-10</sub> alkyl;
- N(R<sub>631</sub>)-C(S)-C<sub>1-10</sub> alkyl;
- 5 -N(R<sub>631</sub>)-S(O)<sub>2</sub>-C<sub>1-10</sub> alkyl;
- C(O)-C<sub>1-10</sub> alkyl;
- C(O)-O-C<sub>1-10</sub> alkyl;
- N<sub>3</sub>;
- aryl;
- 10 -substituted aryl;
- heteroaryl;
- substituted heteroaryl;
- heterocyclyl;
- substituted heterocyclyl;
- 15 -C(O)-aryl;
- C(O)-(substituted aryl);
- C(O)-heteroaryl; and
- C(O)-(substituted heteroaryl);

R<sub>331</sub> and R<sub>431</sub> are each independently selected from the group consisting of:

- 20 -hydrogen;
- halogen;
- alkyl;
- alkenyl;
- X-alkyl; and
- 25 -N(R<sub>631</sub>)<sub>2</sub>;

or when taken together, R<sub>331</sub> and R<sub>431</sub> form a fused aryl or heteroaryl ring that is unsubstituted or substituted by one or more substituents selected from the group consisting of:

- 30 -halogen;
- alkyl;

-alkenyl;  
 -X-alkyl; and  
 -N(R<sub>631</sub>)<sub>2</sub>;

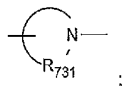
5 or when taken together, R<sub>331</sub> and R<sub>431</sub> form a fused 5 to 7 membered saturated ring, containing 0 to 2 heteroatoms and unsubstituted or substituted by one or more substituents selected from the group consisting of:

10 -halogen;  
 -alkyl;  
 -alkenyl;  
 -X-alkyl; and  
 -N(R<sub>631</sub>)<sub>2</sub>;

each R<sub>531</sub> is independently selected from the group consisting of:

15 hydrogen;  
 C<sub>1-6</sub> alkyl;  
 C<sub>3-7</sub> cycloalkyl; and  
 benzyl; or

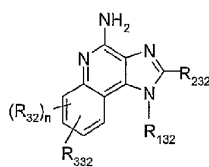
20 when Y is -N(R<sub>531</sub>)C(O)-, -C(O)N(R<sub>531</sub>)-, -N(R<sub>531</sub>)C(O)N(R<sub>531</sub>)-, -N(R<sub>531</sub>)S(O)<sub>2</sub>-, -S(O)<sub>2</sub>N(R<sub>531</sub>)-, -N(R<sub>531</sub>)C(O)O-, or -OC(O)N(R<sub>531</sub>)- and the nitrogen of the N(R<sub>531</sub>) group is bonded to Z, then R<sub>531</sub> can join with Z to form a ring having the structure



25 each R<sub>631</sub> is independently hydrogen or C<sub>1-10</sub> alkyl;  
 R<sub>731</sub> is C<sub>3-8</sub> alkylene; and  
 X is -O- or -S-;

with the proviso that if W is -C(O)-, -S(O)<sub>2</sub>-, -OC(O)O-, or -N(R<sub>531</sub>)C(O)N(R<sub>531</sub>)- then each Y is a bond;  
 and pharmaceutically acceptable salts thereof.

In another embodiment, the IRM compound can be chosen from 6-, 7-, 8-, or 9-position aryl or heteroaryl substituted 1*H*-imidazo[4,5-*c*]quinolin-4-amines of the following Formula (XXXII):



XXXII

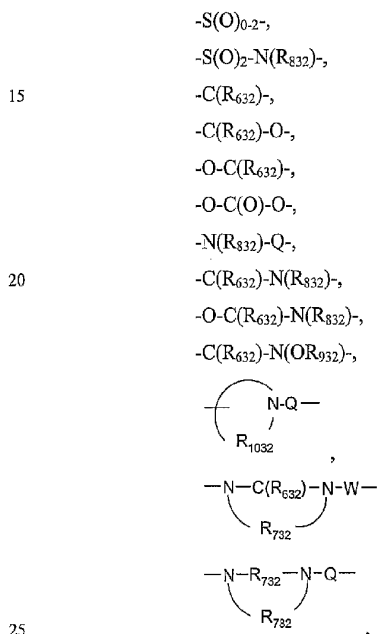
wherein:

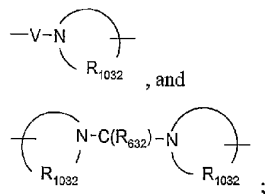
- $R_{332}$  is selected from the group consisting of alkyl, alkoxy, hydroxy, and trifluoromethyl;
- $n$  is 0 or 1;
- $R_{132}$  and  $R_{232}$  are independently selected from the group consisting of hydrogen and non-interfering substituents;
- $R_{332}$  is selected from the group consisting of:
- Z-Ar,
  - Z-Ar'-Y- $R_{432}$ ,
  - Z-Ar'-X-Y- $R_{432}$ ,
  - Z-Ar'- $R_{532}$ , and
  - Z-Ar'-X- $R_{532}$ ;
- Ar is selected from the group consisting of aryl and heteroaryl both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, methylenedioxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkyl, amino, alkylamino, and dialkylamino;

Ar' is selected from the group consisting of arylene and heteroarylene both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkyl, amino, alkylamino, and dialkylamino;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

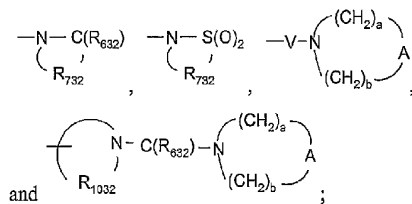




Z is selected from the group consisting of a bond, alkylene, alkenylene, and alkyne;

5 R<sub>432</sub> is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl  
 10 groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and  
 15 heterocyclyl, oxo;

R<sub>532</sub> is selected from the group consisting of:



20 each R<sub>532</sub> is independently selected from the group consisting of =O and =S;  
 each R<sub>732</sub> is independently C<sub>2-7</sub> alkylene;  
 each R<sub>332</sub> is independently selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;  
 R<sub>932</sub> is selected from the group consisting of hydrogen and alkyl;



each  $R_{1032}$  is independently  $C_{3-8}$  alkylene;

A is selected from the group consisting of -O-, -C(O)-, -S(O)<sub>0-2</sub>-, -CH<sub>2</sub>-, and -N(R<sub>432</sub>)<sub>2</sub>-;

Q is selected from the group consisting of a bond, -C(R<sub>632</sub>)<sub>2</sub>-,  
 5 -C(R<sub>632</sub>)-C(R<sub>632</sub>)-, -S(O)<sub>2</sub>-, -C(R<sub>632</sub>)-N(R<sub>832</sub>)-W-, -S(O)<sub>2</sub>-N(R<sub>832</sub>)-, -C(R<sub>632</sub>)-O-, and -C(R<sub>632</sub>)-N(OR<sub>932</sub>)<sub>2</sub>-;

V is selected from the group consisting of -C(R<sub>632</sub>)<sub>2</sub>-, -O-C(R<sub>632</sub>)<sub>2</sub>-,  
 -N(R<sub>832</sub>)-C(R<sub>632</sub>)<sub>2</sub>-, and -S(O)<sub>2</sub>-;

W is selected from the group consisting of a bond, -C(O)-, and -S(O)<sub>2</sub>-; and

10 a and b are independently integers from 1 to 6 with the proviso that  $a + b \leq 7$ ; and pharmaceutically acceptable salts thereof.

Illustrative non-interfering  $R_{132}$  substituents include:

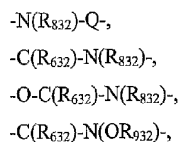
-R<sub>432</sub>,  
 -X-R<sub>432</sub>,  
 15 -X-Y-R<sub>432</sub>,  
 -X-Y-X-Y-R<sub>432</sub>, and  
 -X-R<sub>532</sub>;

wherein:

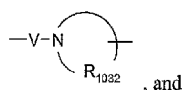
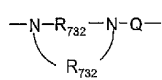
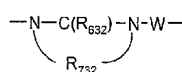
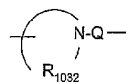
20 each X is independently selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

each Y is independently selected from the group consisting of:

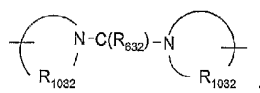
25 -S(O)<sub>0-2</sub>-,  
 -S(O)<sub>2</sub>-N(R<sub>832</sub>)<sub>2</sub>-,  
 -C(R<sub>632</sub>)<sub>2</sub>-,  
 -C(R<sub>632</sub>)-O-,  
 -O-C(R<sub>632</sub>)<sub>2</sub>-,  
 30 -O-C(O)-O-,



5



, and

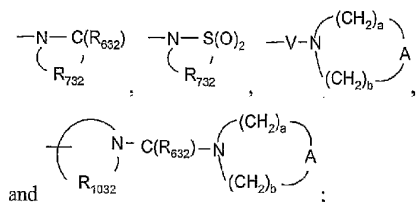


10

R<sub>432</sub> is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

20

R<sub>532</sub> is selected from the group consisting of:

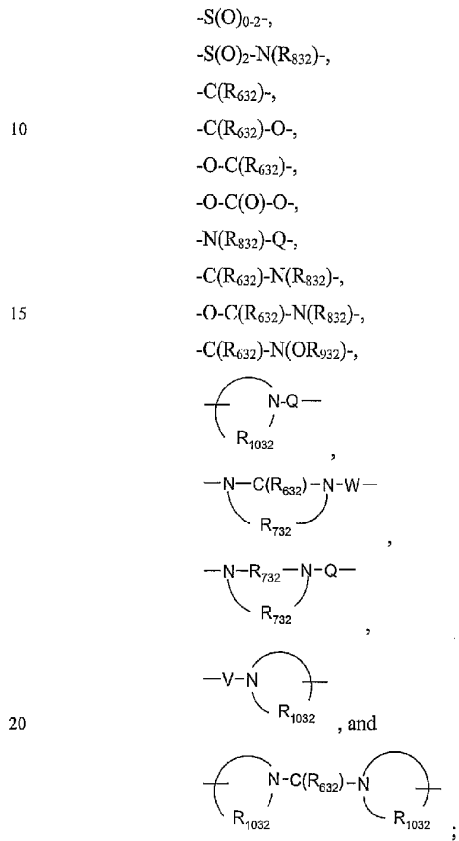


- each R<sub>632</sub> is independently selected from the group consisting of =O and =S;
- each R<sub>732</sub> is independently C<sub>2-7</sub> alkylene;
- 5 each R<sub>832</sub> is independently selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;
- each R<sub>932</sub> is independently selected from the group consisting of hydrogen and alkyl;
- each R<sub>1032</sub> is independently C<sub>3-8</sub> alkylene;
- 10 A is selected from the group consisting of -O-, -C(O)-, -S(O)<sub>0-2</sub>-, -CH<sub>2</sub>-, and -N(R<sub>432</sub>)-;
- each Q is independently selected from the group consisting of a bond, -C(R<sub>632</sub>)-, -C(R<sub>632</sub>)-C(R<sub>632</sub>)-, -S(O)<sub>2</sub>-, -C(R<sub>632</sub>)-N(R<sub>832</sub>)-W-, -S(O)<sub>2</sub>-N(R<sub>832</sub>)-, -C(R<sub>632</sub>)-O-, and -C(R<sub>632</sub>)-N(OR<sub>932</sub>)-;
- 15 each V is independently selected from the group consisting of -C(R<sub>632</sub>)-, -O-C(R<sub>632</sub>)-, -N(R<sub>832</sub>)-C(R<sub>632</sub>)-, and -S(O)<sub>2</sub>-;
- each W is independently selected from the group consisting of a bond, -C(O)-, and -S(O)<sub>2</sub>-; and
- a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;
- 20 Illustrative non-interfering R<sub>232</sub> substituents include:
  - R<sub>432</sub>,
  - X-R<sub>432</sub>,
  - X-Y-R<sub>432</sub>, and
  - X-R<sub>532</sub>;
- 25 wherein:

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylenc, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O-

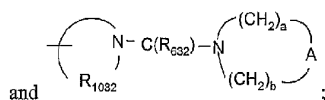
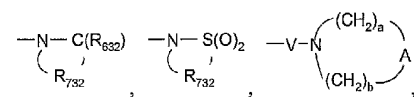
5 groups;

Y is selected from the group consisting of:



R<sub>432</sub> is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R<sub>532</sub> is selected from the group consisting of:



each R<sub>632</sub> is independently selected from the group consisting of =O and =S;  
 each R<sub>732</sub> is independently C<sub>2-7</sub> alkylene;  
 each R<sub>832</sub> is independently selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R<sub>932</sub> is selected from the group consisting of hydrogen and alkyl;

each R<sub>1032</sub> is independently C<sub>3-8</sub> alkylene;

A is selected from the group consisting of -O-, -C(O)-, -S(O)<sub>0.2-</sub>, -CH<sub>2</sub>-, and -N(R<sub>432</sub>)-;

Q is selected from the group consisting of a bond, -C(R<sub>632</sub>)-,

-C(R<sub>632</sub>)-C(R<sub>632</sub>)-, -S(O)<sub>2</sub>-, -C(R<sub>632</sub>)-N(R<sub>832</sub>)-W-, -S(O)<sub>2</sub>-N(R<sub>832</sub>)-, -C(R<sub>632</sub>)-O-, and -C(R<sub>632</sub>)-N(OR<sub>932</sub>)-;

V is selected from the group consisting of -C(R<sub>632</sub>)-, -O-C(R<sub>632</sub>)-,

$-N(R_{632})-C(R_{632})-$ , and  $-S(O)_2-$ ;

W is selected from the group consisting of a bond,  $-C(O)-$ , and  $-S(O)_2-$ ; and  
a and b are independently integers from 1 to 6 with the proviso that  $a + b \leq 7$ ;

5           Herein, "non-interfering" means that the ability of the compound or salt to modulate (e.g., induce or inhibit) the biosynthesis of one or more cytokines is not destroyed by the non-interfering substituent.

          As used herein, the terms "alkyl", "alkenyl", "alkynyl" 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 10  
10           cycloalkyl and cycloalkenyl. Unless otherwise specified, these groups contain from 1 to 20 carbon atoms, with alkenyl and alkynyl groups containing from 2 to 20 carbon atoms. In some embodiments, these groups have a total of up to 10 carbon atoms, up to 8 carbon atoms, up to 6 carbon atoms, or up to 4 carbon atoms. Cyclic groups can be monocyclic or polycyclic and preferably have from 3 to 10 ring carbon atoms.  
15           Exemplary cyclic groups include cyclopropyl, cyclopropylmethyl, cyclopentyl, cyclohexyl, adamantyl, and substituted and unsubstituted bornyl, norbornyl, and norbornenyl.

          Unless otherwise specified, "alkylene", "alkenylene", and "alkynylene" are the divalent forms of the "alkyl", "alkenyl", and "alkynyl" groups defined above. For  
20           example, an arylalkenyl group comprises an alkylene moiety to which an aryl group is attached.

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

          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 "hetero atom" refers to the atoms O, S, or N.

The term "heteroaryl" includes aromatic rings or ring systems that contain at least one ring hetero atom. 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, quinazoliny, pyrazinyl, 1-oxidopyridyl, pyridazinyl, triazinyl, tetrazinyl, oxadiazolyl, thiadiazolyl, and so on.

The term "heterocyclyl" includes non-aromatic rings or ring systems that contain at least one ring hetero atom 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, tetrahydropyranyl, quinuclidinyl, homopiperidinyl, homopiperazinyl, and the like.

The terms "arylene," "heteroarylene," and "heterocyclylene" are the divalent forms of the "aryl," "heteroaryl," and "heterocyclyl" groups defined above. Likewise, "arylenyl," "heteroarylenyl," and "heterocyclenyl" are the divalent forms of the "aryl," "heteroaryl," and "heterocyclyl" groups defined above. For example, an alkylarylenyl group comprises an arylene moiety to which an alkyl group is attached.

Unless otherwise specified, the aryl, heteroaryl, and heterocyclyl groups of Formulas IX - XXX can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, methylenedioxy, ethylenedioxy, alkylthio, haloalkyl, haloalkoxy, haloalkylthio, halogen, nitro, hydroxy, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylthio, arylalkoxy, arylalkylthio, heteroaryl, heteroaryloxy, heteroarylthio, heteroarylalkoxy, heteroarylalkylthio, amino, alkylamino, dialkylamino, heterocyclyl, heterocycloalkyl, alkylcarbonyl, alkenylcarbonyl, alkoxycarbonyl, haloalkylcarbonyl, haloalkoxycarbonyl, alkylthiocarbonyl, arylcarbonyl, heteroarylcarbonyl, heterocyclylcarbonyl, aryloxy, heteroaryloxy, arylthiocarbonyl, heteroarylthiocarbonyl, alkanoyloxy, alkanoylthio, alkanoylamino, aryloxy, aroylthio, aroylamino, alkylaminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryldiazinyl,

alkylsulfonylamino, arylsulfonylamino, arylalkylsulfonylamino, alkylcarbonylamino,  
alkenylcarbonylamino, arylcarbonylamino, arylalkylcarbonylamino,  
heteroarylcarbonylamino, heteroarylalkylcarbonylamino, alkylsulfonylamino,  
alkenylsulfonylamino, arylsulfonylamino, arylalkylsulfonylamino,  
5 heteroarylsulfonylamino, heteroarylalkylsulfonylamino, alkylaminocarbonyl,  
dialkylaminocarbonyl, arylaminocarbonyl, arylalkylaminocarbonyl,  
alkenylaminocarbonyl, heteroarylaminocarbonyl, heteroarylalkylaminocarbonyl,  
alkylaminocarbonylamino, alkenylaminocarbonylamino, arylaminocarbonylamino,  
arylalkylaminocarbonylamino, heteroarylaminocarbonylamino,  
10 heteroarylalkylaminocarbonylamino and, in the case of heterocyclyl, oxo. If any other  
groups are identified as being "substituted" or "optionally substituted", then those  
groups can also be substituted by one or more of the above enumerated substituents.

The IRM compounds and salts thereof described herein include any of their  
pharmaceutically acceptable forms, such as isomers (e.g., diastereomers and  
15 enantiomers), solvates, polymorphs, and the like. In particular, if a compound is  
optically active, the invention specifically includes the use of each of the compound's  
enantiomers as well as racemic mixtures of the enantiomers.

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

In certain embodiments, the IRM is an imidazonaphthyridine amine. In other  
embodiments, the IRM is 2-methyl-1-(2-methylpropyl)-1*H*-imidazo[4,5-  
*c*][1,5]naphthyridin-4-amine.

The amount of an IRM compound that will be therapeutically effective in a  
25 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  
30 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 or prophylactic effect, such as cytokine induction, inhibition of TH2 immune response, antiviral or antitumor activity, reduction or elimination of postsurgical scarring, reduction or resolution of actinic keratosis or pre-actinic keratosis lesions, reduction in the recurrence of actinic keratosis, or protection against uv-induced epidermal neoplasia, or as an adjuvant for therapeutic and prophylactic vaccines, including DNA, whole cell, protein subunit, attenuated virus, and all other vaccines, where the formulation may be applied before, during and/or after vaccine delivery.

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. In certain embodiments, the amount or concentration of the IRM compound is at least 0.0001% by weight, such as, for example, at least 0.001%, at least 0.003%, at least 0.005%, at least 0.01%, at least 0.03%, at least 0.10%, at least 0.20%, at least 0.25%, at least 0.27%, at least 0.30%, and at least 1.0%, by weight based on the total weight of the formulation. In other embodiments, the amount of the IRM compound is at most 10% by weight, such as, for example, at most 5.0%, at most 3.0%, at most 1.0%, at most 0.5%, at most 0.4%, at most 0.35%, at most 0.33%, and at most 0.3%, by weight based on the total weight of the formulation.

20

#### Preservative System

The formulation includes a preservative system. The preservative system includes one or more compounds that inhibit microbial growth (e.g., fungal and bacterial growth) within the formulation (for example, during manufacturing and use). The preservative system includes at least one preservative compound chosen from sorbic acid, esters or salts thereof, such as, for example, isopropyl sorbate, calcium sorbate, potassium sorbate, sodium sorbate, and triethanolammonium sorbate. Combinations of these may be used in formulations of the present invention. Such preservatives adversely affect the stability of the formulations as described herein.

25

According to the present invention, the sorbic acid preservative (i.e., sorbic acid, esters or salts thereof, or combinations thereof) is preferably present in a formulation in an amount of at least 0.005% by weight, more preferably at least 0.01% by weight, even more preferably at least 0.02% by weight, even more preferably at least 0.05% by weight, and even more preferably at least 0.08% by weight, based on the total weight of the formulation. The sorbic acid preservative is preferably present in a formulation in an amount of no greater than 1% by weight, more preferably no greater than 0.5% by weight, even more preferably no greater than 0.2% by weight, even more preferably no greater than 0.12% by weight, and even more preferably, no greater than 0.10% by weight, based on the total weight of the formulation.

In certain embodiments, in addition to the sorbic acid preservative, the preservative system will generally include at least one additional (i.e., secondary) preservative compound, such as, for example, methylparaben, ethylparaben, propylparaben, butylparaben, and phenoxyethanol. Various combinations of these compounds can be included in the preservative system. In some embodiments of the invention, the secondary preservative compound is methylparaben.

In some embodiments of the invention, the secondary preservative compound is present in an amount of at least 0.01% by weight, such as for example, at least 0.02%, at least 0.03%, at least 0.04%, and at least 0.05%, by weight based on the total weight of the formulation. In other embodiments of the invention the secondary preservative compound is present in an amount of at most 0.5 %, such as for example, at most 0.4%, at most 0.3%, and at most 0.2%, by weight based on the total weight of the formulation.

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, propylene glycol, and poly(ethylene glycol)(4) monolaurate. Combinations of such enhancing solubilizers can be used in formulations of the present invention.

In some embodiments of the present invention, propylene glycol is present in an amount of at least 1.0% by weight, such as for example, at least 2.0%, at least 3.0%, at least 4.0%, and at least 5.0%, by weight based on the total weight of the formulation. In

other embodiments of the present invention, propylene glycol is present in at most 10.0% by weight, such as for example, at most 8.0%, at most 6.0%, and at most 5.0%, by weight based on the total weight of the formulation.

5 Antioxidants

Surprisingly, it has been discovered that the stability issue of the IRM/sorbic acid preservative combination can be addressed through the addition of one or more antioxidants. Antioxidants suitable for use herein are those that inhibit the autoxidation of the sorbic acid preservative. In particular, antioxidants having hydrogen atom  
10 donating functionality have demonstrated much greater improvement than others. Although not intending to be limiting, it is believed that antioxidants react with autoxidation intermediates (typically, radicals) of the sorbic acid preservative to form products that do not react with the IRM.

Suitable antioxidants are those that are pharmaceutically acceptable and  
15 described in the International Cosmetic Ingredient Dictionary and Handbook, Ninth Edition, Volume 4, 2002, and in the USP NF 2004: The United States Pharmacopeia, 27<sup>th</sup> Revision and The National Formulary, 22<sup>nd</sup> Edition.

Examples of suitable antioxidants include ascorbic acid (D and/or L enantiomers), ascorbyl palmitate (D and/or L enantiomers), butylated hydroxyanisole  
20 (BHA), butylated hydroxytoluene (BHT), cysteine (D and/or L enantiomers), propyl gallate, sodium formaldehyde sulfoxylate, sodium thiosulfate, sulfur dioxide, tocopherol, including all of its stereoisomers, and tocopherol polyethylene glycol 1000 succinate, including all of its stereoisomers.

Preferred antioxidants are those containing hydrogen atom donating functional  
25 groups. Examples of such antioxidants include ascorbic acid, ascorbyl palmitate, BHT, BHA, cysteine, propyl gallate, sodium formaldehyde sulfoxylate, tocopherol including all of its stereoisomers, and tocopherol polyethylene glycol 1000 succinate, including all of its stereoisomers.

More preferred antioxidants are those containing aromatic hydroxy groups  
30 capable of hydrogen atom donation. Examples of such antioxidants include BHA,

BHT, propyl gallate, tocopherol, including all of its stereoisomers, and tocopherol polyethylene glycol 1000 succinate, including all of its stereoisomers.

Most preferred antioxidants are BHA and BHT, which can be used in combination.

5           According to the present invention, the antioxidant is preferably present in a formulation in an amount of at least 0.001% by weight, more preferably at least 0.005% by weight, even more preferably at least 0.008% by weight, and even more preferably at least 0.01% by weight, based on the total weight of the formulation. The antioxidant is preferably present in a formulation in an amount of no greater than 0.3% by weight,  
10       more preferably no greater than 0.2% by weight, and even more preferably no greater than 0.012% by weight, and even more preferably no greater than 0.1% by weight, based on the total weight of the formulation.

          According to the present invention, the sorbic acid preservative (i.e., sorbic acid/ester/salt) to antioxidant weight ratio is preferably at least 1:20, more preferably at  
15       least 1:1, and even more preferably at least 5:1. The sorbic acid to antioxidant weight ratio is preferably no greater than 1000:1, more preferably no greater than 20:1, and even more preferably no greater than 10:1.

#### Chelating Agents

20           In certain embodiments of the present invention, the formulation can also include at least one chelating agent. The chelating agent functions to stabilize the antioxidant(s) present in the formulation.

          Chelating agents are compounds that complex with metal ions. Suitable chelating agents are those that are pharmaceutically acceptable and described in the  
25       International Cosmetic Ingredient Dictionary and Handbook, Ninth Edition, Volume 4, 2002.

          Suitable chelating agents include ethylenediaminetetraacetic acid (EDTA) and citric acid, hydrates thereof, salts thereof, and hydrates of the salts thereof. Examples of such chelating agents include ethylenediaminetetraacetic acid disodium salt,

ethylenediaminetetraacetic acid disodium salt dihydrate, and citric acid monohydrate.

Various combinations of chelating agents can be used if desired.

According to the present invention, if included, the chelating agent is preferably present in a formulation in an amount of at least 0.001% by weight, more preferably at least 0.005% by weight, even more preferably at least 0.01% by weight, and even more preferably at least 0.05% by weight, based on the total weight of the formulation. The chelating agent is preferably present in a formulation in an amount of no greater than 0.2% by weight, and more preferably no greater than 0.1% by weight, based on the total weight of the formulation.

According to the present invention, if included, the antioxidant to chelating agent weight ratio is preferably at least 1:200, more preferably at least 1:10, and even more preferably at least 1:5. The antioxidant to chelating agent weight ratio is preferably no greater than 300:1, more preferably no greater than 10:1, and even more preferably no greater than 2:1.

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#### Fatty Acids

The topical formulations of the invention can additionally include a fatty acid. As used herein, the term "fatty acid" means a carboxylic acid, either saturated or unsaturated having 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-chain 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 certain embodiments, the amount of the fatty acid is at least 0.05% by weight, at least 1.0% by weight, at least 3.0% by weight, at least 5.0% by weight, at least 6.0% by weight, at least 7.0% by weight, at least 10% by weight, at least 15% by weight, or at least 25% by weight, based on the total weight of the formulation. In certain embodiments, the amount of the fatty acid is at most 40% by weight, at most 30% by weight, at most 15% by weight, at most 10% by weight, or at most 8.0% by weight based on the total weight of the formulation. The fatty acid component of the formulation can comprise one or more fatty acids.

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#### Hydrophobic Component

The topical formulations of the invention can additionally include 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.

Formulations intended for dermal or topical use typically have amounts of an oil phase and a hydrophobic, aprotic component sufficient to provide desirable qualities such as spreadability and feel.

Examples of useful hydrophobic, aprotic components include but are not limited to fatty acid esters, for example, isopropyl myristate, isopropyl palmitate, diisopropyl dimer dilinoleate; medium-chain (e.g., 8 to 14 carbon atoms) triglycerides, for example, caprylic/capric triglyceride; cetyl esters; 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. Various combinations of such hydrophobic, aprotic components can be used if desired.

In certain embodiments, the amount of the hydrophobic, aprotic component is at least 1.0% by weight, at least 3.0% by weight, at least 3.5% by weight, at least 4.0% by weight, at least 4.5% by weight, at least 5.0% by weight, or at least 10% by weight, based on the total weight of the formulation. In certain embodiments, the amount of the hydrophobic, aprotic component is at most 30% by weight, at most 15% by weight, at most 10% by weight, or at most 5.0% by weight based on the total weight of the formulation.

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%.

#### Viscosity Enhancing Agent

The formulations of the present invention can also comprise a viscosity enhancing agent. When water is the continuous phase, the viscosity enhancing agent will be a hydrophilic viscosity enhancing agent. Examples of suitable hydrophilic viscosity enhancing agents include cellulose ethers such as hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, and carboxymethylcellulose; polysaccharide gums such as xanthan gum; and homopolymers and copolymers of acrylic acid crosslinked with allyl sucrose or allyl pentaerythriol such as those polymers designated as carbomers in the United States Pharmacopoeia. Suitable carbomers include, for example, those available as CARBOPOL 934P, CARBOPOL 971P, CARBOPOL 940, CARBOPOL 974P, CARBOPOL 980, and PEMULEN TR-1 (USP/NF Monograph; Carbomer 1342), all available from Noveon, Cleveland, Ohio. In one embodiment of the present invention, the viscosity enhancing agent is chosen from CARBOPOL 974P and 980.

In certain embodiments, the amount of the viscosity enhancing agent, when used, is at least 0.1% by weight, at least 0.2% by weight, at least 0.5% by weight, at least 0.6% by weight, at least 0.7% by weight, at least 0.9% by weight, or at least 1.0%

by weight, based on the total weight of the formulation. In certain embodiments, the amount of the viscosity enhancing agent, when used, is at most 10% by weight, at most 5.0% by weight, at most 3.0% by weight, at most 2.0% by weight, or at most 1.5% by weight, based on the total weight of the formulation.

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#### Emulsifier

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, DE).

10

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 5.0% by weight, and from 0.75% to 3.5% by weight. In certain embodiments, the amount of the emulsifier, if used, is present in an amount of at least 0.1% by weight, at least 0.5% by weight, at least 0.75% by weight, at least 1.0% by weight, at least 2.5% by weight, at least 3.5% by weight, or at least 5.0% by weight, based on the total weight of the formulation. In certain embodiments, the amount of the emulsifier, if used, is present in an amount of at most 10% by weight, at most 5.0% by weight, or at most 3.5% by weight, based on the total weight of the formulation.

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#### pH Adjuster

The formulations of the present invention may additionally include at least one pH adjuster. Suitable pH adjusters include organic bases and inorganic bases such as, for example, KOH and NaOH (e.g., aqueous formulations). 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.

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#### Illustrative Formulations

Preferred formulations of the present invention are as follows. The water used is typically purified water.

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In one embodiment of the present invention, a pharmaceutical formulation includes:

0.001% by weight to 5.0% by weight of an imidazonaphthyridine amine (preferably, 2-methyl-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine);

10

0.02% by weight to 0.2% by weight of a sorbic acid preservative selected from the group consisting of sorbic acid, esters thereof, salts thereof, and combinations thereof;

0 to 10.0% by weight of propylene glycol;

15

0.05% by weight to 0.2% by weight of methylparaben;

0.001% by weight to 0.2% by weight of butylated hydroxyanisole, butylated hydroxytoluene, or combinations thereof;

0 to 0.1% by weight of ethylenediaminetetraacetic acid, a hydrate thereof, a salt thereof, a hydrate of a the salt thereof, or combinations thereof;

20

1% by weight to 30% by weight of isostearic acid;

1% by weight to 15% by weight of a medium-chain triglyceride;

0.2% by weight to 2.0% by weight of a carbomer;

0.1% by weight to 6.0% by weight of a poloxamer; and

water;

25

wherein the formulation has a pH of 4.0 to 6.0 and the weight percentages are based on the total weight of the formulation.

In one embodiment, a pharmaceutical formulation includes:

0.3% by weight of 2-methyl-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine;

30

0.15% by weight sorbic acid;  
5.0% by weight propylene glycol;  
0.2% by weight methylparaben;  
0.1% by weight butylated hydroxyanisole;  
5 0.05% by weight ethylenediaminetetraacetic acid disodium salt dihydrate;  
7.0% by weight isostearic acid;  
4.0% by weight of caprylic/capric triglyceride;  
1.0% by weight of a carbomer;  
3.5% by weight of a poloxamer;  
10 0.8% by weight of an aqueous solution of 20% by weight NaOH in water; and  
77.9% by weight water;  
wherein the weight percentages are based on the total weight of the formulation.

In one embodiment, a pharmaceutical formulation includes:  
15 0.30% by weight of 2-methyl-1-(2-methylpropyl)-1H-imidazo[4,5-  
c][1,5]naphthyridin-4-amine;  
0.10% by weight sorbic acid;  
5.00% by weight propylene glycol;  
0.20% by weight methylparaben;  
20 0.01% by weight butylated hydroxyanisole;  
0.05% by weight ethylenediaminetetraacetic acid disodium salt dihydrate;  
7.00% by weight isostearic acid;  
4.00% by weight of caprylic/capric triglyceride;  
1.00% by weight of a carbomer;  
25 3.50% by weight of a poloxamer;  
0.80% by weight of an aqueous solution of 20% by weight NaOH in water; and  
78.04% by weight water;  
wherein the weight percentages are based on the total weight of the formulation.

30 In one embodiment, a pharmaceutical formulation includes:

0.3% by weight of 2-methyl-1-(2-methylpropyl)-1*H*-imidazo[4,5-  
 c][1,5]naphthyridin-4-amine;  
 0.1% by weight sorbic acid;  
 5.0% by weight propylene glycol;  
 5 0.2% by weight methylparaben;  
 0.01% by weight butylated hydroxyanisole;  
 0.05% by weight ethylenediaminetetraacetic acid disodium salt dihydrate;  
 7.0% by weight isostearic acid;  
 4.0% by weight of caprylic/capric triglyceride;  
 10 1.0% by weight of a carbomer;  
 3.5% by weight of a poloxamer;  
 0.8% by weight of an aqueous solution of 20% by weight NaOH in water; and  
 78.0% by weight water;  
 wherein the weight percentages are based on the total weight of the formulation.

15

In one embodiment, a pharmaceutical formulation includes:

0.03% by weight of 2-methyl-1-(2-methylpropyl)-1*H*-imidazo[4,5-  
 c][1,5]naphthyridin-4-amine;  
 0.15% by weight sorbic acid;  
 20 5.0% by weight propylene glycol;  
 0.2% by weight methylparaben;  
 0.1% by weight butylated hydroxyanisole;  
 0.05% by weight ethylenediaminetetraacetic acid disodium salt dihydrate;  
 5.0% by weight isostearic acid;  
 25 4.0% by weight of caprylic/capric triglyceride;  
 1.0% by weight of a carbomer;  
 3.5% by weight of a poloxamer;  
 0.8% by weight of an aqueous solution of 20% by weight NaOH in water; and  
 80.17% by weight water;  
 30 wherein the weight percentages are based on the total weight of the formulation.

In one embodiment, a pharmaceutical formulation includes:  
0.1% by weight of 2-methyl-1-(2-methylpropyl)-1*H*-imidazo[4,5-  
c][1,5]naphthyridin-4-amine;  
5 0.15% by weight sorbic acid;  
5.0% by weight propylene glycol;  
0.2% by weight methylparaben;  
0.1% by weight butylated hydroxyanisole;  
0.05% by weight ethylenediaminetetraacetic acid disodium salt dihydrate;  
10 5.0% by weight isostearic acid;  
4.0% by weight of caprylic/capric triglyceride;  
1.0% by weight of a carbomer;  
3.5% by weight of a poloxamer;  
0.8% by weight of an aqueous solution of 20% by weight NaOH in water; and  
15 80.1% by weight water;  
wherein the weight percentages are based on the total weight of the formulation.

#### Methods of Application

Formulations according to the present invention can be applied to any suitable  
20 location, for example topically to dermal and/or mucosal surfaces, or internally to a  
particular tissue location. In the case of dermal application, for example, 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  
25 present invention is directed to a method for the treatment of a dermal and/or mucosal  
associated condition comprising applying to skin one of the foregoing formulations. As  
used herein, a "dermal and/or mucosal associated condition" means an inflammatory,  
infectious, neoplastic or other condition that involves a dermal and/or mucosal surface  
or that is in sufficient proximity to a dermal and/or mucosal surface to be affected by a  
30 therapeutic agent topically applied to the surface. Examples of a dermal and/or mucosal

associated condition include warts, atopic dermatitis, postsurgical scars, lesions caused by a herpes virus, and epidermal neoplasias, such as for example actinic keratosis, pre-actinic keratosis lesions, malignant melanomas, basal cell carcinoma, and squamous cell carcinoma.

5           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  
10           considered the most important manifestation of sun-induced skin damage.

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

          The precise amount of formulation effective for treating a dermal and/or  
15           mucosal associated condition will vary according to factors known in the art including but not limited to the particular IRM compound, the particular formulation, the intended dosing regimen, the particular condition being treated, the state of the subject's immune system (e.g., suppressed, compromised, stimulated), and the species to which the formulation is being administered. In some embodiments the amount of formulation is  
20           an amount sufficient to deliver a dose of about 0.02 mg to about 15 mg of IRM compound. In other embodiments the amount of formulation is an amount sufficient to deliver a dose of about 0.2 mg to about 2.5 mg of IRM compound. In other  
          embodiments the amount of formulation is an amount sufficient to deliver a dose of about 0.5 mg to about 1.7 mg of IRM compound. In one particular embodiment a dose  
25           of 0.75 mg of IRM compound is delivered. In another particular embodiment a dose of 1.5 mg of IRM compound is delivered.

          The dosing regimen will vary at least in part on many factors known in the art including but not limited to the particular IRM compound, the particular formulation, the amount of formulation being administered, the particular condition being treated,  
30           the state of the subject's immune system (e.g., suppressed, compromised, stimulated),

and the species to which the formulation is being administered. In some embodiments the formulation is administered at least once a week, at least twice a week, or at least three times a week. In other embodiments the formulation is administered at most seven times a week, at most six times a week, at most five times a week, or at most four  
5 times a week. In some embodiments the formulation is administered for at least two weeks, for at least four weeks, for at least six weeks, or for at least eight weeks. In other embodiments the formulation is administered for at most sixteen weeks, for at most twelve weeks, or for at most eight weeks. In some embodiments, about 200 to about 600 mg of formulation is administered twice a week for eight weeks. In one  
10 particular embodiment, about 250 mg of the formulation described in Example 22 below is administered twice a week for eight weeks. In another particular embodiment, about 500 mg of the formulation described in Example 22 below is administered twice a week for eight weeks.

15

#### EXAMPLES

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  
20 invention.

#### TEST METHODS

##### Test Method 1 – IRM 1 Compound Content and Sorbic Acid Content

A gradient reversed phase high performance liquid chromatography (HPLC)  
25 method was used to determine the amount of 2-methyl-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine (IRM Compound 1) and sorbic acid in cream formulations.

HPLC parameters: Analytical column: ZORBAX RX-C8, 5.0 micron particle, 150 x 4.6 mm (available from Agilent Technologies, Wilmington, Delaware, USA);  
30 Column temperature: 30°C; Detector: UV at 254 nm; Flow Rate: 1.0 mL/min; Injection

5 volume: 25  $\mu$ L; Mobile phase A: 62% aqueous (0.2% sodium 1-octanesulfonate, 0.2% triethylamine, 0.2% of 85% phosphoric acid), 21% acetonitrile, 17% methanol; Mobile Phase B: 20% aqueous (0.2% sodium 1-octanesulfonate, 0.2% triethylamine, 0.2% of 85% phosphoric acid), 42% acetonitrile, 38% methanol; Data acquisition time: 23 minutes; HPLC run time: approximately 30 minutes.

10 Gradient program: 0 minutes: 100% mobile phase A, 0% mobile phase B; 2.5 minutes: 100% mobile phase A, 0% mobile phase B; 10 minutes: 49% mobile phase A, 51% mobile phase B; 14 minutes: 49% mobile phase A, 51% mobile phase B; 20 minutes: 0% mobile phase A, 100% mobile phase B; 23 minutes: 0% mobile phase A, 100% mobile phase B; 25 minutes: 100% mobile phase A, 0% mobile phase B; 30 minutes: 100% mobile phase A, 0% mobile phase B.

15 IRM Compound 1 sample solution: A portion of the cream formulation (1000 mg for creams containing 0.01, 0.03, 0.05 and 0.1% IRM and 250 mg for creams containing 0.3, 0.6, and 1.0% IRM) was accurately weighed into a volumetric flask (50 mL for the 1000 mg samples and 100 mL for the 250 mg samples). Approximately 40 mL of diluent (prepared by combining 200 parts of acetonitrile, 790 parts water, and 10 parts phosphoric acid, all parts by volume) was added to the 50 mL flask or 80 mL to the 100 mL flask. The flask was sonicated with occasional shaking for 20 minutes or until the cream was completely dispersed. The solution was allowed to cool to ambient  
20 temperature and then diluted to volume with diluent. A portion of the solution was filtered using a syringe equipped with a 0.2 micron PTFE filter to provide the sample solution.

25 Sorbic acid sample solution: A 250 mg portion of cream was accurately weighed into a 100 mL volumetric flask. Approximately 80 mL of diluent (prepared by combining 200 parts of acetonitrile, 790 parts water, and 10 parts phosphoric acid, all parts by volume) was added to the flask. The flask was sonicated with occasional shaking for 20 minutes or until the cream was completely dispersed. The solution was allowed to cool to ambient temperature and then diluted to volume with diluent. A portion of the solution was filtered using a syringe equipped with a 0.2 micron PTFE filter to provide  
30 the sample solution.

## Test Method 2 – BHA Content

A gradient reversed phase high performance liquid chromatography (HPLC) method was used to determine the amount of BHA in cream formulations containing IRM Compound 1.

HPLC parameters: Analytical column: ZORBAX Bonus RP, 3.5 micron particle, 150 x 3.0 mm; Column temperature: 40°C; Detector: UV at 290 nm; Flow Rate: 0.5 mL/min; Injection volume: 20 µL; Mobile phase A: 0.1% formic acid in water; Mobile Phase B: 0.05% formic acid in acetonitrile; Data acquisition time: 12 minutes; HPLC run time: approximately 20 minutes.

Gradient program: 0 minutes: 60% mobile phase A, 40% mobile phase B; 10 minutes: 5% mobile phase A, 95% mobile phase B; 12 minutes: 5% mobile phase A, 95% mobile phase B; 13 minutes: 60% mobile phase A, 40% mobile phase B; 20 minutes: 60% mobile phase A, 40% mobile phase B.

Sample solution: A portion (approximately 1000 mg) of the cream formulation was accurately weighed into a 100 mL volumetric flask. Approximately 80 mL of diluent (prepared by combining 600 parts of acetonitrile, 400 parts of water, and 1 part formic acid, all parts by volume) was added and the flask was sonicated with occasional shaking for 10 minutes or until the cream was well dispersed. The solution was allowed to cool to ambient temperature and then diluted to volume with diluent. A portion of the solution was filtered using a syringe equipped with a 0.2 micron PTFE filter to provide the sample solution.

## Test Method 3 - IRM Compound 1 Content

A gradient reversed phase high performance liquid chromatography (HPLC) method was used to determine the amount of 2-methyl-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine (IRM Compound 1) in cream formulations using BHA and BHT as the antioxidants.

HPLC parameters: Analytical column: ZORBAX Bonus RP, 3.5 micron particle, 150 x 4.6 mm (available from Agilent Technologies, Wilmington, Delaware, USA);



Column temperature: 35°C; Detector: UV at 240 nm; Flow Rate: 1.0 mL/min; Injection volume: 30 µL; Mobile phase A: 0.05% trifluoroacetic acid in water; Mobile Phase B: 0.05% trifluoroacetic acid in acetonitrile; Data acquisition time: 25 minutes; HPLC run time: 35 minutes.

5 Gradient program: 0 minutes: 80% mobile phase A, 20% mobile phase B; 5 minutes: 80% mobile phase A, 20% mobile phase B; 15 minutes: 75% mobile phase A, 25% mobile phase B; 25 minutes: 35% mobile phase A, 65% mobile phase B; 28 minutes: 10% mobile phase A, 90% mobile phase B; 29 minutes: 80% mobile phase A, 20% mobile phase B; 35 minutes: 80% mobile phase A, 20% mobile phase B.

10 Sample solution: A portion of the cream formulation (2500 mg for creams containing 0.03% IRM; 1500 mg for creams containing 0.1% IRM; and 500 mg for creams containing 0.3% IRM) was accurately weighed into a volumetric flask (50 mL for creams containing 0.03% IRM; 100 mL for creams containing 0.1 or 0.3% IRM).  
15 Approximately 40 mL of diluent (prepared by combining 200 parts of acetonitrile, 790 parts water, and 10 parts phosphoric acid, all parts by volume) was added to the 50 mL flask or 80 mL to the 100 mL flask. The flask was shaken or vortexed to dislodge any cream from the neck of the flask and then sonicated with occasional shaking for 10 minutes or until the cream was completely dispersed. The solution was allowed to cool to ambient temperature and then diluted to volume with diluent. A portion of the  
20 solution was filtered using a syringe equipped with a 0.2 micron PTFE filter to provide the sample solution.

#### Test Method 4 - Sorbic Acid and BHA Content

25 A gradient reversed phase high performance liquid chromatography (HPLC) method was used to determine the amount of sorbic acid and BHA in cream formulations containing IRM Compound 1.

HPLC parameters: Analytical column: ZORBAX Bonus RP, 3.5 micron particle, 150 x 4.6 mm; Column temperature: 35°C; Detector: UV at 285 nm; Flow Rate: 1.0 mL/min; Injection volume: 25 µL; Mobile phase A: 0.05% trifluoroacetic acid in water;

Mobile Phase B: 0.05% trifluoroacetic acid in acetonitrile; Data acquisition time: 12 minutes; HPLC run time: 18 minutes.

Gradient program: 0 minutes: 60% mobile phase A, 40% mobile phase B; 10 minutes: 5% mobile phase A, 95% mobile phase B; 12 minutes: 5% mobile phase A, 95% mobile phase B; 13 minutes: 60% mobile phase A, 40% mobile phase B; 18 minutes: 60% mobile phase A, 40% mobile phase B.

Sample solution: A portion (approximately 1000 mg) of the cream formulation was accurately weighed into a 100 mL volumetric flask. Approximately 80 mL of diluent (prepared by combining 600 parts of acetonitrile, 400 parts of water, and 1 part trifluoroacetic acid, all parts by volume) was added and the flask was sonicated with occasional shaking for 10 minutes or until the cream was well dispersed. The solution was allowed to cool to ambient temperature and then diluted to volume with diluent. A portion of the solution was filtered using a syringe equipped with a 0.45 micron PTFE filter to provide the sample solution.

15

#### Preparation of Cream Formulations

The cream formulations in the Examples below were prepared using the following general method.

Oil phase preparation: The IRM compound and the BHA or BHT were dissolved in the isostearic acid and medium chain triglycerides, with heat if necessary. Generally the CARBOPOL 980 was then dispersed in the oil phase.

Water phase preparation: Edetate disodium dihydrate, methylparaben, sorbic acid, propylene glycol, and POLOXAMER 188 were added to the water and mixed until dissolved, with heat if necessary. If the CARBOPOL was not dispersed in the oil phase, it was dispersed in the water phase.

Phase combination: The oil phase was added to the water phase at ambient conditions. The emulsion was then homogenized. Sodium hydroxide was added either before or after phase combination. The 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 of pH 5.

30

## Examples 1-6

Table 1 summarizes topical formulations made in accordance with the present invention in a percentage weight-by-weight basis. The formulations were packaged in aluminum tubes with an epoxy phenolic lacquer liner.

Ingredient	Ex 1	Ex 2	Ex 3	Ex 4	Ex 5	Ex 6
IRM 1	0.01	0.03	0.10	0.30	0.60	1.00
Isostearic acid	5.00	5.00	5.00	7.00	10.00	10.00
*Medium-chain Triglycerides	4.00	4.00	4.00	4.00	4.00	4.00
CARBOPOL 980	1.00	1.00	1.00	1.00	1.00	1.00
POLOXAMER 188	3.50	3.50	3.50	3.50	3.50	3.50
Propylene glycol	5.00	5.00	5.00	5.00	5.00	5.00
Methylparaben	0.20	0.20	0.20	0.20	0.20	0.20
Sorbic acid	0.15	0.15	0.15	0.15	0.15	0.15
BHA	0.10	0.10	0.10	0.10	0.10	0.10
Edetate disodium dihydrate	0.05	0.05	0.05	0.05	0.05	0.05
Sodium hydroxide Solution 20% w/w	0.80	0.80	0.80	0.80	0.80	0.80
Purified water	80.19	80.17	80.10	77.90	74.60	74.20

\*Caprylic/capric triglyceride available under the trade names CRODAMOL GTCC-PN (Croda, Inc) and MIGLYOL 812N (Sasol).

The creams of Examples 1-6 were stored at 40°C at 75% relative humidity. At selected time points samples were analyzed for IRM 1, sorbic acid (SA), and BHA content. The results are shown in Table 2 below. The initial values (0 month) are the average of 6 independent determinations (2 samples from each of 3 tubes); the values for the later time points are the average of 2 independent determinations (2 samples from 1 tube). Values are not normalized for weight loss that may have occurred during

storage. Test Method 1 was used to determine the IRM 1 content and sorbic acid content. Test Method 2 was used to determine the BHA content.

Ingredient and Time point (40°C/75%RH)	Content (% w/w)					
	(% Initial)					
	Ex 1	Ex 2	Ex 3	Ex 4	Ex 5	Ex 6
IRM 1 – 0 month	0.01004 (100.0)	0.0302 (100.0)	0.1001 (100.0)	0.306 (100.0)	0.609 (100.0)	1.008 (100.0)
IRM 1 – 1 month	0.01009 (100.5)	0.0302 (100.0)	0.1004 (100.3)	0.306 (100.0)	0.612 (100.5)	1.017 (100.9)
IRM 1 – 2 month	0.00990 (98.6)	0.0301 (99.7)	0.0999 (99.8)	0.308 (100.7)	0.602 (98.9)	0.993 (98.5)
IRM 1 – 3 month	0.01012 (100.8)	0.0297 (98.3)	0.0985 (98.4)	0.301 (98.4)	0.615 (101.0)	1.026 (101.8)
IRM 1 – 6 month	0.01008 (100.4)	0.0301 (99.7)	0.1000 (99.9)	0.307 (100.3)	0.616 (101.1)	1.025 (101.7)
SA – 0 month	0.152 (100.0)	0.155 (100.0)	0.152 (100.0)	0.149 (100.0)	0.150 (100.0)	0.150 (100.0)
SA – 1 month	0.152 (100.0)	0.153 (98.7)	0.152 (100.0)	0.148 (99.3)	0.150 (100.0)	0.150 (100.0)
SA – 2 month	0.155 (102.0)	0.152 (98.1)	0.151 (99.3)	0.149 (100.0)	0.149 (99.3)	0.148 (98.7)
SA – 3 month	0.152 (100.0)	0.151 (97.4)	0.149 (98.0)	0.147 (98.7)	0.147 (98.0)	0.148 (98.7)
SA – 6 month	0.150 (98.7)	0.153 (98.7)	0.153 (100.7)	0.148 (99.3)	0.150 (100.0)	0.150 (100.0)
BHA – 0 month	0.1029 (100.0)	0.1057 (100.0)	0.1086 (100.0)	0.1030 (100.0)	0.1025 (100.0)	0.1030 (100.0)

Ingredient and Time point (40°C/75%RH)	Content (% w/w) (% Initial)					
	Ex 1	Ex 2	Ex 3	Ex 4	Ex 5	Ex 6
	BHA – 1 month	0.1049 (101.9)	0.1017 (96.2)	0.1019 (93.8)	0.1005 (97.6)	0.1019 (99.4)
BHA – 2 month	0.0995 (96.7)	0.1026 (97.1)	0.1029 (94.8)	0.1002 (97.3)	0.1001 (97.7)	0.0975 (94.7)
BHA – 3 month	0.0978 (95.0)	0.1011 (95.6)	0.0984 (90.6)	0.0978 (95.0)	0.0984 (96.0)	0.0973 (94.5)
BHA – 6 month	0.1029 (100.0)	0.1004 (95.0)	0.1007 (92.7)	0.1001 (97.2)	0.1008 (98.3)	0.1018 (98.8)

## Examples 7 &amp; 8

5 Table 3 summarizes topical formulations made in accordance with the present invention in a percentage weight-by-weight basis and a formulation prepared without an antioxidant (C1). The formulations were packaged in glass containers.

Ingredient	Ex 7	Ex 8	Ex C1
IRM 1	0.30	0.30	0.30
Isostearic acid	7.00	7.00	7.00
*Medium-chain Triglycerides	8.00	8.00	8.00
CARBOPOL 980	1.00	1.00	1.00
POLOXAMER 188	2.50	2.50	2.50
Propylene glycol	5.00	5.00	5.00
Methylparaben	0.20	0.20	0.20
Sorbic acid	0.15	0.15	0.15
BHA	0.10	-	-
BHT	-	0.10	-
Edetate disodium dihydrate	0.05	0.05	0.05
Sodium hydroxide Solution 20% w/w	0.80	0.80	0.80
Purified water	74.90	74.90	75.00

\*Caprylic/capric triglyceride available under the trade names CRODAMOL GTCC-PN (Croda, Inc) and MIGLYOL 812N (Sasol).

5 The creams of Examples 7, 8, and C1 were stored at 40°C at 75% relative humidity and at 55°C at ambient humidity. At selected time points samples were analyzed using Test Method 1 described above for IRM 1 and sorbic acid content. The results are shown in Table 4 below where each value is for 1 sample from 1 container of cream. Values were not normalized for weight loss that may have occurred during storage.

10

Ingredient - Time point (Conditions)	Content (% w/w) (% Initial)		
	Ex 7	Ex 8	Ex C1
IRM 1 - 0 month (40°C)	0.303 (100.0)	0.303 (100.0)	0.304 (100.0)
IRM 1 - 1 month (40°C)	0.302 (99.7)	0.306 (101.0)	0.302 (99.3)
IRM 1 - 2 month (40°C)	0.305 (100.7)	0.308 (101.7)	0.307 (101.0)
IRM 1 - 3 month (40°C)	0.308 (101.7)	0.315 (104.0)	0.303 (99.7)
IRM 1 - 6 month (40°C)	0.305 (100.7)	0.313 (103.3)	0.296 (97.4)
SA - 0 month (40°C)	0.147 (100.0)	0.147 (100.0)	0.147 (100.0)
SA - 1 month (40°C)	0.146 (99.3)	0.147 (100.0)	0.140 (95.2)
SA - 2 month (40°C)	0.145 (98.6)	0.147 (100.0)	0.133 (90.5)
SA - 3 month (40°C)	0.147 (100.0)	0.150 (102.0)	0.126 (85.7)
SA - 6 month (40°C)	0.146 (99.3)	0.148 (100.7)	0.119 (81.0)
IRM 1 - 0 weeks (55°C)	0.303 (100.0)	0.303 (100.0)	0.304 (100.0)
IRM 1 - 2 weeks (55°C)	0.302 (99.7)	0.304 (100.3)	0.301 (99.0)

Ingredient - Time point (Conditions)	Content (% w/w) (% Initial)		
	Ex 7	Ex 8	Ex C1
IRM 1 - 4 weeks (55°C)	0.303 (100.0)	0.308 (101.7)	0.301 (99.0)
IRM 1 - 6 weeks (55°C)	0.307 (101.3)	0.311 (102.6)	0.301 (99.0)
IRM 1 - 8 weeks (55°C)	0.311 (102.6)	0.314 (103.6)	0.298 (98.0)
SA - 0 weeks (55°C)	0.147 (100.0)	0.147 (100.0)	0.147 (100.0)
SA - 2 weeks (55°C)	0.146 (99.3)	0.147 (100.0)	0.138 (93.9)
SA - 4 weeks (55°C)	0.146 (99.3)	0.148 (100.7)	0.133 (90.5)
SA - 6 weeks (55°C)	0.148 (100.7)	0.148 (100.7)	0.125 (85.0)
SA - 8 weeks (55°C)	0.148 (100.7)	0.149 (101.4)	0.118 (80.3)

## Examples 9-18

Table 5 summarizes topical formulations made in accordance with the present invention in a percentage weight-by-weight basis. The formulations were packaged in aluminum tubes with an epoxy phenolic lacquer liner. The formulations of Examples 9-18 were stored at 40°C at 75% relative humidity. At selected time points samples were analyzed for IRM 1, sorbic acid (SA), and BHA content. The results are shown in Table 6 below where the initial values of IRM and SA are the average of 6 independent determinations (2 samples from each of 3 tubes), the initial BHA values are the average



of 3 independent determinations (1 sample from each of 3 tubes), and the values for later time points are the values for one sample from 1 tube. Values are not normalized for weight loss that may have occurred during storage. Test Method 1 was used to determine the IRM 1 content and sorbic acid content. Test Method 2 was used to

5 determine the BHA content.

Table 5

Ingredient	Ex 9	Ex 10	Ex 11	Ex 12	Ex 13	Ex 14	Ex 15	Ex 16	Ex 17	Ex 18
IRM 1	0.30	0.30	0.30	0.30	0.30	0.30	0.30	0.30	0.30	0.30
Isostearic acid	7.00	7.00	7.00	7.00	7.00	7.00	7.00	7.00	7.00	7.00
*Medium-chain Triglycerides	4.00	4.00	4.00	4.00	4.00	4.00	4.00	4.00	4.00	4.00
CARPOPOL 980	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Poloxamer 188	3.50	3.50	3.50	3.50	3.50	3.50	3.50	3.50	3.50	3.50
Propylene glycol	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00
Methylparaben	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20	0.20
Sorbic acid	0.01	0.10	0.06	0.10	0.06	0.10	0.08	0.08	0.08	0.08
BHA	0.06	0.10	0.006	0.01	0.011	0.018	0.08	0.008	0.015	0.015
Edetate disodium dihydrate	-	-	-	-	-	-	-	-	-	0.05
Sodium hydroxide Solution 20% w/w	**	**	**	**	**	**	**	**	**	**
Purified water	***	***	***	***	***	***	***	***	***	***

\*Caprylic/capric triglyceride available under the trade names CRODAMOL GTCC-PN (Croda, Inc) and MIGLYOL 812N (Sasol).  
 \*\* qs to pH 5  
 \*\*\*: qs to 100

Table 6

Ingredient - Timepoint	Content (% w/w)																					
	(% Initial)																					
	Ex 9	Ex 10	Ex 11	Ex 12	Ex 13	Ex 14	Ex 15	Ex 16	Ex 17	Ex 18		Ex 9	Ex 10	Ex 11	Ex 12	Ex 13	Ex 14	Ex 15	Ex 16	Ex 17	Ex 18	
IRM 1 - 0 month	0.312 (100.0)	0.311 (100.0)	0.307 (100.0)	0.308 (100.0)	0.309 (100.0)	0.310 (100.0)	0.308 (100.0)	0.307 (100.0)	0.309 (100.0)	0.309 (100.0)		0.312 (100.0)	0.311 (100.0)	0.307 (100.0)	0.308 (100.0)	0.309 (100.0)	0.310 (100.0)	0.308 (100.0)	0.307 (100.0)	0.309 (100.0)	0.309 (100.0)	0.309 (100.0)
IRM 1 - 2 month	0.310 (99.4)	0.310 (99.7)	0.306 (99.7)	0.308 (100.0)	0.311 (100.6)	0.309 (99.7)	0.308 (100.0)	0.307 (100.0)	0.309 (99.7)	0.308 (99.7)		0.310 (99.4)	0.310 (99.7)	0.306 (99.7)	0.308 (100.0)	0.311 (100.6)	0.309 (99.7)	0.307 (100.0)	0.308 (100.0)	0.309 (99.7)	0.308 (99.7)	0.308 (98.1)
IRM 1 - 4 month	0.313 (100.3)	0.310 (99.7)	0.313 (102.0)	0.308 (100.0)	0.311 (100.6)	0.306 (98.7)	0.308 (100.0)	0.307 (100.0)	0.311 (100.6)	0.306 (98.7)		0.313 (100.3)	0.310 (99.7)	0.313 (102.0)	0.308 (100.0)	0.311 (100.6)	0.306 (98.7)	0.307 (100.0)	0.311 (100.6)	0.310 (100.2)	0.311 (100.3)	0.310 (100.3)
IRM 1 - 6 month	0.314 (100.6)	0.310 (99.7)	0.311 (101.3)	0.309 (100.3)	0.314 (101.6)	0.319 (102.9)	0.309 (100.3)	0.311 (101.3)	0.314 (101.6)	0.319 (102.9)		0.314 (100.6)	0.310 (99.7)	0.311 (101.3)	0.309 (100.3)	0.314 (101.6)	0.319 (102.9)	0.311 (101.3)	0.314 (101.6)	0.313 (101.3)	0.313 (101.3)	0.316 (102.3)
SA - 0 month	0.0598 (100.0)	0.1012 (100.0)	0.0600 (100.0)	0.1006 (100.0)	0.0608 (100.0)	0.1014 (100.0)	0.0600 (100.0)	0.1006 (100.0)	0.0608 (100.0)	0.1014 (100.0)		0.0598 (100.0)	0.1012 (100.0)	0.0600 (100.0)	0.1006 (100.0)	0.0608 (100.0)	0.1014 (100.0)	0.0600 (100.0)	0.1006 (100.0)	0.0803 (100.0)	0.0809 (100.0)	0.0807 (100.0)
SA - 2 month	0.0580 (97.0)	0.0986 (97.4)	0.0586 (97.7)	0.0987 (98.1)	0.0596 (98.0)	0.0995 (98.1)	0.0987 (98.1)	0.0986 (98.1)	0.0596 (98.0)	0.0995 (98.1)		0.0580 (97.0)	0.0986 (97.4)	0.0586 (97.7)	0.0987 (98.1)	0.0596 (98.0)	0.0995 (98.1)	0.0987 (98.1)	0.0986 (98.1)	0.0789 (98.3)	0.0794 (98.1)	0.0788 (97.6)
SA - 4 month	0.0571 (95.5)	0.0962 (95.1)	0.0582 (97.0)	0.0956 (95.0)	0.0585 (96.2)	0.0968 (95.5)	0.0956 (95.0)	0.0957 (95.1)	0.0585 (96.2)	0.0968 (95.5)		0.0571 (95.5)	0.0962 (95.1)	0.0582 (97.0)	0.0956 (95.0)	0.0585 (96.2)	0.0968 (95.5)	0.0957 (95.1)	0.0956 (95.0)	0.0773 (96.3)	0.0779 (96.3)	0.0792 (98.1)
SA - 6 month	0.0565 (94.5)	0.0951 (94.0)	0.0578 (96.3)	0.0957 (95.1)	0.0590 (97.0)	0.0998 (95.7)	0.0957 (95.1)	0.0957 (95.1)	0.0590 (97.0)	0.0998 (95.7)		0.0565 (94.5)	0.0951 (94.0)	0.0578 (96.3)	0.0957 (95.1)	0.0590 (97.0)	0.0998 (95.7)	0.0957 (95.1)	0.0957 (95.1)	0.0780 (97.1)	0.0776 (95.9)	0.0812 (100.6)
BHA - 0 month	0.0610 (100.0)	0.1016 (100.0)	0.0658 (100.0)	0.1000 (100.0)	0.0610 (100.0)	0.1018 (100.0)	0.0610 (100.0)	0.1000 (100.0)	0.0610 (100.0)	0.1018 (100.0)		0.0610 (100.0)	0.1016 (100.0)	0.0658 (100.0)	0.1000 (100.0)	0.0610 (100.0)	0.1018 (100.0)	0.0610 (100.0)	0.1000 (100.0)	0.0078 (100.0)	0.0150 (100.0)	0.0151 (100.0)
BHA - 2 month	0.0532 (87.2)	0.0865 (85.1)	0.0643 (73.9)	0.0078 (78.3)	0.0090 (81.7)	0.0148 (82.5)	0.0078 (78.3)	0.0043 (73.9)	0.0090 (81.7)	0.0148 (82.5)		0.0532 (87.2)	0.0865 (85.1)	0.0643 (73.9)	0.0078 (78.3)	0.0090 (81.7)	0.0148 (82.5)	0.0078 (78.3)	0.0043 (73.9)	0.0063 (81.1)	0.0119 (79.3)	0.0156 (103.1)

Table 6

Ingredient - Timepoint	Content (% w/w) (% Initial)																		
	Ex 9	Ex 10	Ex 11	Ex 12	Ex 13	Ex 14	Ex 15	Ex 16	Ex 17	Ex 18	Ex 19	Ex 20	Ex 21	Ex 22	Ex 23	Ex 24	Ex 25	Ex 26	
BHA - 4 month	0.0430 (70.5)	0.0717 (70.6)	0.0036 (62.4)	0.0061 (60.9)	0.0077 (70.1)	0.0125 (69.7)	0.0706 (75.5)	0.0054 (69.5)	0.0099 (66.0)	0.0146 (96.8)									
BHA - 6 month	0.0388 (63.6)	0.0690 (67.9)	0.0030 (51.7)	0.0055 (55.0)	0.0068 (61.8)	0.0114 (63.3)	0.0649 (69.4)	0.0043 (55.1)	0.0095 (63.3)	0.0147 (97.4)									

## Examples 19-24

Table 7 summarizes topical formulations made in accordance with the present invention in a percentage weight-by-weight basis. The formulations were packaged in aluminum tubes with an epoxy phenolic lacquer liner. The formulations of Examples 19-24 were stored at 40°C at 75% relative humidity. At selected time points samples were analyzed for IRM 1, sorbic acid (SA), and BHA content. The results are shown in Table 8 below where the initial values of IRM SA, and BHA are the average of 3 independent determinations, and the values for later time points are from 1 tube. Values are not normalized for weight loss that may have occurred during storage. Test Method 3 was used to determine IRM 1 content. Test Method 4 was used to determine SA and BHA content.

Ingredient	Ex 19	Ex 20	Ex 21	Ex 22	Ex 23	Ex 24
IRM 1	0.03	0.30	0.30	0.30	0.30	0.30
Isostearic acid	5.00	7.00	7.00	7.00	7.00	7.00
*Medium-chain Triglycerides	4.00	4.00	4.00	4.00	4.00	4.00
CARBOPOL 980	1.00	1.00	1.00	1.00	1.00	1.00
POLOXAMER 188	3.50	3.50	3.50	3.50	3.50	3.50
Propylene glycol	5.00	5.00	5.00	5.00	5.00	5.00
Methylparaben	0.20	0.20	0.20	0.20	0.20	0.20
Sorbic acid	0.10	0.10	0.10	0.10	0.10	0.10
BHA	0.01	-	0.01	0.01	0.01	0.01
Edetate disodium dihydrate	0.05	0.05	-	0.05	0.03	0.01
Sodium hydroxide Solution 20% w/w	0.80	0.80	0.80	0.80	0.80	0.80
Purified water	80.31	78.05	78.09	78.04	78.06	78.08

\*Caprylic/capric triglyceride available under the trade names CRODAMOL GTCC-PN (Croda, Inc) and MIGLYOL 812N (Sasol).

Ingredient – Time Point	Content (% w/w)					
	(% Initial)					
	Ex 19	Ex 20	Ex 21	Ex 22	Ex 23	Ex 24
IRM 1 – 0 month	0.0298 (100.0)	0.303 (100.0)	0.303 (100.0)	0.301 (100.0)	0.302 (100.0)	0.303 (100.0)
IRM 1 – 2 month	0.0299 (100.3)	0.300 (99.0)	0.306 (101.0)	0.303 (100.7)	0.306 (101.3)	0.305 (100.7)
IRM 1 – 4 month	0.0299 (100.3)	0.300 (99.0)	0.304 (100.3)	0.304 (101.0)	0.304 (100.7)	0.305 (100.7)
IRM 1 – 6 month	0.0299 (100.3)	0.296 (97.7)	0.302 (99.7)	0.305 (101.3)	0.306 (101.3)	0.306 (101.0)
SA – 0 month	0.0996 (100.0)	0.0966 (100.0)	0.0995 (100.0)	0.0997 (100.0)	0.1005 (100.0)	0.1007 (100.0)
SA – 2 month	0.0983 (98.7)	0.0909 (94.1)	0.0980 (98.5)	0.0994 (99.7)	0.1000 (99.5)	0.0996 (98.9)
SA – 4 month	0.1003 (100.7)	0.0825 (85.4)	0.0976 (98.1)	0.0996 (99.9)	0.0993 (98.8)	0.0988 (98.1)
SA – 6 month	0.0996 (100.0)	0.0756 (78.3)	0.0969 (97.4)	0.0997 (100.0)	0.0997 (99.2)	0.0999 (99.2)
BHA – 0 month	0.0095 (100)	*ND	0.0097 (100)	0.0098 (100)	0.0100 (100)	0.0099 (100)
BHA – 2 month	0.0092 (97)	ND	0.0085 (88)	0.0098 (100)	0.0100 (100)	0.0099 (100)
BHA – 4 month	0.0096 (101)	ND	0.0083 (86)	0.0101 (103)	0.0101 (101)	0.0094 (95)
BHA – 6 month	0.0094 (99)	ND	0.0076 (78)	0.0101 (103)	0.0102 (102)	0.0100 (101)

\*ND = not determined

Table 9 summarizes topical formulations made in accordance with the present invention in a percentage weight-by-weight basis. The formulations were packaged in aluminum tubes with an epoxy phenolic lacquer liner.

Ingredient	Ex 25	Ex 26	Ex 27	Ex 28	Ex 29
IRM 1	0.01	0.05	0.10	0.10	0.10
Isostearic acid	5.00	5.00	5.00	5.00	5.00
*Medium-chain Triglycerides	4.00	4.00	4.00	4.00	4.00
CARBOPOL 980	1.00	1.00	1.00	1.00	1.00
POLOXAMER 188	3.50	3.50	3.50	3.50	3.50
Propylene glycol	5.00	5.00	5.00	5.00	5.00
Methylparaben	0.20	0.20	0.20	0.20	0.20
Sorbic acid	0.10	0.10	0.10	0.10	0.10
BHA	0.01	0.01	0.01	0.01	0.01
Edetate disodium dihydrate	0.05	0.05	0.05	0.05	0.05
Sodium hydroxide Solution 20% w/w	0.80	0.80	0.80	0.40	1.20
Purified water	80.33	80.29	80.24	80.64	79.84

\*Caprylic/capric triglyceride available under the trade names CRODAMOL GTCC-PN (Croda, Inc) and MIGLYOL 812N (Sasol).

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The complete disclosures of the patents, patent documents, and publications cited herein are incorporated by reference in their entirety as if each were individually incorporated, except that if there is any apparent conflict or inconsistency the present disclosure is  
 10 controlling. Various modifications and alterations to this invention will become apparent to those skilled in the art without departing from the scope and spirit of this invention. It should be understood that this invention is not intended to be unduly limited by the illustrative embodiments and examples set forth herein and that such examples and embodiments are

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presented by way of example only with the scope of the invention intended to be limited only by the claims set forth herein as follows.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" or  
5 "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as  
10 an acknowledgment or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.



**The claims defining the invention are as follows:**

1. A pharmaceutical formulation comprising:
  - an immune response modifier (IRM) compound comprising a 2-aminopyridine moiety fused to a five-membered nitrogen-containing heterocyclic ring;
  - a preservative system comprising a sorbic acid preservative selected from the group consisting of sorbic acid, esters thereof, salts thereof, and combinations thereof;
  - and
  - an antioxidant.
2. The formulation of claim 1 further comprising a fatty acid.
3. The formulation of claim 2 further comprising a hydrophobic, aprotic component miscible with a fatty acid and comprising a hydrocarbyl group of 7 or more carbon atoms.
4. The formulation of claim 1 wherein the antioxidant is selected from the group consisting of ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, cysteine, propyl gallate, sodium formaldehyde sulfoxylate, tocopherol, and combinations thereof.
5. The formulation of claim 1 wherein the preservative system comprises sorbic acid, isopropyl sorbate, calcium sorbate, potassium sorbate, sodium sorbate, triethanolamine sorbate, or combinations thereof.
6. The formulation of claim 1 wherein the preservative system further includes a preservative enhancing solubilizer.
7. The formulation of claim 1 further comprising a chelating agent.
8. The formulation of claim 1 further comprising a hydrophilic viscosity enhancing agent.

9. A pharmaceutical formulation comprising:  
0.001% by weight to 5.0% by weight of an immune response modifier (IRM) compound comprising a 2-aminopyridine moiety fused to a five-membered nitrogen-containing heterocyclic ring;  
a preservative system comprising:  
0.02% by weight to 0.2% by weight of a sorbic acid preservative selected from the group consisting of sorbic acid, esters thereof, salts thereof, and combinations thereof;  
0 to 10.0% by weight of a preservative enhancing solubilizer; and  
0.05% by weight to 0.2% by weight of a secondary preservative compound;  
0.001% by weight to 0.2% by weight of an antioxidant comprising hydrogen atom donating functionality;  
0 to 0.1% by weight of a chelating agent;  
1% by weight to 30% by weight of a fatty acid;  
1% by weight to 15% by weight of a medium-chain triglyceride;  
0.2% by weight to 2.0% by weight of a viscosity enhancing agent;  
0.1% by weight to 6.0% by weight of an emulsifier; and  
water;  
wherein the formulation has a pH of 4.0 to 6.0 and the weight percentages are based on the total weight of the formulation.

10. The formulation of any one of claims 1 through 9 wherein the IRM is selected from the group consisting of imidazoquinoline amines, tetrahydroimidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, 1,2-bridged imidazoquinoline amines, imidazonaphthyridine amines, tetrahydroimidazonaphthyridine amines, oxazoloquinoline amines, thiazoloquinoline amines, oxazolopyridine amines, thiazolopyridine amines, oxazolophthyridine amines, thiazolonaphthyridine amines, imidazoquinoline-1,4-diamines, 1*H*-imidazo dimers fused

to pyridine amines, quinoline amines, tetrahydroquinoline amines, naphthyridine amines, tetrahydronaphthyridine amines, and combinations thereof.

11. The formulation of claim 10 wherein the IRM is an imidazonaphthyridine amine.

12. A pharmaceutical formulation comprising:  
0.001% by weight to 5.0% by weight of an imidazonaphthyridine amine;  
0.02% by weight to 0.2% by weight of a sorbic acid preservative selected from the group consisting of sorbic acid, esters thereof, salts thereof, and combinations thereof;  
0 to 10.0% by weight of propylene glycol;  
0.05% by weight to 0.2% by weight of methylparaben;  
0.001% by weight to 0.2% by weight of butylated hydroxyanisole, butylated hydroxytoluene, or combinations thereof;  
0 to 0.1% by weight of ethylenediaminetetraacetic acid, a hydrate thereof, a salt thereof, a hydrate of the salt thereof, or combinations thereof;  
1% by weight to 30% by weight of isostearic acid;  
1% by weight to 15% by weight of a medium-chain triglyceride;  
0.2% by weight to 2.0% by weight of a carbomer;  
0.1% by weight to 6.0% by weight of a poloxamer, and  
water;  
wherein the formulation has a pH of 4.0 to 6.0 and the weight percentages are based on the total weight of the formulation.

13. The formulation of claim 12 wherein the imidazonaphthyridine amine is 2-methyl-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine.

14. The formulation of claim 11 wherein the imidazonaphthyridine amine is 2-methyl-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine.

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15. Pharmaceutical formulations as defined in any one of claims 1, 9 or 12, substantially as hereinbefore described with reference to the accompanying examples or description.